The Health Committee

The Health Committee is appointed by the House of Commons to examine the expenditure, administration, and policy of the Department of Health and its associated bodies.

Current membership

Mr David Hinchliffe MP (Labour, Wakefield) (Chairman)
Mr David Amess MP (Conservative, Southend West)
John Austin MP (Labour, Erith and Thamesmead)
Mr Keith Bradley MP (Labour, Manchester Withington)
Mr Simon Burns MP (Conservative, Chelmsford West)
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Dr Richard Taylor MP (Independent, Wyre Forest)

Powers

The Committee is one of the departmental select committees, the powers of which are set out in House of Commons Standing Orders, principally in SO No 152. These are available on the Internet via www.parliament.uk.

Publications

The Reports and evidence of the Committee are published by The Stationery Office by Order of the House. All publications of the Committee (including press notices) are on the Internet at www.parliament.uk/parliamentary_committees/health_committee.cfm
A list of Reports of the Committee in the present Parliament is at the back of this volume.

Committee staff

The current staff of the Committee are Dr David Harrison (Clerk), Keith Neary (Second Clerk), Laura Hilder (Committee Specialist), Christine Kirkpatrick (Committee Specialist), Frank McShane (Committee Assistant), Mr Darren Hackett, (Committee Assistant), and Rowena Macdonald (Secretary).

Contacts

All correspondence should be addressed to the Clerk of the Health Committee, House of Commons, 7 Millbank, London SW1P 3JA. The telephone number for general enquiries is 020 7219 6182. The Committee’s email address is healthcom@parliament.uk.

Footnotes

In the footnotes of this Report, references to oral evidence are indicated by ‘Q’ followed by the question number. Written evidence is cited by reference to Volume II of this Report, in the form of Memorandum numbers (e.g. PI 01) or Appendix numbers (e.g. Appendix 1).
Witnesses

**Thursday 9 September 2004**

Dr Felicity Harvey, Head of Medicines, Pharmacy and Industry Group, Dr Jim Smith, Chief Pharmaceutical Officer, Professor Sally Davies, Director of Research and Development, Department of Health, Professor Kent Woods, Chief Executive, Medicines and Healthcare products Regulatory Agency, and Dr Monica Darnbrough, Director, Bioscience Unit, Department of Trade and Industry.

**Thursday 14 October 2004**

Dr Des Spence, UK Spokesperson, No Free Lunch, Mr Graham Vidler, Head, Policy, Consumer’s Association, Dr Ike Iheanacho, Editor, Drug and Therapeutics Bulletin, and Dr Peter Wilmshurst, Consultant Cardiologist, Royal Shrewsbury Hospital

Mr Richard Brook, Chief Executive, Mind, Professor David Healy, Cardiff University, and Professor Andrew Herxheimer, Emeritus Fellow, UK Cochrane Centre, Oxford

**Thursday 11 November 2004**

Dr Iona Heath, Past Chairman, Committee on Medical Ethics, Royal College of General Practitioners, Dr Tim Kendall, Deputy Director, Royal College of Psychiatrists Research Unit, Mr Matt Griffiths, Senior Charge Nurse and Joint Prescribing Adviser, Royal College of Nursing, Mr John D’Arcy, Chief Executive, National Pharmaceutical Association, Mr Rob Darracott, Director, Corporate and Strategic Development, Royal Pharmaceutical Society of Great Britain and Dr Richard Nicholson, Editor, Bulletin of Medical Ethics

**Thursday 25 November 2004**

Ms Melinda Letts, Chairman, Committee on Safety of Medicines Working Group on Patient Information and Paul Flynn MP, Chairman, Commons All-Party Group on Rheumatoid Arthritis

Mr Phil Woolas MP, Trustee, Beat the Benzos Campaign and Mr Cliff Prior, Chief Executive, Rethink Severe Mental Illness, Mr Jim Thomson, Chief Executive, Depression Alliance, Mr Glynn McDonald, Head, Policy and Campaigns, Multiple Sclerosis Society, Dr Helen Wallace, Deputy Director, GeneWatch UK and Ms Jenny Hirst, Co-Chairman, Insulin-Dependent Diabetes Trust
Thursday 2 December 2004

Sir Richard Sykes, Rector, Imperial College, London, Professor Patrick Vallance, Professor, Clinical Pharmacology and Head, Department of Medicine, University College, London and Sir Iain Chalmers, Editor, The James Lind Library

Dr Roberto Solari, Chief Executive Officer, MRC Technology, Medical Research Council, Dr Malcolm Boyce, Chairman, Association for Human Pharmacology in the Pharmaceutical Industry and Mr Harpal Kumar, Chief Operating Officer, Cancer Research UK and Chief Executive Officer, Cancer Research Technology

Thursday 16 December 2004

Ms Margot James, European President, Ogilvy Healthworld, Mr Mike Paling, Managing Director, Paling Walters, Mr Richard Horton, Editor, The Lancet, Ms Jenny Hope, Medical Correspondent, Daily Mail and Ms Lois Rogers, Medical Editor, Sunday Times

Thursday 13 January 2005

Mr Eddie Gray, Senior Vice President and General Manager, and Dr Stuart Dollow, Vice President, Medical Division, GlaxoSmithKline, Mr Chris Brinsmead, Marketing Co-President and Dr John Patterson, Executive Director, Development, AstraZeneca

Dr Richard Barker, Director General, and Mr Vincent Lawton, President, Association of the British Pharmaceutical Industry, Dr David Chiswell, Chairman, BioIndustry Association and Mr Simon Clark, Chairman, British Generic Manufacturers Association

Tuesday 20 January 2005

Professor Sir Alasdair Breckenridge, Chairman, Professor Kent Woods, Chief Executive, and Dr June Raine, Director, Post-Licensing Division, Medicines and Healthcare products Regulatory Agency

Professor Sir Michael Rawlins, and Mr Andrew Dillon CBE, Chief Executive, National Institute for Clinical Excellence

Thursday 3 February 2005

The Lord Warner, Parliamentary Under-Secretary of State for Health [Lords], Dr Felicity Harvey, Head of Medicines, Pharmacy and Industry Group, Department of Health and Dr June Raine, Director, Post-Licensing Division, Medicines and Healthcare products Regulatory Agency
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Additional papers have been received from the following and have been reported to the House but to save printing costs they have not been printed and copies have been placed in the House of Commons library where they may be inspected by members. Other copies are in the Record Office, House of Lords and are available to the public for inspection. Requests for inspection should be addressed to the Record Office, House of Lords, London SW1. (Tel 020 7219 3074) hours of inspection are from 9:30am to 5:00pm on Mondays to Fridays.

Royal National Institute of the Blind (PI 4)
Andre Menache (PI 8)
Professor Kevin Outterson (PI 9)
David Thrower (PI 10)
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Monica Russell (PI 52)
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Hugh James, Solicitors (PI 56)
Ms Ramzia Kabbani (PI 61)
Mr Chris Clarke (PI 62)
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Margaret MacRae (PI 126)
Oral evidence

Taken before the Health Committee
on Thursday 9 September 2004

Members present:

Mr David Amess
Mr Simon Burns
Mr Keith Bradley
Mrs Patsy Calton
Jim Dowd

Mr Jon Owen Jones
Ms Siobhan McDonagh
Dr Richard Taylor

In the absence of the Chairman, Dr Doug Naysmith was called to the Chair

Memorandum by the Department of Health (P 11)

The Influence of the Pharmaceutical Industry

1. Introduction
2. Drug Innovation
3. Conduct of Medical Research
4. Provision of Drug Information and Promotion
5. Provision of Professional and Patient Education
6. Regulatory Review of Drug Safety and Efficacy
7. Product Evaluation, including assessments of value for money

1. Introduction

1.1 The Government welcomes the opportunity provided by the Health Select Committee inquiry to set out its policies in respect of medicines and the pharmaceutical industry. This memorandum describes the Government’s overall relationship with the pharmaceutical industry, and the specific policies applying to each of the areas highlighted by the Committee in its terms of reference.

Government Relations with the Pharmaceutical Industry

1.2 Government relations with the pharmaceutical industry are co-ordinated from the Department of Health. Other Government Departments with close interests include the Department of Trade and Industry, the Treasury, and the Department for International Development.

1.3 The medicines produced by pharmaceutical companies make an important contribution to the healthcare received by patients in the NHS. The presence of substantial pharmaceutical R&D facilities in the UK provides scope for beneficial links with the NHS and wider academic research and science base. Pharmaceutical companies also provide highly skilled employment opportunities, and generate export earnings, which are of benefit to the economy more widely.

1.4 The Government’s aim is that in its engagement with this important industry it secures beneficial outcomes in all these areas. Its approach where possible is to work in consultation and partnership with the pharmaceutical industry. However, given the importance in this field of ensuring patient safety and promoting appropriate use of medicines in the NHS, the Government has a range of regulatory powers which it may exercise in the interest of patients.

1.5 The Government holds regular (twice-yearly) meetings with the research-based industry in the Ministerial Industry Strategy Group (MISG). This group is chaired by Lord Warner for Government, and includes Ministerial representation from DTI, HM Treasury and DfES. The industry representatives come from pharmaceutical companies (British and foreign) with operations in the UK, chaired by Sir Tom McKillop, CEO of AstraZeneca. The MISG complements meetings and other discussions that may take place between industry representatives and Government Ministers, and was set up as a result of the Pharmaceutical Industry Competitiveness Task Force (PICTF) report, which was submitted to the Prime Minister in March 2001.
**Government Policies affecting the Pharmaceutical Industry**

1.6 Key areas of Government policy affecting the pharmaceutical industry and its interaction with the research and healthcare system are as follows:

- **The research infrastructure**—both basic science important for early-stage discovery research, and clinical trials of medicines in the NHS.

- **Innovation policy**, which encourages the commercial exploitation of R&D.

- **The regulatory system** for licensing medicines and monitoring their safety in subsequent use—run in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA), although increasingly an EU-wide activity.

- NHS systems and policies for **prescribing** of medicines, including provision of information and advice to aid effective and appropriate selection of medicines to meet patients’ needs. This now includes guidance from the National Institute of Clinical Excellence (NICE) on the clinical and cost effectiveness of medicines. This area of policy also increasingly recognises the importance of patient involvement and decision-making on medicines in partnership with professionals.

- Systems for **control of prices and reimbursement** for medicines used in the NHS. The Pharmaceutical Price Regulation Scheme (PPRS) controls prices of branded medicines sold to the NHS, while a separate system governs the generic medicines sector. Both of these are currently subject to review, and in the case of the PPRS, currently under negotiation with the industry association.

1.7 These areas are covered in more detail below, organised according to the Committee’s terms of reference. The sections of the memorandum set out the systems, policies and processes in place, identifying where relevant the opportunity for the pharmaceutical industry or individual pharmaceutical companies to have some influence on decisions or approaches that may affect its interests.

1.8 Other areas of Government policy can have an impact on the pharmaceutical industry and form part of the discussions that take place with different Government departments—for instance, trade policy, intellectual property law, general regulatory matters (such as on waste, chemicals), and skills and workforce matters. These are outside the subjects covered by this Inquiry.

1.9 The Government believes that the conduct of its relationship with the pharmaceutical industry affords an appropriate level of influence, proportionate to its interests as a stakeholder, and in line with others who also have a stake in Government policies and decisions related to medicines. It will of course take a close interest in the Committee’s Inquiry and consider any recommendations that flow from it.

2. **Drug Innovation**

2.1 Medicines represent an important part of healthcare services for preventing and treating illness. In common with other elements of healthcare—whether models of disease progression, methods of diagnosis, or surgical techniques—the medicines available now do not meet all healthcare needs effectively. New and better medicines could offer more effective treatment for patients, just as patients now benefit from medicines that were not available a decade ago.

2.2 Innovation and research in medicines is therefore of central interest for healthcare systems and health professionals. The Government is keen for the NHS to be not only an effective deliverer of healthcare services, but a service built on research and improvement in patient care. The NHS has for many years been one of the leading places in the world for clinical research into medicines. Section 3 below sets out recent initiatives to build on this and to capitalise on the NHS’s strengths in this area.

2.3 It is worth noting, however, that innovation in itself does not always represent a useful or a clinically and cost effective advance in treatment. New technologies and treatments are generally more costly, at least in the short term, than existing options. It is important, therefore, for judgements to be made as to the benefits offered by a new medicine, so as to ensure that the resources available for healthcare are used to secure the most effective treatment. This was one of the purposes of establishing the National Institute for Clinical Excellence (NICE), which is covered further in Section 7.

2.4 The pharmaceutical industry’s role in drug research and innovation is substantial. Although much of the basic science underpinning new medicines originates in the academic sector, the discovery and development of medicines is primarily carried out in the private sector by pharmaceutical companies who seek to take products through the necessary trials and testing and bring them to the market. This requires significant investment, which companies expect to be able to recoup through sales of the medicine. Pharmaceutical companies operate in the global market, so many medicines used in the NHS have been discovered and developed in other countries, while the medicines developed here are sold worldwide.
The UK as a Location for Pharmaceutical Innovation

2.5 The UK has traditionally been one of the world’s leaders in pharmaceutical innovation and continues to be at the forefront of development. Many of the world’s leading companies have chosen to carry out research here, and R&D investment continues to grow. In 2003, Britain’s pharmaceutical industry invested a total of £3.5 billion in R&D. Twenty-five of the world’s top-selling 100 medicines were discovered and developed in the UK, more than any other country except the USA.

2.6 This leading position is based on the excellence of the UK’s science base, with world-renowned research institutions in the academic sector, the charitable sector and in the NHS. UK universities are recognised for their strength in teaching and research in chemical, biological and molecular science and technology, offering pharmaceutical and biotechnology companies access not only to research knowledge but also a pool of highly skilled graduates to employ.

2.7 These are strengths that the Government wishes to maintain and build on. The Government’s new Science & Innovation Investment Framework, published as part of the Spending Review in July 2004, outlines the commitment to make the UK one of the most competitive locations in the world for science, research & development and innovation. The framework sets out a 10-year investment plan, backed up with plans for a fundamental review of funding needs and policy priorities for science, engineering and innovation. This builds on the DTI Innovation Report published in 2003.

2.8 The Government’s aim is to grow the level of innovation across the UK supporting economic growth and better public services, underpinned by rising R&D intensity in both public and private sectors. To reach the Government’s goal for the UK R&D intensity to reach 2.5% by 2014 (compared with 1.9% now) will require continued growth in investment from leading businesses, such as those in the pharmaceutical sector, which already have a substantial presence in the UK. It will also require growth in new science-based companies operating in emerging sectors such as biotechnology. The science & innovation investment framework sets out the Government’s plans for using a strengthened public research base, including in the National Health Service, working more closely with companies, to attract, retain and grow more business R&D investment in the UK.

Areas where additional incentives are required

2.9 Overall, the Government believes that the current model—whereby medicines are developed by the private sector in response to what they perceive to be the demand of healthcare systems—is more effective and efficient than alternatives that could be considered (such as nationalising the drug industry, or by Government directing the research that the industry should undertake).

2.10 However, there are notable areas where this approach is not sufficient to incentivise research into medicines that are needed. In such cases additional measures are required. A current example is that of medicines for children, where the Government supports specific measures to incentivise research on the safety and efficacy of medicines for paediatric use. Work is being taken forward to improve the situation at national level, but given the global focus of the industry, the Government believes that it is important to take action at EU level as well.

3. Conduct of Medical Research

3.1 Medical research in the United Kingdom relies on a series of long-standing partnerships between, on the one hand, the Health Departments and bodies responsible for providing health care, and on the other, universities and those that fund them. The basis for these partnerships is that they operate within a framework of accepted standards. This section describes aspects of Government policy in England that provide the context for these partnerships, and for the interaction between the NHS and industry.

Policy on R&D in the NHS

3.2 Research and Development for a First Class Service (Department of Health, 2000) brought the partnership policy up to date, in light of the Government’s plans for modern and dependable health care. That policy statement recognised that industry is the largest funder of health-related R&D in the United Kingdom; and that much of the R&D funded by industry involves the universities and the NHS.

Research governance

3.3 One plank of the partnership policy is that all medical research should follow the principles of research governance. Consistent quality standards, appropriate to the research methodology, should apply. The research should be consistent with NHS bodies’ duty towards patients, and with their statutory responsibilities. All R&D in the NHS involving patients (or their organs, tissue or confidential data) is subject to ethical review. There must be systems for consent. It is expected that research will be conducted with the active involvement of patients, carers and other users of the NHS.
3.4 Regulation and guidance is necessary to safeguard the dignity, rights, safety and well-being of patients and other participants. The research governance process also reassures individuals that their interests will come first if they consent to take part in medical research. Public confidence in the conduct of research goes hand in hand with the Government’s aim of giving everyone who wants it, the chance to take part in clinical trials to show that new treatments are safe and effective.

**Research Governance Framework**

3.5 To promote clear understandings between the NHS and its partners, the Department of Health issued a *Research Governance Framework for Health and Social Care* in 2001. It brought together standards based on the law and good practice. The approach in this guidance is to list groups of responsibilities, helping each of the partners understand what others normally expect of them. The explicit aim is to encourage agreements among collaborators recording how these duties will be carried out.

3.6 For the most part, this guidance applies long-standing ethical principles, recorded in international statements of good practice since the Second World War. The World Medical Assembly adopted the Declaration of Helsinki in 1964, amending it in 1975, 1983, 1989, 1996 and 2000. The International Committee on Harmonisation agreed in 1996 to adopt into law the same standards of Good Clinical Practice (GCP) in pharmaceutical clinical trials in the European Union, the United States of America, and Japan. In the EU, Directive 2001/20/EC (the Clinical Trials Directive) required Member States to apply the principles of GCP to both commercial and non-commercial clinical trials with medicines. For the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 adopted the conditions and principles of GCP.

3.7 The GCP principles cover:
- the balance of risks and benefits;
- the rights, safety and well-being of individuals;
- standards of information, scientific quality and trial design;
- ethical review;
- the qualifications of clinicians and those conducting the trial;
- consent;
- data quality;
- confidentiality;
- manufacture and use of medicines in the trial; and
- quality systems.

3.8 The conditions are that an ethics committee and the licensing authority are satisfied the benefits justify the risks; individuals’ rights are safeguarded, and there is provision for insurance or indemnity.

3.9 While some of these principles and conditions are specific to pharmaceutical trials, most give practical effect to general standards of good practice. For this reason, the Medical Research Council issued guidelines on applying the same principles in other types of non-commercial trial. A second edition of the Research Governance Framework will give further advice on applying the principles in proportion to risk, for example in social care research.

**Implementation of research governance**

3.10 The Department of Health supported its guidance on research governance with a national implementation plan from 2001 to 2004. The implementation plan also helped the NHS overhaul its systems for clinical research in advance of the implementation of the Clinical Trials Directive.

3.11 The Department paid close attention to creating a safe and positive environment for both publicly funded medical research and commercial contract research. It is Government policy that industry must meet the full costs of work that the NHS undertakes for industry under contract. It is also Government policy to establish the NHS as the world leader in contributions to clinical research.

**Industry and clinical research**

3.12 The Pharmaceutical Industry Competitiveness Task Force (PICTF) included a working group on clinical research. That group has continued to debate ways to ensure effective working between industry and the NHS. Its focus was on practical measures to avoid delay and to improve value for money in commercial clinical research. It also aimed to reach public agreement on guiding principles.

3.13 The working group developed an R&D partnership agreement (PICTF 2002). It recorded a shared commitment to good research governance, and a joint understanding of the differences between commercial and non-commercial research. It recognised the need for clear understandings about standards to guarantee that industry involvement will not create conflicts of interest compromising the independence of non-commercial collaborative research when there is a contribution from industry.
**Contract research**

3.14 For contract research, the working group concluded that one way to avoid delay would be to adopt a standard form of contract between NHS Trusts and pharmaceutical companies. Experts developed a model clinical trial agreement, introduced in 2003. The Association of the British Pharmaceutical Industry (ABPI) commended it to industry, and the Department of Health commended it to the NHS.

3.15 The Department amended the NHS Finance Manual to remove potential confusion about the approach NHS bodies should take when costing and charging for contract research. Officials and clinical trials experts from industry took part in a programme of communications to explain the importance of clinical trials to the NHS, and expose possible causes of delay. This took place in 2003 for secondary care, and in 2004 for primary care.

**NHS permission for R&D**

3.16 The permission of the NHS body responsible for each clinical research site is required before that part of a study may begin. This requirement works alongside NHS Indemnity policy. NHS Indemnity means NHS bodies accept vicarious liability for clinical negligence. It includes negligent harm during clinical research when the NHS body has a duty of care to the person harmed. For commercial clinical trials, DH guidance links NHS Indemnity to a standard indemnity specifying the liabilities a company will accept.

3.17 NHS bodies and industry drew attention to confusion about NHS permission as in some cases NHS bodies were unclear about the scrutiny required in different cases.

3.18 The Department of Health issued supplementary advice to the NHS in early 2004. It explained the purpose of NHS permission. It confirmed NHS bodies should use this process to highlight and manage any significant risks a study might pose to anyone within their duty of care. It encouraged them to keep bureaucratic procedures to the minimum and to facilitate high quality research. It encouraged them to rely on the work of others in the research governance and regulatory framework, such as ethics committees and the Medicines and Healthcare products Regulatory Agency. The advice clarified Primary Care Trusts’ responsibility for providing a safe system of care. It explained the implications when General Practitioners conduct commercial clinical trials recruiting NHS patients; and the implications when they conduct trials privately, recruiting people who understand the NHS is not liable for the research.

**Ethical review**

3.19 There is a long tradition of independent ethical review of medical research in the United Kingdom. In England, Health Authorities have been responsible for establishing local NHS Research Ethics Committees (RECs), which have operated within Department of Health guidance since 1991. In 1997, a UK-wide working group recommended establishing multi-centre Research Ethics Committees to give a single opinion on studies such as clinical trials. Otherwise, NHS ethics committees have continued to fall within the responsibility of each of the Health Departments.

3.20 Before 1997, investigators had to apply to the NHS REC for each area in which they proposed to conduct a trial. There was no central booking system, as there is now. There was no training to help members understand their role, or allow them to compare notes about their approach. There were no national standard operating procedures. It was not unusual for different committees to ask for different amendments to the protocol. There were no time-limits on the exchange of questions and papers between NHS RECs and investigators.

3.21 Multi-centre NHS RECs have alleviated some of these difficulties. In recent years, the Department has also provided a Central Office for Research Ethics Committees to provide much stronger operational support for all NHS RECs. It has promoted the adoption of national systems to help NHS RECs and their administrators work more effectively and consistently.

3.22 Through the PICTF clinical research working group, the Department and industry discussed a number of issues related to ethical review which were delaying clinical trials. One issue was the quality of industry submissions. Feedback from NHS RECs identified a need for improvement in the quality of information intended for research participants. Another source of delay was inconsistency between opinions, when investigators chose to submit proposals for local review. These and other factors still sometimes made the ethical review process very time-consuming.

3.23 The Clinical Trials Directive required Member States to take the measures necessary for the establishment and operation of ethics committees for clinical trials with medicines. The Medicines for Human Use (Clinical Trials) Regulations 2004 provided for a UK Ethics Committee Authority (UK ECA) that could maintain a single consistent framework of national oversight for the ethical review of medicinal trials. Rather than have the Secretary of State act alone, the Regulations provide for the countries of the United Kingdom to act together at Ministerial level through a UK ECA.

3.24 The Directive was specific about issues ethics committees should consider before reaching an opinion, the time scales within which they should work, and the requirement for a single national opinion. It also set time limits of 60 days (or 90 to 180 days for certain types of trial). In case of an unfavourable
opinion, chief investigators can appeal. The implementation of these provisions will meet most of industry’s concerns about consistency and timeliness. The Regulations reflect international standards, and the UK ECA will work within them.

3.25 The UK ECA will be responsible for establishing, recognising and monitoring committees. It will not appoint or dismiss their members. That will be the responsibility of each ethics committee’s appointing authority. The UK ECA has become the appointing authority for recognised ethics committees only as a transitional measure. The Regulations do not threaten the independence of ethics committees, but for the first time put the force of law behind their independent role in reviewing trial protocols. It will be illegal to begin a trial without a positive opinion from an ethics committee, or to make substantial amendments to the protocol without going back to the committee.

3.26 However, some independent ethics committees were uncertain who should be their appointing authority. The Central Office for NHS Research Ethics Committees (COREC) offered to act as their appointing authority in the first instance. COREC is an expert unit of St George’s NHS Trust. It provides training and other operational services for the NHS ethical review system, under contract to the Department of Health. It also provides the administrative support for multi-centre NHS Research Ethics Committees. COREC took steps on behalf of the Department of Health to support ethics committees in preparing to operate under the Regulations. It also worked with the ABPI to provide training for investigators on the ethical requirements. The UK ECA has not decided which authorities should carry out the UK ECA’s functions under the Regulations in future, or whether to pass any functions to COREC.

3.27 Ethical review of all research affecting the dignity, rights, safety or well-being of individuals should respect internationally recognised principles. The UK ECA will provide the means for the Health Departments to act jointly to uphold common standards across the whole system, not just clinical trials. The Regulations enable the UK ECA to perform its functions largely through others. This will allow Ministers to avoid micro-management or interference, while clearly maintaining the degree of accountability required by the Directive.

Access to research findings

3.28 The general policy is that, once established, the findings of health and social care research should be made available to those participating in the research and to all those who could benefit from them, through publication and/or other appropriate means. The first step is that all research supported by NHS funds has to be registered. The National Research Register is a publicly accessible database. It contains over 115,000 records.

3.29 The Department encourages industry to make the findings of contract research available, so far as is consistent with the protection of intellectual property, regulatory requirements and normal commercial confidentiality. Negative as well as positive results may also be of scientific value, even when they do not lead to publication in peer review journals.

3.30 The NHS/industry R&D Partnership Agreement recorded that companies would notify NHS trial sites of plans for the registration of contracted clinical trials. It also noted the ABPI’s policy on voluntary registration of clinical trials. The ABPI set up an industry clinical trials database on which companies are invited to register phase III trials three months after obtaining the first licence in a major market; and to register phase IV (post marketing) trials prospectively.

3.31 From a regulatory perspective pharmaceutical companies must submit all research data, whether positive or not, to the MHRA in support of any application for a marketing authorisation for a medicinal product. This is a requirement in EU pharmaceutical legislation (EC Directive 2001/83/EC) and the relevant UK implementing legislation. Data are evaluated by the MHRA to ensure that the quality, safety and efficacy of the product are satisfactory for its intended use prior to the approval of a marketing authorisation. These data are submitted to the MHRA in confidence.

3.32 There are no provisions which enable MHRA to require that the applicant must publish its research results, positive or not. Nevertheless, in the interests of public health, MHRA has taken the decision to publish summaries of clinical trial data relating to SSRIs in children and adolescents and to risperidone on the Internet to support recent regulatory action and communications.

Research for Patient Benefit Working Party

3.33 In November 2003, following reports from the Bioscience Innovation and Growth Team and the Academy of Medical Sciences the Government set up the Research for Patient Benefit Working Party (RBPWP), under the Chairmanship of Professor Sir John Pattison, Director of Research and Development at the Department of Health. The remit of the RBPWP was to consider ways to strengthen the infrastructure for clinical research in the NHS. The Working Party included experts from industry, clinicians, patient representatives, the research community and research funders including industry. It established a strong consensus around a common vision of the future for the NHS: “Developing clinical research, through investment in a widely-applicable clinical infrastructure, with an appropriate workforce capability, and with better regulation.” Its final report was submitted to Lords Warner and Sainsbury before Easter.
**UK Clinical Research Collaboration**

3.34 The RPBWP Report suggested that a UK Clinical Research Collaboration (UKCRC) should be established. The Secretary of State for Health declared the Government’s plan to implement this recommendation in his speech during the health budget debate on 22 March 2004. The UKCRC has been established as a partnership between Government, the voluntary sector, patients and industry. Its membership is similar to the RPBWP in the first instance. It will have a small, dedicated core team headed by a Chief Executive.

**The NHS clinical research infrastructure**

3.35 The RPBWP recommended the establishment of major new clinical infrastructure in the NHS. This will consist of a managed set of research networks which, over time, will enable research to be conducted across the full spectrum of disease and clinical need. This world class infrastructure will facilitate the conduct of clinical trials and other well designed studies in the broad area of clinical research. The Government has announced substantial increases in NHS Research & Development funding over the next four years to establish this new NHS research infrastructure.

3.36 The cancer research networks already exist. Initially, new networks will cover mental health, medicines for children, Alzheimers disease, stroke and diabetes. In due course, all diseases and specialties will be covered.

3.37 The network will support trials funded by both commercial and non-commercial organisations. In line with the Department’s general policy, the NHS will recover from industry the cost of the use it makes of this infrastructure.

3.38 The NHS infrastructure will include experimental medicine, translational research and large-scale trials. There will be arrangements for liaison with industry either as part of the individual networks (as with cancer and mental health) and/or in the national co-ordinating centre under the oversight of the UKCRC. This builds on the collaborative working already started in the National Cancer Research Network and the National Translational Cancer Research Network.

3.39 One of the roles of the UKCRC will be to help develop the common elements of these research networks in the NHS and oversee their development. Subgroups will also look at issues such as career structure for clinical researchers, incentives within the NHS and regulation.

4. **Provision of Drug Information and Promotion**

4.1 This section of the Memorandum covers the frameworks for promotion and advertising of medicines. Provision of information for patients is covered in the following section on patient and professional education.

**Advertising of Medicines**

4.2 The pharmaceutical industry is required to comply with the Medicines (Advertising) Regulations 1994 and the Medicines (Monitoring of Advertising) Regulations 1994 when advertising medicines in the UK. These implement Directive 92/28/EC, codified under Title VIII of Directive 2001/83/EC. The legislation applies to all forms of advertising including the Internet. The Regulations apply separate requirements and restrictions to advertising directed at the general public, and at health professionals (“persons qualified to prescribe or supply medicines”).

4.3 The Regulations strictly prohibit advertisement to the general public that is likely to lead to the use of a prescription only medicine (POM). The regulations do not prevent the issue of factual information to the general public about a prescription medicine, or general health issues such as health education campaigns, provided such material does not promote, either directly or indirectly, a particular medicinal product. Such information, presented in the form of factual, informative statements, is not considered to fall within the scope of the advertising regulations.

4.4 All advertising is required to be consistent with the Summary of Product Characteristics approved by the Medicines and Healthcare products Regulatory Agency (MHRA). It must also encourage rational use of the product by presenting it objectively and without exaggerating its properties and must not be misleading.

**MHRA Regulation**

4.5 The MHRA carries out its statutory role through the assessment of selected advertising prior to issue, by monitoring published advertisements and by investigating complaints.

4.6 The MHRA has the power to require sight of advertisements in advance of publication. It usually exercises this power to require pre-vetting where:

— The product is a newly licensed and intensively monitored medicine;
— The product has been reclassified to make it available without prescription for the first time; or
— Where the product’s previous advertising has breached the regulations.

4.7 The MHRA’s Advertising Unit carries out monitoring of prescription-only medicine advertising in medical journals and other publications, concentrating particularly on newly launched products. The Unit also investigates complaints about advertising from any source, including health professionals and the public.

4.8 The MHRA’s powers allows them to determine whether advertising breaches the Regulations and can require advertising to be withdrawn and corrective statements made. An Independent Review Panel was established in 1999 to provide independent advice to the MHRA where it is asked to determine whether an advertisement breaches the Regulations.

Industry self-regulation

4.9 The MHRA’s procedures for regulating advertising operate independently of industry self-regulatory systems. The main bodies involved in the self-regulatory system are the Prescription Medicines Code of Practice Authority (PMCPA), the Proprietary Association of Great Britain (PAGB), the Advertising Standards Authority (ASA), and Ofcom.

4.10 Both PAGB and PMCPA administer Codes of Practice for the promotion of medicines. These reflect and extend beyond the legal requirements and provide interpretation of how they are applied. The PMCPA operates a procedure for adjudication on complaints under its Code for prescription medicines. The PAGB operates a system of pre-vetting advertisements to the public and a complaints system for advertisements to health professionals for OTC medicines.

Medicines Advertising Liaison Group

4.11 The MHRA convenes meetings of the Medicines Advertising Liaison Group at regular intervals to discuss new developments and current issues in regulation of medicines advertising to ensure a consistent approach. Members include the PMCPA, PAGB, ASA, Ofcom, Radio Advertising Clearance Centre and Broadcast Advertising Clearance Centre, Advertising Association and British Dental Trades Association. Industry bodies are consulted on the MHRA’s guidance notes and the MHRA is similarly consulted on changes to any of the self-regulatory codes.

Transparency

4.12 The MHRA reports on the outcome of all complaint investigations and these are published on the MHRA website. From 1 December 2003 to 30 June 2004 16 complaints were reported to the MHRA website. The publication of a summary report of complaints received is intended to provide guidance to advertisers on how the Regulations are interpreted and also act as an information resource for advertisers, consumers and the media on decision making and actions taken by the MHRA in advertising casework. This has a number of potential benefits including improved compliance with the Regulations.

4.13 Guidance on the Agency’s interpretation of the Regulations is provided in “Advertising and Promotion of Medicines in the UK”, available on the MHRA website. Specific guidance has also been published on advertising in pregnancy and on disease awareness campaigns and articles on advertising issues are also published regularly in the MHRA updating service, MAIL.

Promotion of Medicines to Professionals

4.14 The promotional activities of pharmaceutical companies with General Practitioners and other professionals are governed by a range of controls.

4.15 Where collaborative partnerships involve a pharmaceutical company then the proposed arrangements must comply fully with the Medicines (Advertising) Regulations 1994 (regulation 21 “inducements and hospitality”). These require that:
— Promotional material and claims made by industry representatives are not exaggerated, and are consistent with the Summary of Product Characteristics.
— Industry representatives organising meetings are only permitted to provide appropriate hospitality and/or meet any reasonable, actual costs, which may have been incurred.
— Hospitality must be secondary to the purpose of the meeting.
— The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed that level which the recipients would normally adopt when paying for themselves, or that which could be reciprocated by the NHS.
— It should not extend beyond those whose role makes it appropriate for them to attend the meeting.
4.16 Any person who contravenes regulation 21(1) is guilty of an offence, and liable, on summary conviction to a fine not exceeding £5,000, and on conviction on indictment to a fine, or to imprisonment for a term not exceeding two years or both. Anyone contravening regulation 21(5) is also guilty of an offence and liable on summary conviction to a fine not exceeding £5,000. The MHRA Guidelines on Promotion and Advertising set out the standards to be followed.

4.17 The Departmental guidance HSG(93)5 Standards of Business Conduct for NHS Staff and Commercial Sponsorship—Ethical Standards for the NHS (November 2000) give clear guidance to NHS employers and staff in maintaining strict ethical standards in the conduct of NHS business, including on receiving sponsorship.

4.18 If an agreement is entered into, the clinicians' judgement should always be based upon clinical evidence that the product is best for the patients and value for money.

4.19 All NHS staff are bound by a Code of Conduct. A model code is attached to Commercial Sponsorship—Ethical Standards for the NHS and makes it quite clear that staff are expected to declare gifts, benefits or sponsorship of any kind and refuse gifts etc which may be seen to compromise their personal judgement or integrity. It provides guidance for those staff, and independent contractors, who are not already covered by such a code. It outlines what they are expected to do as an employee or contractor working in the NHS. It includes in an annex a section about how to deal with situations that may present potential conflict.

4.20 Health professionals are subject to their own codes of conduct which are maintained by their professional colleges and councils. For example, the GMC guidance Good Medical Practice states that doctors must not ask for or accept any inducement, gift or hospitality which may affect or be seen to affect their judgement. Nor should they offer such inducements to colleagues.

4.21 The ABPI established the Prescription Medicines Code of Practice Authority (PMCPA) in 1993 to operate its code of practice on promoting medicines to health care staff of prescription only medicines. Where NHS staff (or anyone else) believe that the code of practice has not been adhered to they can make a formal complaint to the PMCPA.

4.22 NHS employers are required to put in place monitoring arrangements to ensure that staff register any sponsorship and are held accountable for it. This may be through scrutiny by an appropriate committee, eg local audit or ethics committees, as part of their normal activity, as well as through publication in the Annual Report, where this is practicable. An official register of interests should be established as part of the monitoring arrangements. These measures help ensure that patients receive quality healthcare based on good clinical practice and not unduly influenced by promotion from the industry.

5. Provision of Professional and Patient Education

Professional Education

5.1 Doctors are taught how to prescribe as part of their training, and are kept informed of developments in medicines through a number of routes outlined below. In recent years the Government has extending prescribing to non-medical professions. Over 25,500 nurses are trained to prescribe from the Nurse Prescribers Formulary. In 2002 the Government introduced the Nurse Prescribers Extended Formulary to enable more nurses to prescribe from a wider range of medicines for a broader range of medical conditions, and over 2,300 nurses have qualified to do this. The Government is now in discussion with the pharmacy profession to develop a framework for independent prescribing by pharmacists. In addition, some nurses and pharmacists are already supplementary prescribers and the Department of Health is currently carrying out a public consultation, which proposes to extend this to some allied health professionals.

National Prescribing Centre

5.2 The National Prescribing Centre (NPC) was established in 1996 to promote high quality, cost-effective prescribing and medicines management, in the wider context of evidence-based practice, through a co-ordinated and targeted programme of activities supporting relevant NHS professionals and senior management.

5.3 The NPC’s main areas of work are to provide information on medicines and their use, to provide education and training, and to disseminate good practice. Examples of NPC’s work include the dissemination of information and good practice through various NPC publications such as MeReC Bulletins and Briefings; Connect newsletters; Information Resource documents; New Drugs in Clinical Development as well as through various publications, such as “Medicines and the NHS: a guide for Directors”. In addition, the NPC delivers a co-ordinated programme of events aimed at supporting
prescribing advisers and other senior Strategic Health Authority professionals and managers; PCT leads, managers and advisers; GPs and other relevant professionals across the NHS. This is achieved through targeted therapeutic workshops, day seminars and national conferences.

5.4 The NPC is funded by the Department of Health and the National Institute for Clinical Excellence, with a combined budget of just over £1.5 million per year.

NICE

5.5 The publication of health technology appraisals by NICE inform both prescribers and patients of the clinical and cost effectiveness of new medicines. Appraisals are published on the NICE website. Ministers have recently outlined a broad programme of action to support the NHS in implementing NICE guidance, including greater awareness at the local level.

British National Formulary (BNF)

5.6 The British National Formulary is an independent publication produced by the British Medical Association together with the Royal Pharmaceutical Society of GB, which gives information on medicines that are available for prescription on the NHS. The Department of Health has a three-year contract to purchase up to 175,000 copies of the BNF twice yearly. DH distributes copies free of charge to all doctors, pharmacists and Extended Formulary Nurse Prescribers in England, at a cost of around £2.9 million per year.

The Drug and Therapeutics Bulletin (DTB)

5.7 The Drug and Therapeutics, Bulletin (DTB) is an independent eight-page bulletin, published monthly by the Consumers Association. It provides critical impartial reviews of treatments. DH purchases published bulletins at a cost of around £1.4 million per year for all doctors in England. From May 2004, DTB is also available electronically to NHS staff through the National Electronic Library for Health.

5.8 Both the BNF and the DTB are highly regarded reference publications that form an important part of the Department’s drive to encourage clinical and cost effective prescribing in the NHS.

Industry Sponsored Activities

5.9 The legislation on advertising covers the activities of pharmaceutical companies in offering sponsorship and hospitality at meetings for scientific purposes and at promotional meetings providing information about their products. As set out in section 4, this is controlled by self-regulation by industry bodies supported by the statutory role of the MHRA. The law requires that hospitality at meetings must be reasonable and secondary to the main purpose of the meeting.

5.10 Industry sponsored meetings provide a useful addition to the other sources of medicines information and education available to healthcare professionals, provided the law is complied with. Companies also have an important role to play in the education of pharmacists and their staff when medicines first become available over the counter. For innovative switches, this information is considered by the CSM as part of the switch application and is routinely reviewed by the MHRA prior to issue to ensure that appropriate messages are conveyed.

Patient Education and Information

5.11 Clear and relevant information is vital if patients are to use medicines safely and effectively. Patients increasingly want to play a bigger part in making decisions about their care and treatment and expect clear information to make an informed decision. The provision of information about medicines is a key lever for increasing appropriate access to, uptake of and appropriate use of medicines by all sections of the community. It is also a vital enabler for people to make informed choices about prescribed medicines with their health professional, which will in turn improve patient satisfaction and health outcomes.

5.12 European Law (Title V of Council Directive 2001/83/EC on the labelling of medicinal products for human use and on package leaflets) sets out the requirements for detailed information, which must accompany medicines to ensure a high degree of consumer protection and safe use of medicines. This information includes warnings, precautions, adverse events and instructions for use, written in understandable terms for the patients. All medicines placed on the UK market are now accompanied by statutory labelling and patient information approved by the MHRA in line with the legal requirements.
Patient Information Leaflets

5.13 Marketing authorisation holders are required by law to submit Patient Information Leaflets (PILs) for approval to the MHRA. In addition to the statutory requirements, the UK led the development of guidance at a European level covering amongst other things readability of the information provided. This includes a model leaflet and guidance on user testing.

Improvements to PILs

5.14 In order to improve patient information research suggests that more information is necessary in the following areas:

- What the medicine is and how it works—this would include information on the disease being treated and the mode of action of the drug;
- Do's and don’ts—making those parts of the patient information that deal with dosage, precautions, contraindications and warnings more user friendly;
- How to take the medicine properly; and
- Risk communication.

5.15 To address these needs, the Committee on Safety of Medicines set up a Working Group on Patient Information which met for the first time in November 2003. This includes members from professional, lay, patient and academic backgrounds and ABPI and PAGB nominees. The aim of the Group is to improve the quality of information provided with medicines in order to meet the needs of patients. The Group will produce an initial report to CSM by the end of 2004. The Group is currently developing guidance on risk communication in the PIL, including headline information to get across key messages, inclusion of information on the benefits of taking the medicine and how to present side effect data and statistical information. The report of the Group will be published later in 2004.

5.16 The outcome of the European review of medicine legislation includes proposals to change the order of information in the PIL, and to move the technical information on manufacturer and composition to the end. The legislative review importantly introduces a requirement for user testing which should help to ensure improvements to the PIL to make them more understandable for patients. Guidance on user testing is being developed by the MHRA, supported by advice from the Working Group. The Group is also advising on possible revisions to the European Guideline on Readability. The legislative changes are due for implementation through national legislation by October 2005.

Labelling Best Practice Guide

5.17 Based on the advice of a Working Group of the Committee on Safety of Medicines on the labelling and packaging of medicines, including health care professional, industry and patent representation, the MHRA published a good practice guide to labelling in March 2003. The guidance sets out what factors should be considered when designing medicines labelling, include layout, size of text and colours used, in particular to minimise the risk of medication error. Although the law requires 15 different pieces of information to appear on a label, users need rapid access to only five key pieces of critical information (name of the medicine, strength, route of administration, dose and warnings). The guidance advises that this information should be co-located on the pack for ease of access. The guidance was published in March 2003.

Disease awareness

5.18 Disease awareness campaigns aim to raise patient awareness of diseases and conditions and the treatment options that may be available. These campaigns are permissible as long as they comply with the legal framework on advertising, which prohibits the promotion of prescription only medicines to the public. In April 2003 the MHRA published guidance on disease awareness campaigns, which had been developed jointly with the ABPI.

Ask About Medicines Week

5.19 The Task Force on Medicines Partnership (set up to improve patient understanding of medicines and better compliance in taking medicines as prescribed) led the work on Ask About Medicines Week (AAMW), which ran in October 2003 and will be repeated in 2004. This is an example of partnership working between the Department of Health, patient groups, industry, and the NHS and health professionals, in the interests of patients.

5.20 As part of AAMW, the medicines information project brought together NHS Direct, the MHRA, industry, and other partners under the umbrella of Medicines Partnership and AAMW, to produce a new form of information for the public, in the context of the medical condition and the main treatment options.
In the first instance, this was in two pilot areas—epilepsy, and colds and flu. The information was provided through NHS Direct Online, linked to medicine guides for individual products available through the Electronic Medicines Compendium.

5.21 Medicine guides are based on the approved Summary of Product Characteristics for the product and may not be promotional. They provide the public with an additional source of information about the safe and effective use of medicines in an accessible format and clear language. Companies are being encouraged to revise their patient information leaflets so as to be similarly comprehensible.

5.22 This work builds on a number of other initiatives designed to increase the knowledge and understanding of patients about their healthcare to allow them to participate fully in decision making about the management of their condition. These include the wider work of the Medicines Partnership, the Expert Patient initiative for those with long term conditions and NHS Direct Online.

6. REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY

The Medicines and Healthcare products Regulatory Agency (MHRA)

About the MHRA

6.1 The regulation of the safety, quality and efficacy of medicines is one of the primary responsibilities of the Medicine and Healthcare products Regulatory Agency (MHRA), the other being the regulation of medical devices. It is the successor body to the Medicines Control Agency (MCA), and came into being on 1 April 2003 when the Secretary of State for Health merged the MCA and the Medical Devices Agency. It operates under a legislative framework consisting of UK and EU legislation and is the executive arm of the Licensing Authority (Government Health and Agriculture Ministers). The Agency is the primary source of expertise within Government on regulation of medicines, healthcare products and medical equipment.

Organisation and Funding

6.2 The operations of the MHRA are funded through a Government Trading Fund. The MHRA’s Trading Fund income consists of a combination of fees and charges under a service level agreement with the Department of Health. The operation of the medicines regulatory system is funded entirely by fees derived from services to industry. Many other EU and third country regulatory agencies receive all or some of their funding from industry. The funding and costs of regulation of medicines and of medical devices will be kept separate, and this will be transparent in the MHRA’s accounts. The normal rules of propriety which apply to all civil servants also apply to MHRA officials and its policy requires staff to declare interests that they believe may affect their impartiality. The current system for managing potential conflicts of interest is under review as part of the MHRA’s implementation of new European pharmaceutical legislation.

6.3 The MHRA has put in place new governance arrangements. A new post of chairman has been created. This role includes chairing the MHRA’s Board, which for the first time includes non-executive members, and overseeing the strategic management of the MHRA. The appointment of non-executive directors introduces an external perspective to the MHRA’s work. In addition, the Chair will represent the organisation and its decisions in public.

6.4 The medicines operation of the MHRA has three main operating divisions, which concentrate on pre-licensing, post licensing and inspection and enforcement issues, and has a budget of some £50 million.

Advisory Bodies

6.5 At present, the MHRA provides the secretariat for and is assisted by a number of independent advisory committees, which are established under the Medicines Act 1968. These include:

— The Medicines Commission (MC) is established under section 2 of the Medicines Act. Its functions include providing advice to the UK Licensing Authority (Government Health and Agriculture Ministers) on policy issues relating to drug regulation. It also acts as an appellate body: for appeals for human and veterinary use marketing authorisation applications which have been refused by the licensing authority on advice from the Committee on the Safety of Medicines (CSM) or the Veterinary Products Committee (VPC); and on proposals to revoke or suspend a national marketing authorisation or to refuse certain applications to vary a marketing authorisation. The Commission also makes recommendations to the UK Licensing Authority on the number and role of committees to be set up under Section 4 of the Act and on suitable members. The Act requires that the Commission’s members should include at least one person with experience and capacity in each of the following: practice of medicine; practice of veterinary medicine; practice of pharmacy; chemistry other than pharmaceutical chemistry; and the pharmaceutical industry. The MC has some 24 members (the Act requires it to have a minimum of 8) and meets four to five times per year. Members are appointed for four-year terms.
The Committee on the Safety of Medicines (CSM) is one of four committees established under Section 4 of the Medicines Act. It advises the Ministers and the UK Licensing Authority on the quality, efficacy and safety of medicines in order to ensure that appropriate public health standards are met and maintained. It also promotes the collection and investigation of information relating to adverse reactions, and considers applications for marketing authorisations.

Conflicts of Interests—Committee Members

6.6 Members of the Medicines Act Advisory committees are required to follow a Code of Practice relating to declarations of interests in the pharmaceutical industry. Chairmen of advisory bodies are required to relinquish any interests they may have in the pharmaceutical industry before they take up post. Both the Code and the details of members’ interests are published annually in the Advisory Bodies’ Reports and are available on the MHRA’s website. The purpose of the Code is to ensure that conflicts of interest are avoided. The Code of Practice followed by these committees is robust and is fully enforced at each meeting to ensure the integrity of the advice given to Ministers by those committees.

6.7 The current arrangements for advisory bodies have remained essentially unchanged since their introduction under the Medicines Act of 1968. However, over time there have been significant changes to the environment in which the MHRA operates—notably a large increase in the influence of European legislation has progressively superseded many of the provisions of the Medicines Act. The introduction of the EMEA and the centralised system has also changed the operations of the advisory committees.

6.8 In light of these developments, the MHRA decided to review the advisory bodies’ structure, and consulted publicly on proposals for a change in the current arrangements in February 2004. The proposals centre on the establishment of an overarching Commission on the Safety of Medicines and a number of Therapeutic Advisory Groups, which would advise the Commission on specific products. The consultation document also considered new rules governing the interest held by experts, proposing in particular that the Chairman and members of the Commission, and the Chairmen of the TAGs should not have any personal financial interests in the pharmaceutical industry. The consultation ended on 17 May 2004, and full consideration is being given to the responses received.

Pre-Licensing Systems

Product assessment

6.9 All medicinal products have to be licensed before they can be marketed in the UK unless they meet one of a small number of exemptions. This covers a very wide range of medicine types ranging from those available over-the-counter in pharmacies and on general sale to the latest prescription-only new drugs. It also involves medicines based on chemical, homoeopathic, herbal and biological sources as well as the developing and future technologies such as gene therapy, biotechnology and nanotechnology.

6.10 The regulatory principles applied are common to all types of medicines and are based on evaluation of their quality, safety and efficacy. The evaluation of these three properties is not undertaken in isolation since they are closely linked. For example, product quality is assessed not just in absolute terms but taking into account its effect on safety and efficacy and considering the manufacturing standards in place. The assessment of safety and efficacy must include an evaluation of the risk:benefit balance since the acceptability of unintended side-effects will be different for life-saving drugs than for those used to treat minor ailments.

6.11 The Licensing Division of MHRA is responsible for carrying out these assessments for all new products to be marketed. Multidisciplinary teams of assessors’ work on the product licence applications and can consult external experts on a formal or informal basis when needed. All new drug products are assessed and then submitted formally to the Committee on Safety of Medicines (CSM), the statutory committee responsible for advising Ministers on regulatory issues, for advice.

Procedures for product assessment

6.12 The legal basis for controlling marketing authorisations derives from European legislation which sets the data standards, the procedures to be followed and the framework for establishing scientific guidelines. These help maintain high standards for product approval and the continuity of the single market in pharmaceuticals.

6.13 The European legislation has established two main procedures for licensing approval in the Community, National authorisations can be obtained from a Member State’s competent authority and other Member States can then offer these for recognition. The high quality of UK authorisations and co-operative working practices has encouraged many pharmaceutical companies (including some non-UK based companies) to choose the UK as the reference Member State for these procedures. When the UK is offered other Member State authorisations for recognition we have chosen, as a matter of prudent policy, to subject them to a high level of scrutiny.
6.14 The alternative Centralised procedure is administered by the European Medicines Agency (a decentralised body of the European Union based in London) and grants a single authorisation for the whole Community although the scientific assessment is carried out by one or more “rapporteurs” from National authorities and is reviewed by a Committee of similar experts from all the Member States. The scope of this Centralised procedure (currently confined to particularly innovative drugs) is set to grow but the MHRA plans to play a full part in the assessment and approval process and continue to be the “rapporteur of choice”.

Quality assurance

6.15 In view of the significance of its decisions for public health, the work of the Licensing Division is subject to a number of quality assurance systems as well as internal and external audit. These include:

— ensuring the high level of professional competence of its expert staff through recruitment, training and appraisal;
— investigations of disparities between assessor recommendations and consultative committee advice;
— senior assessor and management review of assessment reports and communications with applicant companies;
— business process audits; and
— re-assessment through European mutual recognition procedures.

Public health protection and industry regulation

6.16 In addition to its aim of protecting and improving public health through the regulatory control of medicines, the MHRA also has an obligation to work with the pharmaceutical industry so that it can continue to develop and market high quality products for the benefit of patients.

6.17 One of MHRA’s roles is the provision of scientific and regulatory advice to companies during the development of new products and before they submit the application for licensing. This service has been provided for many years but has recently become more formalised with the provision of detailed written advice following face-to-face meetings. This was introduced in response to feedback from industry that they would be prepared to pay some of our costs in providing high-quality advice, which could help ensure they submit approvable applications.

6.18 The UK pharmaceutical industry includes not just the R&D-based companies but also a large and successful generic products industry, small parallel import companies, herbal product, traditional and homeopathic remedy companies and those whose primary business is over-the-counter proprietary medicines. All of these have significant contributions to make for public health in this country and abroad. The MHRA role is to minimise the regulatory burden on such a diverse industry sector whilst protecting the health of patients and helping ensure wider availability of affordable medicines in the UK.

6.19 It is important to note that significant quantities of branded prescription medicines are “parallel-imported” into the UK from other Member States with lower prices. The Parallel Imports Unit in the MHRA operates the parallel import licensing system that assures the quality of such products before they are approved for use in the UK.

Post Licensing Systems

Pharmacovigilance

6.20 Pharmacovigilance is the process of identifying and responding to drug safety issues arising with marketed medicines. The objectives of pharmacovigilance are:

— the long-term monitoring of medicines to identify previously unrecognised safety hazards;
— the assessment of the risks and benefits of medicines to determine what action, if any, is necessary; and
— the provision of information to health professionals and patients to optimise the safe and the effective use of medicines and monitoring the impact of any action taken.

6.21 The Post-Licensing Division of the MHRA is responsible for monitoring the safety of all medicines marketed in the UK. As laid down in European Community legislation, the regulatory authorities of the European Member States exchange information and work closely together on drug safety matters.
Why is pharmacovigilance necessary?

6.22 All effective medicines have the potential to cause side effects. Most of these side effects are not serious and are predictable from the known actions of the drug. Other side effects are rare and may only occur in a small proportion of the people taking the drug. These side effects may be severe and sometimes fatal. Therefore it is vital that the safety of all medicines is monitored in routine clinical practice throughout their marketed life. The most effective way to do this is to collect reports of suspected side effects or adverse drug reaction (ADR) reports via a spontaneous reporting scheme.

Sources of data and methods

6.23 Data from the UK spontaneous reporting scheme, the Yellow Card Scheme, underpins the process of pharmacovigilance in the UK. The value of spontaneous reporting schemes is in the early detection of possible drug safety hazards (the generation of hypotheses). Once a hypothesis has been generated, other methods are used to confirm and quantify the risk. The other data sources regularly used in the monitoring of drug safety in the UK include:

— formal safety studies,
— the published medical literature,
— information from pharmaceutical companies and other Regulatory Authorities throughout the world, and
— information on the level of drug prescribing.

6.24 There is also an international database of around 1.5 million ADR reports operated by the World Health Organisation to which the MHRA has on-line access.

6.25 Many possible signals of new drug safety hazards of varying importance are routinely identified from any of the sources described above. These signals are then evaluated and prioritised according to their potential public health implications. When major issues are identified a full risk assessment is conducted covering all the relevant information from a number of sources and the impact of the new risk on the overall risk-benefit profile of the drug is considered. Independent expert advice is sought from the CSM and its Sub-Committee on Pharmacovigilance (SCOP), and if necessary an expert working group can be convened.

6.26 Such findings may lead to changes in the Marketing Authorisation, which are explained more fully in the section on actions to minimise risk. Most action is taken voluntarily by pharmaceutical companies, but there are also powers to vary, revoke or suspend marketing authorisations. The MHRA works closely with other EC regulatory authorities on pharmacovigilance matters.

Action to minimise risks

6.27 There are a number of possible actions when a new safety issue is confirmed, in order to prevent or minimise the level of risk to patients. Very rarely, if the risks of a medicine are found to outweigh the benefits, it may be necessary to remove the medicine from the market. More usually, the risk of a side effect may be avoided or reduced in the following ways:

— by including warnings in the product information (Summary of Product Characteristics and Patient Information Leaflet) or on the package label;
— by restricting the indications for use of a medicine; and
— by changing the legal status of a medicine, eg from Pharmacy to Prescription Only to increase the level of professional supervision.

6.28 Communication of information on the nature of the risk to health professionals and patients helps them to make informed choices about treatment options and also helps in the management of ADRs should these occur. It may be necessary to inform doctors and pharmacists by letter or fax cascade if the issue is urgent or via the regular drug safety bulletin *Current Problems in Pharmacovigilance* which is produced by the MHRA/CSM.

Monitoring outcomes

6.29 The MHRA currently monitors the outcome of regulatory action by tracking changing in prescribing habits using prescription databases and tracking the reporting of suspected adverse drug reactions using information from the Yellow Card Scheme. One of the priorities of the future pharmacovigilance strategy is the development of methods to allow direct measurement of the impact on public health of the regulatory actions taken.
The Yellow Card scheme

6.30 The Yellow Card Scheme was set up in 1964 following the Thalidomide tragedy to provide a system for early detection of emerging drug safety hazards and the routine monitoring of all medicines in clinical use. Suspected adverse reactions to marketed medicinal products are reported to the CSM and MHRA, which are jointly responsible for running the Yellow Card Scheme. Reports are primarily submitted voluntarily by GPs, hospital doctors, dentists, coroners, pharmacists and nurses. Reports are also received via the pharmaceutical industry, which has a statutory obligation to report suspected serious adverse drug reactions (ADRs).

6.31 The value of spontaneous reporting schemes, such as the Yellow Card Scheme, in early detection of drug safety issues is universally recognised. It has a proven track record of identifying new drug safety hazards and is recognised to be one of the best in the world in terms of the level of reporting. Underreporting of ADRs is an inherent feature of spontaneous reporting schemes. Although this means that data from the Scheme have limited usefulness in terms of quantifying the frequency of an ADR, it does not detract from the ability of the scheme to identify new drug safety hazards. In a bid to increase reporting, the Agency has taken a proactive approach and has made it easier than ever before to report through the Yellow Card Scheme and in October last year launched its electronic Yellow Card, allowing health professionals to report online through the MHRA’s website. It also opened the Scheme to include all nurses as reporters. The MHRA is now also considering pilots of arrangements for patient reporting of ADRs.

Inspection and enforcement

6.32 The surveillance of the manufacture and distribution of products on the market, and the enforcement of relevant UK and EU legislation is becoming an increasingly important aspect of the work of the Agency.

6.33 Inspection work carried out by the MHRA includes:

— Inspection of Good Manufacturing Practice (GMP), that part of quality assurance which ensures that medicinal products are consistently produced and controlled to the required quality standards. GMP Inspectors conduct inspections of pharmaceutical manufacturers, importers and distributors to assess compliance with EU Principles and Guidelines on GMP and with the relevant details contained in marketing authorisations. Overseas sites named as manufacturing sites for products marketed with the UK are also inspected.

— Good Distribution Practice Inspectors, who conduct inspections of sites used for storage and wholesale distribution of medicinal products. Sites vary in size from small wholesalers who may operate from a single room, to very large industrial warehouses.

— Following implementation of the Clinical Trials Directive, mandatory inspections of Good Clinical Practice in the conduct of clinical research are being conducted in the UK.

— The MHRA has begun to carry out inspections to ensure that systems for reporting ADRs and complying with other pharmacovigilance requirements are operated effectively by marketing authorisation holders. Companies range from large multinationals holding many marketing authorisations to small local companies that may only hold one marketing authorisation. The scope of the programme will include approximately 300 to 400 companies.

Medicines Testing Scheme

6.34 The Medicines Testing Scheme (MTS) supports the Agency’s commitment to safeguarding public health by sampling and testing selected medicinal products on or destined for the UK market. Samples are tested to ensure compliance with accepted quality standards.

Defective Drug Alert System

6.35 Should a quality defect be discovered with a product there is a mechanism for communicating urgent recall and/or safety information about medicinal products to health professionals in the public and private sectors. It supports the statutory duties of licence holders to maintain effective systems and records to enable recall of defective medicinal products from throughout the distribution chain. A Drug Alert is issued where distribution of a defective medicinal product is likely to be widespread and/or if there is a significant risk to patient health.
Enforcement activities

6.36 The MHRA (Medicines) Enforcement Group has responsibility for enforcing medicines legislation in England and does so in Scotland and Wales on behalf of the Scottish Parliament and Welsh Assembly. The Group investigates cases and, where appropriate, brings criminal prosecutions.

6.37 Officers have their own powers conferred by the Medicines Act 1968 and subordinate legislation applying to the Act. These include the right to enter any premises to inspect, to take samples and to require production of any books or documents in the pursuance of their work. Officers are bound by the Police and Criminal Evidence Act (PACE) and PACE codes of practice. It is a criminal offence to obstruct an enforcement officer.

6.38 Enforcement work is supported by an Intelligence Unit and there are extensive contacts with regulatory and law enforcement bodies in the UK, within the EU and worldwide.

7. Product Evaluation, Including Assessments of Value for Money

7.1 Once a medicine has been through the process of obtaining a licence (referred to as a Marketing Authorisation), it is automatically available for use in the NHS. Unlike many other countries, there is no further process for approving a medicine for NHS use. The only exception to this is Schedules 1 and 2 of the NHS (General Medical Services Contracts) (Prescription of Drugs etc) Regulations 2004. Schedule 1 lists the products that may not be prescribed by GPs under the new contract. This may be because the product has no proven therapeutic value. Schedule 2 lists the products that may be prescribed only in specified circumstances. This lists a very small range of products that are subject to modified restrictions.

7.2 Within this framework, however, the Government has put in place processes that can help ensure that the NHS secures the maximum clinical and cost effectiveness from the medicines used as part of the treatment offered to patients.

National Institute for Clinical Excellence

7.3 The National Institute for Clinical Excellence was established in 1999 as an independent organisation whose role is to provide advice to the NHS in England and Wales on the clinical and cost effectiveness of drugs and other treatments. It publishes guidance in the form of health technology appraisals and clinical guidelines. NICE also publishes advice on the safety and efficacy of new interventional procedures.

Selection of topics for NICE

7.4 The pharmaceutical industry, as a stakeholder in the development of clinical and cost effective guidance for the NHS, has a legitimate role to play in the selection of topics for NICE to appraise. The industry:

— (a) provides information to the National Horizon Scanning Centre on the development of new pharmaceutical products and their licensing position; and
— (b) is represented on the Advisory Committee for Topic Selection (ACTS). The role of ACTS is to assess proposals for work topics for NICE against published criteria. ACTS is a large committee. In addition to the pharmaceutical industry (which has one seat) membership is drawn from the Department of Health, Welsh Assembly Government, NICE, professional and patient groups.

7.5 Proposals from ACTS are then considered by a smaller group (the Joint Planning Group). This group provides advice on the relative strategic importance for the Health Departments and the NHS on the proposed work programme for NICE. Advice from JPG (whose membership includes NHS, Department of Health, Welsh Assembly Government and NICE but not the pharmaceutical industry) is considered in turn by Ministers.

7.6 Before Ministers take final decisions on the NICE work programme, officials formally consult stakeholders about the proposed remits. This includes manufacturers of the products concerned.

7.7 The results of the consultation exercise are put to Ministers who then make final decisions on the work programme that is to be referred to NICE.

How does NICE engage with industry?

7.8 NICE engages with industry in two main ways:

— (a) in the development of its processes for assessing the technology appraisals and clinical guidelines referred to NICE as its work programme; and
— (b) as part of the development of its guidance.
7.9 NICE’s processes are consulted on publicly and the pharmaceutical industry (along with the DH and others) is a stakeholder in that consultation. The consultation gives stakeholders the opportunity of commenting on how NICE should go about developing a piece of guidance and separately how NICE should interpret the evidence on which it reaches a judgement. As a stakeholder comments from the industry have the same status as any other stakeholder (including the DH and Welsh Assembly Government).

7.10 In the development of NICE guidance comments are invited from stakeholders at various stages. Stakeholders can influence the guidance through reasoned argument. Comments are submitted for consideration by the appropriate technology appraisal or clinical guideline committee. The pharmaceutical industry has the same status as other stakeholders.

The pharmaceutical industry and the implementation of NICE guidance

7.11 When NICE publishes positive guidance, NICE and the manufacturer can work together to jointly promote the appropriate application of the guidance in clinical practice consistent with the recommendations within the guidance. The boundaries are therefore set by the published guidance.

7.12 The pharmaceutical industry also has a legitimate role in making data available from manufacturers on their products. Such data would provide evidence of uptake and how the product is being used.

Wider policies on value for money in medicines use

7.13 The structures outlined in Section 5, for informing and educating professionals on the use of medicines, contribute to the objective of ensuring that medicines are used to deliver the best clinical and cost effectiveness. The NHS also uses Area Prescribing Committees and prescribing advisers to help ensure that prescribing and use of medicines is clinically and cost effective.

7.14 Local health economies run Area Prescribing Committees or similar committees whose function is to address prescribing and medicines use across the primary-secondary care boundary. The composition of these committees is usually multi-disciplinary and has input from PCTs and local NHS Trusts. They aim to encourage rational prescribing across the local health economy through formulary development and joint approaches to medicines management.

7.15 Prescribing advisers, mainly pharmacists, are employed at various levels in the NHS (in Strategic Health Authorities and PCTs). Their common aim is to encourage and secure rational and cost-effective prescribing. There are now more than 1,200 advisers.

7.16 Government policy on generic prescribing also supports improved cost effectiveness. When issuing a prescription the prescriber should enter the generic name of the medicine rather than a brand name. Prescribing generically allows pharmacists to dispense generically-produced version of the medicine if one is available, which saves the NHS money while providing patients with medicines that are identical to the branded ones. In 2003, 77.8% of prescriptions were written generically.

July 2004

Witnesses: Dr Felicity Harvey, Head of Medicines, Pharmacy and Industry Group, Dr Jim Smith, Chief Pharmaceutical Officer, Professor Sally Davies, Director of Research and Development, Department of Health, Professor Kent Woods, Chief Executive, Medicines and Healthcare products Regulatory Agency, and Dr Monica Darnbrough, Director, Bioscience Unit, Department of Trade and Industry, examined.

Dr Naysmith: Good morning, everyone. It looks as if we have picked on a topic that is of some interest to the general population. I am Doug Naysmith, MP for Bristol North West, and the first thing I have to do is apologise for David Hinchliffe not being here; he has a family commitment that he wanted to attend. He sends his apologies to the Committee and to the people who are giving evidence. Can I ask if any members of the Committee have anything to declare in terms of interests?

Dr Taylor: I would like it put on the record that I was a shareholder in a major pharmaceutical company until yesterday. I sold the shares yesterday.

Q1 Dr Naysmith: That was a very wise thing to do, Richard! In welcoming our witnesses here today, can I thank you very much for coming and for the submission, which presumably all five of you contributed to. I will ask you in a minute to say a word about your role in the Department and the Agency. When you are asked questions, it is not necessary for all five to answer every question. Sometimes that happens, and it can take a long time to go through, but if anyone feels there is a piece of information that they must get in or that the answer to the question is going in the wrong direction, then please indicate; but I will not always call everyone to have a go at every question. Starting on the left, Dr Smith, would you say a word or two?

Dr Smith: I am Dr Jim Smith; I am Chief Pharmaceutical Officer in the Department of Health, and I am responsible for professional pharmacy policy.

Professor Woods: I am Kent Woods, Chief Executive of the Medicines and Healthcare products Regulatory Agency.
**Dr Harvey:** I am Felicity Harvey, and I am the Head of Medicines, Pharmacy and Industry Group within the Department of Health; and within the Department of Health we have the lead co-ordinatory role for sponsorship of the pharmaceutical industry, but also I cover most medicines issues within the Department of Health.

**Professor Davies:** Sally Davies: I am the new Director of R&D for the Department of Health.

**Dr Darnbrough:** I am Dr Monica Darnbrough, Head of the Bioscience Unit in the Department of Trade and Industry.

**Q2 Dr Naysmith:** We will be exploring all these different roles over the next hour or two. Dr Harvey, we have received a large body of evidence from various sources with argue that the pharmaceutical industry wields extensive influence on healthcare policy and systems in this country. Your submission does not really acknowledge this; it is very much a factual statement of what you do and your responsibilities. Do you have any opinions about the influence that the pharmaceutical industry has on healthcare in this country?

**Dr Harvey:** Chairman, might I explain a little about the relationship that government has with the pharmaceutical industry and some of the main areas that this covers? The pharmaceutical industry is a major stakeholder for government in general. We have a multi-faceted relationship, and quite a complex relationship, in terms of the different areas this relates to. Firstly, and one of the important reasons why this relationship has a co-ordinatory focus within the Department of Health, is that the NHS is a major customer of the pharmaceutical industry. Innovative medicines and indeed generic medicines are very important in terms of healthcare, quality of care, and are very much one of the major planks underpinning the national service frameworks, and indeed NICE guidance that goes to the NHS, in terms of the drugs that will have most impact on patient care and patient benefit. Similarly, we have a regulatory relationship with the pharmaceutical industry, which is led by the Medicines and Healthcare products Regulatory Authority. As you know, the MHRA is held in quite high esteem within the European Union in terms of the quality of the work that it does. Thirdly, we have a major relationship with the pharmaceutical industry as a major R&D and innovation industry within the UK. The pharmaceutical industry invests about £3.5 billion per year in R&D in the UK, which is incredibly important for the NHS, particularly in terms of having innovation that we can bring to patients. That R&D is about a quarter of the R&D for the manufacturing within the UK. Lastly, but certainly not least, it is a major industry within the UK and even though it is a global pharmaceutical industry, and we have exports from the UK of about £11.8 billion per year, with a £3.1 billion trade surplus. Therefore, in terms of the relationship that we have with the pharmaceutical industry as a major stakeholder, it is an important industry for the UK. However, if you think of public health and health relationships generally, the relationship the Government has with the industry is pretty well on an equal basis with the very key relationship we have in Health with patients and patient groups, and indeed with NHS professionals and managers.

**Q3 Dr Naysmith:** We will be exploring a number of things you have touched on later, obviously. The purport of my question really was that the National Health Service is a customer of the pharmaceutical industry and lots of people know, because it is a fact, that the pharmaceutical industry has quite a strong influence on formulating the policy of the customer that it is selling drugs to. I just wonder whether the Department of Health is the right place for the promotion of the industrial health of the pharmaceutical industry, which is what that results in. Is that the right place for it to be? We will be asking more detailed questions later on as well, but I am asking in a general way.

**Dr Harvey:** In terms of the focus within the Department of Health, it’s role is one of co-ordination across many government departments, as you are aware, it lies within the Department of Health, because of the importance of pharmaceuticals, in terms of increasing quality of care and patient outcome, for example there has been quite a switch between secondary and tertiary care in recent times, with healthcare now moving to a more primary care focus. It is important that within the Department of Health we understand more of the issues around health, the importance of innovation and research and development, and obviously the wider UK plc issues.

**Dr Darnbrough:** Felicity has outlined the relationship that the Department of Health has with the industry, and perhaps at this early stage of our discussion I could outline a little bit of the background to why the Department of Trade and Industry also has a relationship with the pharmaceutical industry. As many of you will know, when Mrs Hewitt became Secretary of State for Trade and Industry, she had a review of the Department, and at that stage set up a business relations function, outward-looking towards all important economic sectors of industry in the UK. One of those sector units is mine, which looks at biotechnology for all application areas—industrial, agricultural medical, and so on—as well as working with the Department of Health in keeping in touch with the pharmaceutical industry. The business relations side of the Department was encouraged to understand more about the issues facing companies in terms of productivity and competitiveness, which is what our Department is really all about. Therefore, we have quite formalised relationships with some of the pharmaceutical companies in order to understand the issues that are of concern to them. However, when we are having these formal meetings and visiting companies, we very often do that jointly with people from Felicity’s team, and indeed from other parts of the Department of Trade and Industry, and so on.
Q4 Mr Jones: Every year the pharmaceutical industry produces a number of innovative drugs, a proportion of which will have major new therapeutic effects. We have seen evidence that seems to suggest that the proportion of new drugs that have major therapeutic effects is declining. Do you collate any information which looks at innovative drugs being brought in and whether they are truly therapeutically effective, or whether they bring nothing new into the drugs market at all?

Dr Harvey: Perhaps I might start, but it is also relevant to Professor Davies from the R&D perspective. In terms of innovative medicines being brought to the market, as the Committee is aware, we set up the National Institute of Clinical Excellence in 1999. The importance of NICE is that it looks through its appraisal mechanisms at the clinical and cost-effectiveness of all new innovations, be they pharmaceuticals or devices. In terms of the outputs of NICE, which are in most cases underpinned by a three-month funding direction, they will give advice to the NHS on how beneficial a particular drug is and in which clinical indications, very importantly, it is effective—whether it is right throughout its licensed indications, or whether it is just for a few of those licensed indications. If you look at about 79 of the last appraisals that NICE has done, only in 24 has it said this should be used because it is clinically and cost-effective for all of the specified indications under licence. In the majority, it is for just part.

Q5 Mr Jones: I understand the role of NICE in deciding whether or not a drug is clinically effective, but my question was that you may have a new drug on the market that is clinically effective, but it is no more clinically effective than the drugs that exist already. What work does the Department of Health do to assess that, and does it believe that it should have a role in making that sort of information public?

Dr Harvey: If I could return to NICE for a second, when NICE is looking at individual drugs, it does not necessarily look at just one. On many occasions, and looking at the work programme at the moment, there are a number of occasions when it has looked at many drugs within a class. They might be drugs that have come later to the market that have a similar effect, and it does look at the clinical and cost-effectiveness of each of those. In terms of information that is provided for prescribers around the effectiveness of drugs, whether or not something has yet found its way to NICE, we also have work that is done by the National Prescribing Centre, which provides bulletins and various types of information to clinicians about effectiveness of individual drugs. Another publication that the Department of Health provides to doctors is the Drug and Therapeutics Bulletin. That similarly looks at the clinical effectiveness of ranges of drugs in the treatment of particular conditions.

Dr Smith: As Dr Harvey has said, we have a huge range of mechanisms in place to provide information and advice about drugs within a class. They are NHS-directed services. They do not resolve the fundamental issue of whether innovation has taken place in a particular area. For that, we are looking to the fundamental drivers of the research process, but certainly in response to the issue of whether there are a lot of “me too” type drugs coming to the market, they do. We have to be careful here because “me too” drugs are sometimes valuable. There are many classes of drugs where the first example into the market place did not turn out to be the class leader. The “ulcer healing” drugs are a very good example, and there are other examples. I take the point. We have a lot of “me too” drugs and it is very important that we guide and help doctors and other professionals in choosing the most cost-effective, and we do that through a range of mechanisms.

Q6 Mr Jones: You say “doctors and other professionals”—and this is a natural tendency within professions, but the lay public is also capable of reading information. It may be useful, you might think—and the Committee might think—that the general public should be able to acquire information that is objectively assessed—and no other area could do it other than the Department of Health—about whether drugs are bringing in something new or whether the drug is a “me too” drug that does the same as any other drug.

Dr Smith: I think we agree entirely, and the Government is very committed to patient education and the provision of patient advice; and it is doing it in many ways. NICE also publish a booklet that explains each guideline. This is aimed specifically at patients and the public, and more widely than that there is a commitment, a belief, that informing patients about their medicines will make treatment safer and more effective, and will make them more likely to take a medicine properly and get better outcomes. Indeed, as you are suggesting, there is an intrinsic right of patients to be well informed and to be able to be partners in that prescribing decision. We are doing a lot around that. We have a programme called Medicines Partnership, which is promoting this. We have Ask about Medicines Week, which is going to run for the second year, encouraging the public to seek information. We are supporting a programme of tailored information for patients, which is in its infancy, but the vehicle for that will be NHS Direct Online. There will be access to an impartial source of information for the public.

Q7 Mr Jones: As a member of the public, would I be able to get information in the future about drug X which has just been introduced, when the Department of Health says that drug X is—because NICE would have to say it is—clinically effective, but it is no more effective than Y, Z and Q were; or that drug X is particularly clinically effective and does things that the other drugs would not do? Would I be able to get this information in future?

Dr Smith: I think you would.
Q8 Mr Jones: I cannot now, can I?

Dr Smith: You can for drugs that NICE looks at, because they are in the public domain. The other mechanisms that I spoke about are under development, but when they are developed they are aimed at the public, so you will be able to log on to NHS Direct and look at drugs for blood pressure or whatever, and see impartial information that will include value judgments about what is best for a particular disease.

Q9 Mr Jones: The DTI and the DoH recognise that in the role of promoting the industry and the best interests of the industry there is a potential conflict because it is in the industry’s interest that any new drug is seen in the best light possible, but if the DoH were to indicate the usefulness or new therapeutic value or otherwise of a drug, then many new drugs coming into the market would find it very difficult to be sold.

Dr Darnbrough: It is very much a question for the companies themselves what lines of research and development they choose to go down. Obviously, they go down roads where they think there is a real market for their products. However, I do not think we should under-estimate the genuine innovations that are coming out worldwide in the pharmaceutical industry and also in the UK. They are far from all being “me too”.

Q10 Mr Jones: I never suggested they were. I was trying to look at whether we could distinguish between what is a “me too” more clearly and what is not.

Dr Darnbrough: If you look at some of the important drugs that have been developed in the UK over the last 10 years or so, there are things for prostate cancer, epilepsy and schizophrenia that are quite novel, as well as the improved things for hypertension, migraine and schizophrenia and so on. Some very innovative things are coming to the market. My colleague explained the important work of NICE in assessing the cost-effectiveness of using these new things for healthcare in this country.

Professor Davies: There are a number of things that I could usefully talk to. Of our national programme of R&D we spend £115 million through that. We fund a health technology assessment programme for £18 million and in that we do work that has a priority for the NHS. For instance, there is an ongoing trial, head to head, of anti-epileptic drugs. It is not only about drugs; it is about other methods of treatment, and other interventions, clearly, as it is technology in the broadest sense.

Q11 Dr Naysmith: Do you think there has been enough?

Professor Davies: When you ask an R&D director like that, I could be a bottomless pit; but we are doing the top priorities and many more.

Q12 Dr Naysmith: The reason I ask that is that in comparison with the amount of money that the pharmaceutical industry can spend on research, that sounds like a rather small sum.

Professor Davies: We are very proud of what we do in this country, not only through the Government, but the public sector research in this country is bigger than many other countries because of the charity contribution as well, so that we can build on what pharma has done to provide the best things for our patients and our society. One of the other areas I wanted to highlight is our support through technology evaluations for NICE, but in particular the Cochrane Collaboration work that goes on in this country, funded by ourselves, to produce systematic reviews. An individual research study can be misleading on its own to clinicians, because it comes out with one result, and we need to put them all together. Through the Cochrane Collaboration the systematic reviews are done, bringing all the work together from the perspective of the clinical question. In addition to doing that, it compares drugs against drugs and looks at side effects, and also every systematic review has a patient synopsis that explains it in words satisfactory to the patient. These are all available for the whole of the international Cochrane collaboration on the Web, for everyone; so there is access to all of that. We spend over £7 million a year on the systematic reviews and evaluations of support on the Cochrane Collaboration, which is more than any other country.

Q13 Mr Jones: You will understand that in these questions I am trying to understand the potential conflicts of interest that there may be between the customers and the suppliers. Why do you think that the Department of Health is the best placed organisation, being the major customer, to coordinate the relationship between the Government and the industry?

Professor Davies: It is I think because the public health interest is very important, and indeed medicines to the NHS are very important. Through the stakeholder relationship we have with the pharmaceutical industry and very much as a result of PICTF, the Pharmaceutical Industry Competitiveness Task Force, we now have a stakeholder relationship that means the pharmaceutical industry has a much greater awareness of the clinical priority areas for the NHS, the areas that we are seeking to drive up quality of care and better patient outcomes. Through that better understanding between government, the Department of Health and the pharmaceutical industry, that has had many gains for us, in terms of the sort of innovative medicines that have been brought to market, particularly in the areas for example of the national service frameworks that are populated by NICE products like coronary heart disease, diabetes and mental health. There are many examples, and I know that Professor Woods could give some examples of where those innovative medicines have had huge impacts on outcomes for
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9 September 2004 Dr Felicity Harvey, Dr Jim Smith, Professor Sally Davies, Professor Kent Woods and Dr Monica Darnbrough

care, and indeed care pathways, for removing care from secondary and tertiary care more to a primary care base, which is also facilitated by the importance for the Department of chronic disease management at the moment.

Professor Woods: I spent 30 years, up until last year, practising in the NHS as a physician, and I have seen some very considerable therapeutic steps made during that time in areas which one has to look back and think about to realise just how far we have travelled in terms of, for instance, the management of peptic ulcer disease, which was largely a surgical condition when I qualified and is now a medical condition. There have been dramatic changes in the outcome of heart attack, for instance, due to active management with drugs. It is a change that took place in the middle to late eighties and onwards. There was a 40% reduction in the mortality of heart attack in hospital in my own unit. These are really quite dramatic changes. Nonetheless, I should like to go back to the question you posed at the very beginning about the driver to true innovation, as distinct from small incremental growth within drug classes. It is a very complex and very important question. The factors that seem to be important are these. Firstly, as a large customer, can the NHS drive and stimulate innovation by being a discriminating and demanding customer? That is something that the NHS has been doing much more critically and more actively in recent years. However, beneath that is the problem of where true innovation comes from. Where are the therapeutic opportunities to be exploited? That is something that is outside our gift. There is another element, which is the time and cost of drug development, which, as everybody has been aware, has grown slowly in recent years—10 or 12 years of developments, and hundreds of millions of pounds spent on the development of an individual drug. Therefore, the element of commercial risk is much higher for a truly innovative compound in a new therapeutic class than for an incremental development within an established class, where we know broadly what the drug is going to do. There are some very complex factors going on here.

Q14 Mr Jones: Does that not depend upon the size of the market for the drug?

Professor Woods: It does.

Q15 Mr Jones: You can have an innovative drug that does something marvellously new therapeutically, but it only does it for a small number of people.

Professor Woods: Absolutely so.

Q16 Mr Jones: Or you can have a “me too” drug which has a huge market. So that driver is there in terms of “let us get a slice of this particular cake” because it is a very big cake.

Professor Woods: Indeed, and the size of the potential market is a very considerable driver; and the ability and willingness of the market to pay for the product is obviously a very important driver. There is a greater concentration of developmental effort on areas of therapeutics that are large clinical problems, and it does create problems in some areas where, by the nature of things the market forces do not drive innovation equally in relation to need. We have specific examples of that. We have so-called orphan drugs, which are targeted towards very small groups of patients. We have issues around drugs for children, because as a market this is a relatively small part of the clinical population. Therefore it is necessary to have additional mechanisms to help encourage innovation in those areas where the market mechanism itself is not sufficient.

Q17 Dr Taylor: It is the fundamental drivers that we are desperately trying to get at. It would seem fairly obvious to the outsider that the driver, if research is left entirely to the pharmaceutical firms is one of profit. How do we square that with what the public need? What can the Government do to force the pharmaceutical industry away from profit motives? It is a wide, difficult question.

Professor Woods: It is a fundamental question. We as a country, although we are running a developed and advanced healthcare system, are a relatively small proportion of the total pharmaceutical market worldwide. We are talking about a global industry, and therefore even the influence of the NHS as a demanding customer is limited. On the other hand, there are steps that can be taken to at least help support innovation in areas that would not otherwise be commercially attractive. There is, within the European regulatory system, which we are closely integrated with, an orphan drugs mechanism, which has been running for the last four or five years, which gives certain advantages in terms of market exclusivity and waiving of regulatory fees for products that are designated as orphan products. They are treatments for patient groups which represent fewer than five in 10,000 of the European population. These in themselves are not sufficient incentives to completely redirect innovative research, but they help, in so far as we can, to shape a research and development strategy that will not be totally discouraged from addressing relatively rare problems.

Q18 Dr Taylor: We have been told that the industry has expressed irritation about this Orphan Drugs Act, which is rather hard to understand because lack of competition must drive up the prices, which is in their interests really.

Professor Woods: In the European system the orphan drugs regulation is relatively new and still to be fully evaluated. I think about 200 compounds have been designated under that system, and about 12 or 15 have been licensed through the European route. I think it is going to become more of an issue as we see the products of biotechnology working through, because many of these are targeted at quite small groups of people where we understand the genetic basis of disease and we have the potential to develop products that will correct that illness. So it is an area that is a thorny one, a difficult one. The United States has been working on this a little
longer. There was orphan drug legislation enacted in the early eighties, and that again deploys a combination of incentives and commercial concessions, in terms of product exclusivity and tax relief, to encourage development in these areas. I think you have hit on a really fundamental issue.

**Q19 Dr Taylor:** You have mentioned that we are a fairly small player in the world market as it is, and some of the evidence we have is a little bit confusing. The ABPI tell us that a quarter of the world’s 100 most used medicines originated in research and development in the UK. The Department of Health puts it slightly differently—“top-selling and leading”. Is there any significance in these different descriptions? Do they mean anything, or is it just words?

**Dr Harvey:** I do not think there is any significance in the different meaning. It is a fact that of the top 100 medicines, 25 of those have indeed been developed through the research and development within the UK, and that puts us in the UK as second only to the USA in terms of the research and development basis for development of medicines.

**Dr Naysmith:** Richard’s point is the difference between leading and top-selling. How do you define “leading”? Is it the same as the amount of money that the drug firms get in for particular drugs?

**Q20 Dr Taylor:** I had rather sensed the words were being used loosely rather than absolutely accurately. **Dr Harvey:** We describe it as top-selling, but I would have to look at exactly what has been said by the ABPI there. I do not think there is any particular difference.

**Q21 Dr Taylor:** I would echo Professor Woods’ comments about the developments. I have been around a little bit longer, and the developments have been absolutely amazing. One thing that puzzles me is, when a drug is about to run out of patent the industry can make a very small change to it or add a well-known other drug to it. That can then market it again as another patent drug. Is that well-regulated? Are there controls over that sort of thing?

**Professor Woods:** If a new drug is developed, even if a small incremental change to structure or minor chemical variation to structure is made, then it would go through the licensing process in the usual way. Of course, at the end of the patent period for the parent compound, there would be the development of generic drugs, which would introduce a very brisk element of price competition in that area. The scope for extending patent protection by very minor chemical modification is counterbalanced by the opportunity for generic manufacturers to come in with the same product, and price competition is developed.

**Dr Harvey:** As the Committee is probably aware, we have very much a policy for use of innovative medicines, where they have been developed, but when prescribed are done so generically. That has been a fundamental base in the UK and part and parcel of undergraduate training. As a result of that, we now have generic prescribing rates of about 78%. In fact, in some, their generic prescribing rates are as high as 85%. That means clearly that when a drug has come out of patent, then the drug that is dispensed is a generic of that particular medicine; and that is very important for us. We have the highest generic prescribing rates in the whole of Europe.

**Q22 Dr Taylor:** Dr Darnbrough implied that the Government was perfectly happy for drug firms to go down their own path for research. Is that absolutely so?

**Dr Darnbrough:** I was looking at it from the Department of Trade and Industry’s point of view. You have heard several statements from Dr Harvey and others about the increasing discussions between the Department of Health and the companies to talk about what are the actual healthcare priorities for the nation and the patients in the UK.

**Q23 Dr Taylor:** So we have a difference, from your point of view, behind industry. The strongest motive is profit. The Department of Health has to have another priority.

**Dr Darnbrough:** I cannot speak for the industry, and I think you will have to explore this with the companies themselves of course. The dialogue the Government has is a joined-up one, and there are many things that colleagues in the Department of Health and others in the DTI talk about with the companies, including, very importantly, what the healthcare priorities are for people in this country.

**Dr Harvey:** It might be worth Professor Davies adding a bit from the R&D perspective. Obviously, the stakeholder relationship means there is huge awareness of priority areas within the R&D arena.

**Dr Naysmith:** We are planning to look at research later on, so will leave that for the moment.

**Q24 Mrs Calton:** Can we turn to the regulation and the trials, particularly as it applies to patients involved in those trials and the regulatory framework for that. I understand that the good clinical practice that is followed has a confidentiality requirement set out by the ICH, the International Committee of Harmonisation; but it does not permit the regulators to see the full good clinical practice audit. Can that be right? Is that satisfactory?

**Professor Woods:** Since the European Clinical Trials Directive was transposed into UK law, and taking effect from the beginning of May this year, inspection of good clinical practice is a new regulatory role which we have taken on, which gives us as an agency the opportunity to examine the operation of the clinical trial at ground level and to also ensure that any adverse events that occur are reported to us and recorded rapidly, and from sites which may not be in the UK. The clinical trials regulations now give added security in terms of the protection of GCP within the research environment, which were not there before. The clinical research trials community is very mixed. A large part of it is pharmaceutically driven and organised, but there is
a large clinical trials activity which is funded by public sector funders—the major charities, the DoH, the NHS. Therefore, these trials researchers are working in slightly different communities. One of the advantages of the new regulations is that it will allow us to develop consistent standards of good clinical practice across all trials. Indeed the Department of Health R&D division has led the way in developing a research governance framework to ensure that the standards of patient protection and data quality are consistent and are observed.

**Q25 Mrs Calton:** Does that mean that patients are fully protected; if the regulators cannot see the information and see the audit and the results of the audit, but do not see what goes into that?

**Professor Woods:** I would expect that to be part of our inspection function, to monitor and to supervise the standards of GCP being conducted in that trial.

**Q26 Mrs Calton:** Evidence that comes from is not very good, so they are now talking to Cancer Professor Iain Chalmers mentions that the standards of GCP being conducted in that trial. It goes back to the earlier discussion we had about how one can shape the innovation agenda. Who sets that agenda? Essentially, the influences that we have on it are limited, but they are definitely there. Of course, in most industrial contexts a demanding customer helps to influence product innovation. We have to find another word than “vaccine” against smoking. Clearly, this is a major public health area. The venture capital market is not very good, so they are now talking to Cancer Research UK. If, between them, they can come up with a protocol that is of high quality, which addresses the research governance issues that we lay down—and Cancer Research UK always work to that level—then we will look at partnership funding. We have to find another word than “vaccine” against smoking.

**Q27 Dr Naysmith:** Professor Davies, does the Department have a view, when it says, “there is an area where we need some clinical research done, but the drug firms are not interested in it because there may not be much in the way of profit”? Do we have a mechanism for saying “in this particular disease we need something where research is not being done by pharmaceutical companies”? Do we do that?

**Professor Davies:** You have in your submission from us explanation of the research for patient benefit working party, which was set up by the Government as a response to a number of reports, including the Bioscience Innovation and Growth team and the Academy of Medical Sciences. In the process of working through what this working party, chaired by my predecessor Sir John Patterson should do, the drug companies, the pharma companies, supplied us in confidence with drugs in their pipelines. We said, and expressed to them, what we saw of areas of great need, and where there were shared interests for future research. That exposition they said they found very helpful in guiding them for the future. We have yet to see how it plays out, but it was in confidence a list of areas that they were in, and they were moving forward, and our response to it. There are a number of mechanisms. I have been approached for instance by a biotech company that has a vaccine against smoking. Clearly, this is a major public health area. The venture capital market is not very good, so they are now talking to Cancer Research UK. If, between them, they can come up with a protocol that is of high quality, which addresses the research governance issues that we lay down—and Cancer Research UK always work to that level—then we will look at partnership funding in the light of a commercial contract negotiated by a commercial department, to make sure that developments like that happen. We are exploring one at the moment.

**Q28 Dr Naysmith:** We do; we have our own R&D EU regulation it is a single view for the UK as to whether the patient information leaflet is satisfactory. But it is quite clear in their training that they should consider making sure that patients are aware whether this is a public sector trial, a contract, pivotal licensing study, whether it is being done through the NHS or in a private capacity where the NHS is not involved. The patient information leaflets should give adequate information, and it is for the ethics committees, which are independent, to make a judgment.
Q30 Mrs Calton: Do you think it is happening already?
Professor Davies: I do not think it was perfect in the past. As a result of a massive amount of training and education, set up and organised by the Central Office of Research Ethics Committee, there has been a dramatic improvement.

Q31 Mrs Calton: How recently would you say that has been taking place?
Professor Davies: Over the last 12–18 months it has really improved.

Q32 Dr Taylor: Are there any figures for how rapidly ethics committees work and produce results? One gets the feeling that there is so much red tape now involved before you can get on to a worthwhile project, that perhaps some are being delayed and taken elsewhere altogether?
Professor Davies: In the past every ethics committee could do what they wanted, but with the laying of the regulations and from May this year, we have bound all ethics committees to the time line given to us under Article 6 of the EU Directive of 60 days. They are keeping to that and doing very well, but it is a struggle.

Q33 Dr Taylor: Are research organisations, whether drugs firms or the NHS happy with that?
Professor Davies: The drug firms would like to be lower than that, and many are. Some of them are turning it round in a matter of a week or two, but that will take time. The bureaucracy has simplified in that we now have a single form across the country. It is available across the Web. While it superficially appears complex, speaking as a researcher who is also applying for ethics committee application, it works that you can move from one part to another, and it is not as awful as it looks. But the great advantage of a single form is that then it is the same form whether you are applying in the north of England, the west of England or the south of England.

Q34 Dr Naysmith: Can we find a way to make it not look awful?
Professor Davies: COREC has been collecting views and comments and will review the form to try and help make it more apparently user-friendly. It really is not bad in practice.
Dr Naysmith: Once you have done a few, it is easy.

Q35 Jim Dowd: Are you saying that the amount of medical research that is funded by the taxpayer through the MRC and academic institutions, universities et cetera, would only exceptionally look at pharmaceuticals?
Professor Davies: I made no comment on that. The Government funds using taxpayers’ money research through the Department of Education and Skills, the Higher Education Funding Council, into universities. That is biomedical and clinical. We provide, through the Department of Health, support funding of nearly 600 million to trusts and our national R&D programmes, including £497 million to trusts. A certain amount of that does relate to drugs. Much of it is off-licensed, being trialled for off-licence indications, different indications or comparisons. I was only yesterday looking at a trial for men with sickle cell disease, where 50% develop priapism, which is a prolonged painful erection. There is a treatment that looks to be effective, but as it can come and go it is quite difficult to know whether the treatment is working. The drug companies are not interested in this small market, so we are looking at how we can do a proper randomised controlled placebo trial in order to judge whether this is effective. That is in the NHS and the NHS funding.

Q36 Jim Dowd: So the answer is “yes”.
Professor Davies: A certain amount of drug research is undertaken, yes.

Q37 Siobhain McDonagh: Under current regulations, healthy individuals are entered into clinical trials before carcinogenic testing involving rodents is complete. Does the situation protect the dignity, rights, safety and well-being of patients and other participants?
Professor Woods: Now that every clinical trial requires a clinical trials authorisation it is necessary for the proposer of the research to present a persuasive case that what is being proposed is in scientific terms adequately safe for the recipients. It is certainly the case that a great deal of pre-clinical research underpins the first use in man. There may be some aspects of the laboratory evaluation which are running in parallel with very early exposures in man, but, as I say—

Q38 Siobhain McDonagh: Do the same rules apply to women?
Professor Woods: Yes, okay—persons. There is this scrutiny at the point of assessment for a clinical trials authorisation to ensure that the science base, the toxicology that has been done already, is sufficient to justify embarking on this study in people.

Q39 Siobhain McDonagh: Thank you. How many clinical trials does the MHRA examine before approving a drug application? Is the MHRA confident that it completely reviews all the findings necessary, both within and outside the public domain, before licensing a drug?
Professor Woods: The legal responsibility is on the applicant to ensure that in applying for a trial’s authorisation they do give us all the data, whether or not it is in the public domain. That is clearly spelt out in medicines legislation and, of course, it is fundamental to our assessment of a product that we do have access to all the available data.

Q40 Siobhain McDonagh: Is it in the public’s interest and that of the scientific community that all results are not published? Is it in the interests of
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Government and NHS patients to be secretive and permit secrecy about much of industry’s research data?

Dr Naysmith: Just before you answer that, you did say in answer to the question that Siobhain just put that you thought you should get all the information, you thought you are getting it now, but there have been one or two recent examples where pharmaceutical companies have suppressed some information and not provided it. In answer to Siobhain’s question, I would be grateful if you took that into account.

Professor Woods: If we have any evidence that there has been a breach of the regulations, then we have an inspection and enforcement division which will take the necessary action to pursue investigations; the legal framework is clear, that we must have for the assessment process all the data which the applicant possesses.

Q41 Dr Naysmith: Have you ever used that power or has it ever been used?

Professor Woods: Yes, we have had occasion to involve our enforcement group where there has been some evidence to suggest that we have not been given data at the appropriate point. This is not simply at the point of licensing, but if any additional data arrives which is relevant to the safety of a product, again there is a legal obligation on the authorisation holder to tell us about it.

Q42 Dr Naysmith: I think Siobhain’s question was do we think it is in the public’s interest that some of the results are not published?

Professor Woods: The question of public access to trials data is quite a vexed and controversial one. It is probably best to think of it in two areas: firstly, the data which we as a regulatory agency receive in confidence, should that be in the public domain? There are, within the Freedom of Information Act provisions, exceptions—this Act will come into force of course next January—where data submitted in confidence which are trade secrets, which are commercially in confidence, are exempted from the provisions of the Freedom of Information Act. There is a wider question, however, whether the information on a drug once it has received its product licence should then be publicly made available by the manufacturer? That is an area where I think opinions are moving quite quickly and there has been a much greater willingness on the part of the industry—there have been several notable examples recently—to put their trials data into the public domain once the regulatory decision has been made.

Dr Naysmith: We indeed had further discussion about this with NICE when they last were before us and no doubt we will be reviewing it later on. Siobhain, have you anything else to ask?

Siobhain McDonagh: No, thank you.

Q43 Mr Dowd: Can I just look at the questions of promotion of pharmaceuticals and information? According to my figures, the pharmaceutical industry employs some 83,000 people directly, of whom one in 10 approximately are drug representatives visiting health professionals and others, and there is also growth of people who are now called regional medical advisers as well, so it is a substantial part of their operation. We have received many submissions expressing concern at the activity of this army, but from your submission the Department seems pretty sanguine about the current arrangements. In the Medicines Advertising Regulations it states all of the principles behind it, and it all seems fine—except it uses terms like “reasonable” and “appropriate” which of course keep lawyers in work for generations. Who actually enforces this and how often are there prosecutions under this?

Professor Davies: I think in terms of the regulations themselves, they are actually enforced by the MHRA, but in addition to that there is also guidance to the NHS as to management responsibility. Would it be worth talking about the regulations first, and then possibly say something about the management responsibility within the NHS?

Professor Woods: You mentioned two things, one was advertising and the other was the sales force; perhaps we could start with the advertising. There is a mixture of self-regulation and legislation to regulate the advertising of medicines. The formal legal framework goes back to the Medicines Advertising Regulations of 1994 and a clear distinction is made between advertising directed towards patients and advertising directed towards persons qualified to prescribe or supply drugs, in other words doctors and pharmacists. The voluntary framework on advertising is a self-regulatory system which is run separately for the over the counter medicines and for the generics and innovative areas. By and large, that is a very effective system for scrutiny, but we do have powers within the agency to back that up and we do so in three ways: firstly, we will pre-vet advertising material under certain circumstances—that is to say, if we have concerns about the direction in which advertising claims might be slanted, perhaps it is a new drug, newly marketed in a new therapeutic category, perhaps it is a drug which has shifted in its classification so that it is available over the counter. So there is the pre-vetting facility which we use, and in the current year I think there are something like 17 products which are under that pre-vetting of advertising. The second area where we will act is if there has been a complaint about an advertisement thought not adequately to represent the drug in question, and of course the advertiser is expected to produce advertising material which accurately reflects what is in the summary product characteristics which we had agreed with them. So we will investigate complaints and, of course, we maintain surveillance of advertising ourselves in our own unit to look for things that might have slipped through the self-regulation process.

Q44 Mr Dowd: I accept it is extremely difficult, but what mechanism do you employ to monitor what individual drug company representatives are saying to individual prescribers?
Professor Woods: That again comes under the same Regulations of 1994, the Promotion of Medicines. It is a little bit more complicated than simply the legal framework: for instance, there are ethical standards for drug marketing, but there is also a role for the NHS as an employer to have codes of practice as to what its employees may accept, for instance, by way of inducements, by way of freebies, by way of incentives. There are also professional standards, the General Medical Council have said something about this in good medical practice, so it is a complex set of constraints. Perhaps Dr Harvey might be able to enlarge on some of the NHS constraints.

Q45 Dr Naysmith: Of course, employees of the NHS would be bound by that, but of course GPs are contractors to the National Health Service. How would that slight but very important difference affect it?

Dr Harvey: Could I just say that actually in terms of the guidance that the NHS has, that does also include contractors to primary care trusts. In fact, the two pieces of guidance that the Department put out was, firstly, in 1993 the Standards of Business Conduct for NHS Staff, and then later in November 2000 Commercial Sponsorship: Ethical Standards, and that includes a draft code of practice. Within that guidance it is fairly clear about the responsibilities within NHS trusts, PCTs, within management to make clinicians who are prescribing aware of these issues, and it does include in the same way that the regulations do quite a lot of detail in terms of the sorts of things that NHS trusts should put in place. That includes things like declarations of interest, and in terms of gifts that if people have had gifts and things they should be declared, also limits in terms of gifts or support—for example, support for travel to international conferences. That is all laid out very clearly within the guidance and it is the responsibility of NHS management to make sure that all of their clinicians are aware and indeed are abiding by that guidance. As Professor Woods said, it is also covered within good medical practice within revalidation for the GMC that there are codes of practice, it is the duty of the clinician to ensure that when they prescribe they prescribe based on the evidence base and in the best interests of their patient. That is very clear, both within the NHS guidance and also very much within the self-regulatory mechanisms for medical professionals.

Q46 Mr Dowd: Within your submission here you have mentioned the points you have just made, certainly with regard to the standards of business conduct and commercial sponsorship. You say: “If an agreement is entered into the clinician’s judgment should always be based upon clinical evidence that the product is best for the patient . . . ” That is what you said, but it also goes on to say “and value for money.” I thought that was NICE’s job.

Dr Harvey: That comes from the evidence base that we provide for clinicians through the outputs of NICE in terms of the NICE appraisals. As you are aware, the NICE appraisal is both clinical and cost-effectiveness jointly, and in fact much of the information that we put out to the NHS is support in making decisions around effective prescribing to the best needs of their patients.

Q47 Mr Dowd: Can I just take that further, because we have received information that NICE-approved products, when they had been promoted to prescribers, actually showed a distinct increase amongst those who had received such submissions as opposed to those who had not. Do you think that was just making them aware of something they were previously unaware of, or is it the effect of promoting directly to prescribers?

Dr Harvey: Sorry, could you repeat that?

Q48 Mr Dowd: We have received information that representative promotion of NICE-approved products can have a supportive effect. The growth in prescriptions in those doctors who had received calls from representatives was larger than in those who had not received any calls.

Dr Harvey: I think that in addition to what you were referring to in terms of calls that they might have from representatives, one needs to remember that there also is quite a lot of contact with the PCT mechanism in terms of prescribing advisors, the Area Prescribing Committee etc. In an Audit Committee review in 2003 on primary care prescribing, they found that the areas of greatest growth within prescription medicines were actually in those areas that were NSF areas (National Service Framework areas) and indeed those where we had NICE guidance—that is particularly in areas such as CHD, diabetes and also mental health. So, as you would expect there are many sources of information that prescribers receive. Yes, they may well get visits from representatives of the pharmaceutical industry; it will be up to them as to whether or not they see those representatives, but anyway they get a great deal of information through the mechanisms that we alluded to earlier in terms of supporting prescribing and supporting evidence-based prescribing for increasing the quality of care for patients.

Q49 Dr Taylor: Really it is on the same sort of topic, because it staggered us I think with the information we have received to see the proportion of drug firms’ revenue that does go on promotion, so obviously promotion must work. There are all sorts of suspicions that drug reps and promotional meetings do influence prescribing doctors, sometimes in the wrong way. Is there any evidence of inappropriate or uneconomic prescribing of a specific medicine, following on particular events or drug reps visits?

Dr Harvey: I wonder if I could possibly ask Dr Smith to answer.

Dr Smith: Thank you. I think it is true to say that there has been that kind of evidence—it is difficult to find, it is in the research literature, and the people who would really know of course are the companies themselves or maybe the advertising industry, who I do not think put that information into the public
domain. There is evidence in the research literature, but it is a few years ago and it is mainly American; I think the point I would like to make is that prescribing now takes place in a much more managed environment, and over the last five or ten years there has been a sea change in organisation and individual professional approach to prescribing. We have different drug and therapeutics committees, we have prescribing advisers, all primary care trusts are required to have a code of conduct and there are a couple of examples in the Audit Commission report which Dr Harvey referred to of East Yorkshire PCT and Amber Valley PCT who have particularly robust policies for working with the industry. We have come a long way and, without having objective evidence, my take would be that there is a much more level playing field, in fact a playing field much more tilted in favour of the NHS and NHS professionals. That is not to say that influences are not out there, but we are much better equipped to handle them and to make sure professionals prescribe effectively.

Q50 Dr Naysmith: Do you think that a drug firm taking a bunch of young GPs off to Switzerland during the ski-ing season and carrying out a promotion at that time, would that be caught by any ethical requirements? The promotion was fine, it was just that it was accompanied by the ski-ing—and this was not American and it was not a long time ago, it was last year.

Dr Smith: Superficially it would appear to be in breach of the principles that we have very clearly set out in guidance to the NHS, and the 1994 Regulations.

Q51 Dr Taylor: If you are right, the drug firms would be countering this by either increasing their expense on promotion or decreasing their expense on promotion. Have we any evidence of that? We will have to ask the drug firms.

Dr Smith: I think you will, yes. I am not aware of that.

Q52 Mrs Calton: Can I pick up on just a couple of points because we have had answers which have indicated that malpractice, as such, is pretty well covered by existing practice and existing controls, but in our briefing notes Herxheimer has said that it may be more to do with the extent and volume of influence rather than actual malpractice going on. What is your view of that, do you believe that the sheer volume of influence, the extent of it and the pervasive nature of it may actually have more influence than actual malpractice which most of us would recognise?

Dr Harvey: I think it is very much down to individual NHS trusts as to the sort of relationship they might have with an individual pharmaceutical company, be it in support of education, in support of information etc. I think what we would say is that within not only the guidance that has gone out to the NHS, both in 1993 and 2000, but also within the code of practice that the ABPI itself has through the Prescription Medicines Code of Practice Authority, that is actually fairly heavily dealt with, within the mechanisms that we have, and if there are any concerns around the particular practices of an individual company or individual representatives, there are mechanisms going to the Prescription Medicines Code of Practice Authority, or indeed through to the MHRA. If there is a concern about a clinical professional then that concern goes through the NHS trust and the mechanisms there. What we would say is that we do have mechanisms in place, we are providing a large amount of information through various very good sources—for example NICE Drug and Therapeutics Bulletin, and the BNF—we have mechanisms through the prescribing advisers, the area Prescribing Committees, drugs and therapeutics committees. There are lots of structures and information sources within the NHS now and, indeed, monitoring of prescribing to see whether what we are actually prescribing at the end of the day is what we would expect in terms of increasing quality of care and evidence-based practice. The prescribing evidence that we have is indicating that that is the case. We do have an issue around getting NICE positive appraisals into practice and the government responded to that in terms of how we can make that more robust earlier this year, but I think there are a lot of mechanisms that we now have within the NHS that actually support prescribers in trying to ensure that they are prescribing in the best interests of their patients and quality of care.

Professor Davies: Perhaps I could make that alive for you. Speaking as a doctor who still does clinics, if we take a condition where patients who have had cancer or leukaemia, have been treated with chemotherapeutic drugs and have no white cells then get a fever, they have probably got an infection. There is a myriad of very expensive antibiotics that we could use and I am sure the drug companies each would like us to use their own, but we have a protocol for the hospital—almost every hospital does have—where the infectious diseases people, the microbiologists, the clinical pharmacologists have sat down and agreed what is right for the patient in this situation, and then we have bulk purchasing to ensure a sensible buy. So I have a protocol, I do not even have to think at two in the morning. I just say yes, the protocol says those drugs at that dose, we start with that. We change if the situation changes. Another example was a few weeks ago I prescribed a particular iron syrup for an infant who was iron-deficient; 10 minutes later the phone goes, it was pharmacy: “We do not stock that, we will be prescribing the following [ferrous sulphate] the same dose, the same concentration, but a lot cheaper.” So in practice it is beginning to change.

Q53 Mrs Calton: Another point in our briefing notes and something that I have had some personal concern about, which the Royal College of General Practitioners has brought to our attention, is the categorisation of an increasing number of individuals as “abnormal” and that therefore they
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will need a drug to put them right. I have heard this personally from a practising consultant, that large numbers of children need Ritalin, for example, to put right what nature has put wrong. I wonder whether this is a concern that you might have.

Dr Harvey: In terms of clinical areas, clearly there is a lot of guidance and clinical guidelines from all of the professional medical royal colleges, other professional bodies etc, but that is also another function of NICE. It does have its appraisal process, but it also has a clinical guidelines arm to the work that it does as well. That is very important in terms of looking at particular conditions and giving an evidence-based approach to not only the treatment but the diagnosis. What is the most efficacious method of diagnosing and then treating a particular condition? As we are developing the quality strategy within the NHS, more and more of these guidelines are out there in the NHS to inform doctors, and we also support that through decision support, one of the facets that will also be developed further within the national programme for information technology.

Q56 Mr Dowd: Finally, then, to pull it all together from what you have said, are you satisfied that there are sufficient mechanisms in place—I think actually, Dr Harvey, you alluded to this—to make sure prescribers can make the most effective prescribing decisions?

Dr Harvey: I think this is obviously something that we always keep under review, but I think from the information that we have there is a lot of information to prescribers. We also, as I said earlier, have a generic prescribing rate now of 78%, 85% in a few PCTs. And again if you look at the Audit Commission’s report in 2003 of the areas of growth in the drugs budget in terms of prescription medicines, they are in the areas that we would expect that growth to be because of the clinical priority areas that are very important in terms of increasing quality of care in the community. The evidence would indicate I am sure we can always do better, but at the moment we do have mechanisms which are informing clinicians of the sort of evidence-based decisions coming from many different sources, NICE being one of them, that they might make. Clearly, there is clinical freedom and this is actually something which, at the end of the day, is an issue for an individual clinician in their consultation with an individual patient.

Q57 Mr Dowd: Finally, finally, is there anything that you can say succinctly to convince the more sceptical or cynical citizen who believes that the army of drug company representatives are actually just out to sell products rather than to improve public health?

Dr Harvey: I think in terms of the pharmaceutical industry also they are very conscious of the regulations governing this. I would not expect that growth to be because of the clinical priority areas that are very important in terms of increasing quality of care in the community. The evidence would indicate I am sure we can always do better, but at the moment we do have mechanisms which are informing clinicians of the sort of evidence-based decisions coming from many different sources, NICE being one of them, that they might make. Clearly, there is clinical freedom and this is actually something which, at the end of the day, is an issue for an individual clinician in their consultation with an individual patient.

Professor Woods: I can give you some figures for advertising, for instance, because this is something we looked at—in fact it was the precursor organisation, the Medicines Control Agency, which started an internal review of the investigation of advertising complaints. We have continued that, and what we have been doing since December last year is to put on our website the outcome of the investigation of the complaint made about medicines advertising. Between December last year and June this year, 16 complaints were put on the MHRA website, including description of what the complaint was, what the adjudication was and what corrective action was being taken. We use that as a way of helping to reinforce the messages about what is acceptable advertising, and of course we also have a guideline document “Advertising and Promoting Medicines in the UK” which is on our website. There is no ambiguity about what the ground rules are.

Q58 Mr Jones: This evidence session is of course about exploring the relationship between the industry, its customers and its regulators, and I think when the Committee looks back upon the evidence of the session one of the most striking features is that despite great pressing from colleagues, in the last hour and a half none of you have given one example of any single company or any single product that has been improperly provided, so either things are going marvellously well or there is a certain reluctance. Perhaps in answer to future questions, from me or from somebody else, there are some specific examples of products improperly provided that you might give. I want to ask some questions about the role of education. One of the other unique features of this industry is that the industry is effectively the educators of professionals who provide the products. Over half of further education training for doctors is funded by the industry: the industry extensively provides hospitality and courses on training for its products. That may be inevitable in this industry, but do you recognise, Professor Davies, that it is an unsatisfactory position and maybe we should look to see if we could have safeguards or whatever in other ways, so that those
Q60 Mr Jones: Ev 30

Health Committee: Evidence

what relationships in terms of education it might be another area which is potentially more worrying: the clarity for the NHS in terms of what sponsorship, involved in education of practitioners, but there is actually do give an environment where there is great absolutely inevitable that the industry is heavily

Q62 Mr Jones: Dr Harvey:

Dr Harvey: In terms of education generally the have been abuses in the past—Department itself invests some £4 billion in MPET and, as you know, that very much funds undergraduate and postgraduate medical education. We also have the deaneries and the Workforce Confederations that are actually looking to training needs of individuals. Within the new frameworks we have for appraisal and revalidation—and this is both for the consultants and indeed for general practitioners it is important for every individual clinician and every doctor And it is not just doctors, it is for other health care professionals as well, to have a personal development plan. That personal development plan is part and parcel of their appraisal, and will be in discussed with their employer.

Q59 Mr Jones: Sorry, can I go back to my question again? I acknowledged in my question that maybe community the appropriate health body would look about influence on patient groups and whether we might have and what that might mean in terms of comment whether the government has concerns medical royal colleges or other professional bodies subject to government guidance, for example, the Cochrane Collaboration have a whiter than white

Dr Harvey: I think our position is that in terms of the undergraduate and postgraduate training systems. So I think that relationship needs to be looked at. In terms of examples, I would make the point that I have made before, that I think we have seen a huge change in this area over the last few years and a much more systematic and measured approach to prescribing and looking at education and promotion, or promotion masquerading as education, which I amounts. think is what you are getting at, is part of that. There have been abuses in the past—

Q61 Mr Jones: I was not trying to be Delphic, Dr Smith.

Dr Smith: No. Certainly, in previous jobs I have been aware of training programmes supported by industry where companies have attempted to influence the agenda and have been rejected, and the people organising those programmes have said no, you can support this programme, we are happy for you to have a stand at the back of the room but we set the educational content. That would be the model that we should go for. I would just come back to the point that has already been made that within this framework we are measuring and monitoring and managing prescribing as never before, with a whole range of tools, and if there is any suspicion of undue influence within a hospital or within the community the appropriate health body would look into that and would take appropriate action. So I really think the days when you saw a very expensive jamboree, followed by a flood of inappropriate prescribing, are if not gone, very, very rare.

Mr Jones: Thank you, Dr Smith, so I cannot tempt you to give me an example.

Dr Naysmith: We will keep these questions for the ministers when they come, Jon. We will move on.

Q60 Mr Jones: Dr Smith, you looked at one stage as if you had some examples in mind. Could I tempt you?

Dr Smith: I wanted to say two things, Chairman. The first was that when I saw this 50% figure I was slightly incredulous; I am not saying it is wrong, I am just saying I do find it hard to believe because, as Dr Harvey has said, the NHS does invest a lot of money in professional education, huge amounts of money, through a highly developed network of deaneries and postgraduate training systems. So I think that relationship needs to be looked at. In terms of examples, I would make the point that I have made before, that I think we have seen a huge change in this area over the last few years and a much more systematic and measured approach to prescribing and looking at education and promotion, or promotion masquerading as education, which I think is what you are getting at, is part of that. There have been abuses in the past—

Q62 Mr Jones: It may well be, as I acknowledged, absolutely vitable that the industry is heavily involved in education of practitioners, but there is another area which is potentially more worrying: the industry's involvement with patient groups. Patient groups, by their nature, would perhaps be even more vulnerable to influence; would any of you care to comment whether the government has concerns about influence on patient groups and whether we might be considering doing something to control that?

Dr Harvey: I wonder if I might ask Dr Smith to say a few words.

Dr Smith: The first thing to say is that the patient groups are extremely valuable organisations in lobbying, quite properly, putting the case for their clients, for those patients, for that disease area, and we wish to work with them and engage with them to help us develop policy for the management of those diseases. Those groups are charities and a lot of them
do draw support from companies who have products in that sector, that is fairly obvious. We are aware of that, everyone is aware of that, it is quite transparent, so I think in dealing with patient organisations around particular disease areas there is a transparency. We know that the company may well be involved in supporting that organisation and we can take that into account. We saw this in the very early days of the interferons for MS, when the MS Society, quite properly, was engaging government, was engaging health authorities locally, and the company was supporting them. Everyone knew that, it did not influence judgments about whether this medicine was clinically effective or cost effective.

Q63 Dr Naysmith: I think we could have some disagreement about that, but we will leave it at that. What was happening with MS and beta interferon was that at a time when it was not really clinically proven to be useful, the group were demanding that patients be given it. They may have been right, but we will not know the answer to that until the trials come to an end, they have not finished yet. That is the area of concern that we are concerned about.

Dr Smith: My point would be, Chairman, that we were aware of that and those lobbying pressures, which were quite legitimate, were by and large resisted, and people waited until NICE had looked at the evidence and they could make a proper judgment.

Dr Naysmith: People waited with some reluctance in some instances.

Q64 Mr Amess: My colleague has already made some remarks about the witnesses’ performances; I was going to say that I feel they are very weighty and they certainly scare me, but I do not think they are going to be intimidated by any of the questions I intend to ask. I wonder if perhaps just one of you could answer, perhaps briefly, if you feel that the MHRA medicines operation being funded by fees derived from services to industry is appropriate?

Professor Woods: I think that falls to me. The funding of drug licensing from user fees is very much the norm in countries which have effective drug regulatory systems. Our drug licensing activities are funded by the fees we charge 100%, the same is true in the Netherlands, in Sweden it is 95%, in the United States it is 52%, so I think it is pretty well universal that the bulk of the funding for drug regulation comes from fees charged to industry. This raises a general question about the relationship between industry and regulator, and of course that is the norm—the regulated industry generally pays for the costs of regulation, and one can think of many examples.

Q65 Mr Amess: Do you think the legislation though has actually worked in practice as it was intended and that there is truly that element of independence? Professor Woods: I can quote the evidence analysed by the National Audit Office when they examined the Medicines Control Agency in 2002–03 and their report was published in January of last year. They explicitly looked at this and said there was no evidence of lack of impartiality because of our funding mechanism, and they drew attention to the similarity of funding mechanisms in many other countries. So I think there is that reassurance, that in fact our internal systems are entirely robust to prevent any undue influence arising from that.

Q66 Mr Amess: But does the regulatory agency not see the pharmaceutical customers actually as their customers? Is that a healthy thing?

Professor Woods: As part of the framework document to which I operate the industry is a stakeholder and partner in our activities, and that is right and proper. There has of course been, looking more widely at the question of regulation, the government Better Regulation Taskforce looking at this, and the advice has been that it is important for the regulator and the industry being regulated to be in good communication with each other to ensure that regulation works. I am quite comfortable with the fact that we do have a lack of conflict of interest which is not compromised by the funding basis. It has another practical advantage—this is something which both the FDA and we have found over the last 10 or 15 years—that by funding the system on fee income you have an immediate relationship between the workload and resource, and that means that as workload fluctuates income fluctuates and therefore one’s ability to resource the system to perform well is regulated by the workload that comes through. The US was very sceptical about the funding of drug regulation by industry, but the Prescription Drug User Fee Act which came in in 1992 was the start of a process which has been reinforced with successive acts and now more than half of the funding of the FDA’s drug licensing comes from user fees. So I think we are not alone.

Q67 Mr Amess: Thank you for your answer, and when we reflect at the end of this inquiry we will discuss your responses to my question on that particular point. The Committee is very interested to find out how often each of you actually meets the industry. We are not asking for copies of your diaries—although that would be quite interesting really—but roughly can you tell us how many times you have had formal or informal meetings with the industry over the last six months? Lunch, dinners, cups of tea, whatever.

Q68 Mr Dowd: Trips to Switzerland.

Dr Harvey: In my own case no lunches or dinners in the last six months because I have actually been one of the co-chairs for the confidential negotiations on PPRS, so in fact my meetings with them have been limited to negotiations.

Professor Davies: I meet formally through the PICTF mechanism, I co-chair working group 5 on clinical trials, and that will have met twice in that period and we will have had two or three other meetings around those issues. I was a member of the Research for Patient Benefit working party, they
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were on that, that will have been about three meetings, I now chair the UK CRC so that will be two meetings. I had a meeting this week with a senior member of a drug company to request that they should part-fund a study we want to do and had agreement, and I will have had other meetings of that sort, but not even one a week.

Q69 Mr Dowd: Are these meetings with representative groups of the industry? I know you mentioned meeting one individual company there in relation to a specific sponsorship proposal, but are they generally with representative groups of the industry or, and exceptionally, only with individual companies?

Professor Davies: It varies. The set pieces like the UK Clinical Research Collaboration, they are representatives of industry, and of course I was on the Biotechnology Innovation and Growth Team so I met industry through all of that work, I am on the Healthcare Industry’s Taskforce so it is a different industry, but I am meeting them through that. It is predominantly as representatives but then on occasions about specific issues of concern or shared sponsorship or something when it would be with an individual company.

Q70 Mr Burns: Could I just pick up on one point? If I understood some of your evidence a little earlier in the session I got the impression that apart from contact with individual companies, I can think of the answer to your question, and it runs like this: I really only see the industry associations on a regular basis, and I am required by my framework sponsorship or something when it would be with an individual company. I understand some of your evidence a little earlier in the session I got the impression that apart from contact with individual companies, I am meeting them through that. It is predominantly as representatives but then on occasions about specific issues of concern or shared sponsorship or something when it would be with an individual company.

Q71 Mr Burns: So do you meet the industry in that role?

Professor Davies: No, I refused to about 10 years ago. It has no impact on my prescribing and therefore there is no point.

Q72 Mr Burns: You are a jolly busy lady as far as I can see. Dr Darnbrough?

Dr Darnbrough: I would not like to count, but perhaps I could just—

Q73 Dr Naysmith: I am advised by the clerk that we cannot compel people to answer this particular question, so it is up to you if you want to bare your soul.

Dr Darnbrough: Let me just list some of the ways in which I do meet the companies. First of all, I did describe earlier how we have formalised our business relations work, so specifically part of what we do in our unit is to sit down and meet individual companies. We do actually meet therefore with GSK, AstraZeneca and many of the others so that we understand why they find the UK a good place to do their research and manufacturing and so on. We also discuss the difficulties that they are facing. I chair a number of groups which the ABPI and the Bio Industries Association and a number of individual companies and representatives are on them; for example, there is a big group that meets to talk about the regulation that is industry-specific, so the biotech and pharmaceutical regulation that is coming out of Europe and internationally, they would be at those kinds of meetings. One of our priorities at the moment is to tackle the very difficult issue of animal rights extremism, so I am afraid in that context I have had a great deal of contact, both with the trade associations, individual companies working in the pharmaceutical industry and their suppliers. I take part in BBSRC activities and there are members of the industry on their committees. And obviously in my position, having this business relations role, I am often invited to events that the pharmaceutical industry is organising and I attend things when ministers go and open new facilities, or ministers are going to visit and see some of the research that is going on. So there is a whole range of interactions.

Q74 Mr Amess: You are also a very busy lady, doing your job promoting UK plc. Gentlemen, what about you?

Professor Woods: I have been racking my brains to think of the answer to your question, and it runs like this: I really only see the industry associations on a regular basis, and I am required by my framework document to do that on a regular basis. I meet the ABPI, I meet the PAGB, and of course I have responsibilities for medical devices too. In terms of contact with individual companies, I can think of only three since I took up post in January. Two of them have been visits to factories that make non-prescribable medical devices—to see how operating tables are made, among others—and the third was a delegation I received from a company who felt bruised about the way we had treated some of their advertising material and put on our website a critical and corrective response to what we considered to be improper advertising. That is the limit of my contact with individual companies since the beginning of the year.

Q75 Mr Amess: Dr Smith, you must be seeing them all the time presumably?

Dr Smith: No, actually not, maybe half a dozen times in the last six months or so, which is, like colleagues, through committees and working groups that I am either a member of or chair. That is probably the main route. Like Professor Woods, I do have one to one meetings with ABPI representatives and with PAGB for the proprietary over the counter medicine suppliers, and I do occasionally have one to ones with individual companies. I tend to reject these if they are a promotional sort of meeting, but where there is a professional issue involved—for example when we were considering the application for Simvastatin to become an over the counter product, there were huge professional issues for the pharmacy profession, so I met with the company to try to understand the logic and the training and their approaches to this issue. Of course, that was subsequently a successful application, but I had no part in the decision. So it is as and when I need to.
Q76 Mr Amess: Thank you very much indeed, and if you do feel that you want to send us your diaries, we could write a book. The next question is about transparency, which this government is very keen on, and perhaps if just one of you answer it. Does the Department anticipate that the repeal of section 118 of the Medicines Act 1968 and the implementation of relevant provisions of the Freedom of Information Act 2000 will ensure levels of transparency in drug testing?

Professor Woods: If I can answer that, yes, we welcome the change. The 1968 Act, in particular section 118 which quite tightly constrained what we could say in relation to information we had been given for an application, has been an increasing encumbrance to us. It is legislation that dates from a much earlier age and I think that the default is that we would like to be able to release as much information as we can, and therefore the Freedom of Information Act has given us the opportunity to develop a publication scheme, to make it widely known and to look critically at those areas of information which we do not release and have a clear and consistent explanation as to why not. Issues such as commercial confidentiality and the usual exclusions are there, but the default is that we would like to communicate if we can. I would say that we give such an importance to this issue of communication externally that since I came into post we have set in train the establishment of a communications directorate within the Agency. We have never had one before, we will be appointing a head of that directorate within the next few weeks and we will use that initiative to look constructively at our links with patients, with the wider public and with the clinical professions. There is a great deal more that we could do and I think that having a communications directorate within the Agency will enable us to be much more proactive in that.

Q77 Dr Naysmith: You will be glad to hear that we have almost come to an end, but there are a couple of informational questions that we will finish on. One is, what proportion of new drugs are evaluated by NICE and what is the average time that elapses between the launch of a new drug and publication of an appraisal? I think that is probably you again, Professor Woods, or is it Dr Harvey?

Professor Woods: What was the impetus for setting up this unit? Was it purely your good self having a new idea, was there pressure coming in?

Professor Woods: There were several strands. One factor was the National Audit Office report published in 2003, looking at the MCA, which made the comment that the profile of the MCA externally was not high and there was an insufficient awareness of what the MCA was doing and why, both among the general public and in the professions. Having seen it from the other side of the table, I entirely agree with that; therefore, I think there is a task—and it goes back to something which we discussed earlier—for us to make available to patients and the wider public detached, neutral and impartial information about medicines. That is a gap which many people have commented on and I think now, with the options available to us through our website and through other media, we can be much more informative to people about medicines in a way which is seen as utterly non-promotional. Our role is entirely about public health, we do not have to sell any drug or promote any company, but there are many advantages to having a larger volume of information available to the public. If people understand what we do and why we do it I think it will be of great benefit to public health. Dr Harvey: It might actually be me. In terms of the work programme for NICE, the work programme for NICE goes through various stages, firstly through ACTS which is a fairly large advisory committee that has membership from the public, the NHS and industry and NHS commissioners etc. That is the first stage of the work programme development, taking suggestions from the general public, from professional groups etc. It then goes through to a Joint Planning Group before it goes to ministers. That process probably takes about six months, I should think, I do not have the exact figures.

Q78 Mr Amess: My last question—which, to be frank, I do not entirely understand—but our special advisers presumably think this is of enormous significance. When do the regulators issue warnings relating to possible adverse drug effects: when it appears more likely than not that drug treatment may cause harm, or when a risk has been identified as virtually certain?

Professor Woods: I think that again falls to me. We have, I think, a pretty good reputation internationally for getting advice of regulatory change out, if a new hazard is detected. The way we do it is firstly we have our internal scientific resources to assess that hazard, and we also have the advantage of the new external advisory body, the Committee on Safety of Medicines, which can give us very expert advice. But if there is evidence of a public health threat, we can get advice and guidance out very quickly indeed and it may be that the issue of the SSR1 antidepressant Paroxetine was in the minds of whoever wrote that brief. We were able to get advice out within 14 days in the middle of last year, when it became clear to us that there was prescribing of Paroxetine in individuals under the age of 18 for which there is no product licence and where there was evidence accumulating, firstly of lack of efficacy and, secondly, of potential harm. In that situation we put out advice very quickly.

Mr Amess: Excellent, thank you.

Q79 Dr Naysmith: You are going to hear that we have a great deal more that we could do and I think that having a communications directorate within the Agency will enable us to be much more proactive in that.
programme. When they formally go to NICE, in terms of an appraisal it takes about 18 months from the start of the work on that appraisal by NICE to a product actually being put out on their website and sent out to NHS professionals. For appraisal it is about 18 months; for a clinical guideline it is more like about two years, but when NICE are developing their products, be they the appraisals or indeed the clinical guidelines, they go through quite a lot of formal public consultations during that process, so the draft product as it were is actually on their website during that time, but it does take 18 months to two years once they actually have the work programme until the products actually come out the other end.

Q81 Dr Naysmith: I believe that drug firms are sometimes a bit critical of the length of time it takes. Do you think that is a balanced criticism?

Dr Harvey: I think in terms of the processes that NICE has—in fact those were recently looked at by WHO in terms of the quality of the processes that are used—they would say it would be very, very difficult to actually get those time lines down in terms of the amount of evidence that they are using as a basis for either the clinical guideline or the development of the appraisal. There is therefore a gap, obviously, for many new innovations, from them coming to market to actually coming out as a product for NICE, although it may be fair to say that we are trying to get things into the work programme earlier in their development, so that we get the best information for NHS professionals as soon as is possible.

Q82 Dr Naysmith: Thank you. The last question is about the idea of automatic generic substitution, the idea that if doctors do not prescribe a particular brand of drug then automatically the generic substitute is prescribed. That would save quite a lot of money for the National Health Service; is there any estimate of how much it would save and what is the policy on it?

Dr Harvey: In terms of the generic substitution, as you know we have very high rates, the highest in Europe. In terms of an estimate of how much more we might save if that was legislated for as against using the mechanisms that we have outlined through the prescribing advisers etc, we might save somewhere in the region of about £16.5 million for, say, the top 20 selling drugs; generic prescribing is actually the policy of the Department and the policy of the NHS. I think that one of the issues where there may be more savings for the NHS drugs budget is actually in relation to waste, and that is one of the areas that we are looking at very carefully at the moment, and it is one of the issues that we have also been looking at when negotiating the new pharmacy contract. That is an area where there are fairly major potential savings for the NHS, patient compliance and things like that.

Dr Naysmith: Thank you, Jim?

Q83 Mr Dowd: A couple of quick questions on waste. Does the Department have any calculation on the amount of drugs that are prescribed and just not used?

Dr Harvey: Can I suggest Dr Smith might answer that?

Dr Smith: I can try. It is a very difficult area, and the figure that we use and has been used since before I came to the Department is that there is £100 million worth of medicines wasted every year. If you bear in mind that is out of possibly now a £10 billion annual spend, that sounds remarkably low and I would be prepared to accept that it may be higher than that but it is very difficult to measure. It is waste for various reasons: it is waste because of unnecessary prescribing, most often around repeat prescriptions, where there is a package of medicines and they are not all needed. That is how some people end up with a bathroom cabinet full of things because they just do not tell the doctor that they do not need a particular medicine.

Q84 Mr Dowd: Or they do not complete the course.

Dr Smith: Or they do not complete the course, but 80% of prescriptions are repeat medication for long term conditions, so if you have blood pressure tablets, tablets for diabetes and something you only use intermittently like an antacid, the bottles of antacid can pile up in the cupboard. We are tackling that through much closer management of the repeat prescribing and dispensing process. I take your point absolutely, there is waste, we are working very hard to root it out of the system and, going back to Dr Harvey’s point, we think that is more productive in terms of saving money than going down the road of legislating to compel particular generic prescribing behaviours.

Q85 Mr Dowd: Finally, finally, in the absence of generic prescribing procedures, substitution procedures, what in your estimation—and I will be putting this question to the pharmaceutical companies themselves in the course of time, if we can get some before us—is the value of drug representatives extolling the virtue of prescription drugs to pharmacists who are not the prescribers?

Dr Smith: I suppose I had better answer that. You will find that most of the promotional effort of companies is directed towards prescribers, but it is true that increasingly it is targeted towards pharmacists. There are two reasons for that: pharmacists do need to be familiar with products; if a GP is going to start using a product they need to be familiar with it and, actually, it is quite useful to have had a presentation and learn something about it, but also I think pharmacists are increasingly influential in the prescribing process and very many community pharmacists are now doing sessional work in GP surgeries, helping them with formulary development and managing their prescribing. So whether it is a good thing or not, I think it happens. If we are going to allow promotion by pharmaceutical companies, which I think we must in a free society, I think it is proper that they visit
pharmacists. We would expect the primary care trusts to regulate and manage that in the same way as they would manage all other promotional activities and relationships with the industry, and those pharmacists would be bound by the local codes of conduct which we expect them all to have.

Q86 Dr Taylor: Just a very quick request for more information about the yellow card scheme. In the Department’s memorandum you do say “under-reporting of adverse drug reactions is an inherent feature of spontaneous reporting schemes”. Could we have, in due course, a record of annual numbers of yellow cards that are filled in, whether they are going up or down? I gather the electronic yellow card scheme was instituted recently, has that made a difference?

Professor Woods: Perhaps I can very briefly answer that. To the first question the answer is we receive about 19,000 yellow card reports a year from the UK and we receive probably twice that many adverse spontaneous reports from outside the UK, passed on to us from other agencies. The figure of 19,000–20,000 or thereabouts has been pretty steady for several years, with one very atypical year. The electronic card over the internet has been available now for a year or so. It is not widely used, we have seen a few hundred reports through that route, but we do intend to communicate more widely the availability of that route. I should mention that we recently had receipt of an independent review of the yellow card system, which Dr Jeremy Messers led, which has made a number of recommendations about the wider publicity as it were of spontaneous reporting, and that is one of the things I shall be expecting our new communications directorate to get into quite quickly.

Dr Naymsmith: If there are no further questions from any of my colleagues and nothing from any of you that you think you want to tell us, thank you all five, very much indeed, for getting us off to a really good start on this inquiry. Thank you for coming.
MEETINGS WITH THE INDUSTRY

The Committee asked how often the Government team met representatives from the industry in the last six months. When I replied I said that I had curtailed my meetings with industry as I co-chaired the confidential PPRS negotiations. While this is the case I do have a wide range of responsibilities outside of the PPRS, and as part of these I have met industry representatives on four other occasions. I met them twice to discuss the Government proposals on improving the implementation of NICE guidance. I attended the Ministerial Industry Strategy Group with Lord Warner in April, and I also chaired the Industry Strategy Group in July. These were all meetings with the ABPI and not individual companies.

28 September 2004

NICE GUIDANCE TIMELINES

OVERVIEW

1. The Department refers two work programmes to NICE each year, called “waves”. It has worked to standardise the procedure for referrals.

2. The time it takes for a topic to be referred, depends greatly on when the topic enters the process. For each wave of work two meetings of the Advisory Committee for Topic Selection (ACTS) consider whether or not topics should be referred. At the most, a topic takes 12 months to be referred to NICE if it enters a wave at the earliest point, the first meeting for that Wave of ACTS. If a topic is considered at a later point in the wave, at the two Meeting of ACTS, then the process takes only eight months for that topic.

3. Topics deemed suitable for referral by ACTS are given further consideration by the Joint Planning Group (JPG), a team consisting of senior DH officials, the National Clinical Directors and NICE, who consider the topics suggested in a wider strategic policy context. JPG meets twice a year, once for each wave, during the summer and winter.

TECHNOLOGY APPRAISALS

DH Process. (Months indicate cumulative totals)

— Topics considered by one Advisory Committee for Topic Selection (ACTS) meeting—Start.
— Topics considered by two Advisory Committee for Topic Selection (ACTS) meeting—three months.
— Topics considered by the Joint Planning Group (JPG)—six Months.
— Decision by Minister to Consult—five months.
— Consultation on remit and scopes—10 months.
— Normal Referral—12 months.

NICE Process

— Topic referred from DH and Organisations invited to participate—start.
— Submissions on appraisal received from consultees—four months.
— Assessment Report from appraisal committee received by NICE—seven months.
— Consultation on the Assessment Report—eight months.
— Consultation on the Appraisal Consultation Document—10 months.
— Final Appraisal Determination sent to consultees for comment—12 months.
— Appeals period ends—13 months.
— Guidance published and distributed—15 months.

CLINICAL GUIDELINES

DH Process

— Topics considered by one Advisory Committee for Topic Selection (ACTS) meeting—Start.
— Topics considered by two Advisory Committee for Topic Selection (ACTS) meeting—three months.
— Topics considered by the Joint Planning Group (JPG)—six Months.
— Discussion with DH policy leads on context of topics—seven months.
— Formal Referral—11 months.
**NICE Process**
- Topic referred from DH and allocated to relevant National Collaborating Centre—start.
- Final Scope of Guidance Produced—six months.
- Guideline Development Group developed guideline—12 to 18 months.
- First consultation on draft guideline—12–18 months.
- Second consultation on draft guideline 14–20 months.
- National Collaborating Centre works with NICE to finalise guideline—18–24 months.
- Guidance published and distributed—20–26 months.

**Annex B**

**THE YELLOW CARD SCHEME/REVIEW OF ACCESS TO THE YELLOW CARD SCHEME**

**REPORTS RECEIVED PER YEAR**

1. In 2003, 19,272 reports of suspected adverse drug reactions (ADRs) within the UK were reported to the MHRA/CSM. This level of reporting has generally been consistent over the last few years. The sharp increase in reporting seen in 2000 was associated with a nationwide Meningitis C vaccination campaign where Nurses were encouraged to report for the first time. Table 1 below demonstrates the number of UK and foreign reports received since 1999.

<table>
<thead>
<tr>
<th>Received Year</th>
<th>UK Reports</th>
<th>Foreign Reports</th>
<th>Total</th>
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<td>1999</td>
<td>18,486</td>
<td>28,338</td>
<td>46,824</td>
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<tr>
<td>2000</td>
<td>33,153</td>
<td>32,184</td>
<td>65,337</td>
</tr>
<tr>
<td>2001</td>
<td>21,468</td>
<td>40,319</td>
<td>61,787</td>
</tr>
<tr>
<td>2002</td>
<td>17,620</td>
<td>45,569</td>
<td>63,189</td>
</tr>
<tr>
<td>2003</td>
<td>19,272</td>
<td>43,332</td>
<td>62,604</td>
</tr>
<tr>
<td>2004 (reports received by 20/09/04)</td>
<td>14,122</td>
<td>31,862</td>
<td>45,984</td>
</tr>
</tbody>
</table>

**UNDER REPORTING**

2. The value of spontaneous reporting schemes, such as the Yellow Card Scheme, in early detection of drug safety issues is universally recognised. It has a proven track record of identifying new drug safety hazards and is recognised to be one of the best in the world in terms of the level of reporting. Under reporting of ADRs is an inherent feature of spontaneous reporting schemes. Although this means that data from the Scheme have limited usefulness in terms of quantifying the frequency of an ADR, it does not detract from the ability of the scheme to identify new drug safety hazards.

**ELECTRONIC REPORTING**

3. The MHRA and CSM launched a new electronic Yellow Card on their website on 31 October 2002, to provide a rapid and convenient way to report suspected adverse drug reactions (ADRs) for health professionals. To date, the MHRA has received 598 reports of suspected ADRs via the Internet. A one-year evaluation has been carried out and electronic reports were found to be comparable with paper reports, with respect to the proportion of serious ADRs reported and reports associated with new, intensively monitored drugs. Table 2 below demonstrates the number of Internet electronic reports received quarterly since October 2002.

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Number of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>October—December 2002</td>
<td>32</td>
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<tr>
<td>January—March 2003</td>
<td>56</td>
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<tr>
<td>April—June 2003</td>
<td>77</td>
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<tr>
<td>July—September 2003</td>
<td>79</td>
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<tr>
<td>October—December 2003</td>
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<td>January—March 2004</td>
<td>83</td>
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<tr>
<td>April—June 2004</td>
<td>106</td>
</tr>
<tr>
<td>July—September 2004</td>
<td>99</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>598</strong></td>
</tr>
</tbody>
</table>
4. To encourage and promote awareness of electronic reporting, a new, distinctive website providing rapid and direct access to the electronic Yellow Card (yellowcard.gov.uk) was launched on 19 February 2004. The Agency is working to promote and increase the awareness and usability of the electronic Yellow Card.

THE REVIEW OF ACCESS TO THE YELLOW CARD SCHEME

5. On 21 July 2003, Ministers announced an independent Review into the access to and use of data collected by the Yellow Card Scheme. The Review was led by—Dr Jeremy Metters—former Deputy Chief Medical Officer.

6. The “Report of an Independent Review of Access to the Yellow Card Scheme” was published on 4 May 2004 to coincide with the 40th anniversary of the Scheme. The full report includes 24 main recommendations including to allow greater access to the data generated by the Yellow Card Scheme to ensure the full potential of the data is realised. A full public consultation exercise (MLX 308) was commenced on the recommendations and ended on 28 July 2004. The MHRA is currently reviewing the responses received and in light of the results the MHRA/CSM will consider each of the recommendations of the Review.

7. One recommendation has been accepted immediately by Ministers—the introduction of patient reporting to the Scheme. A Working Group has been set up to advise on the piloting of different arrangements for patient reporting of suspected ADRs and on methods to gauge their effectiveness.
Memorandum by “NO FREE LUNCH UK” (PI 05)

We are a group of medical practitioners who seek to challenge the current relationship between the pharmaceutical industry and the medical professions. We have had direct contact with industry and its representatives in the front line of the NHS. We are aware of widespread conflicts of interest in medicine that both undermine confidence in the professions and have a direct detrimental impact on patient care. We are concerned by the increasingly medicalisation of society which in turn is undermining societies sense of well being. We accept that the industry has a legitimate right to pursue profit but equally we have a professional obligation to protect our patients from organisations whose motivation is profit.

No other public servants would be allowed the level of hospitality enjoyed by the medical professions. We are calling for a compulsory register of contact, hospitality, fees and gifts for medical professionals. This would be open to peers and the public.

Lastly the current voluntary code of practice through the ABPI is inadequate and we call for more robust regulation of this £9 billion industry that so directly affects peoples lives.

We have no conflicts of interest in this campaign and merely seek to protect the profession and our patients.

Terms of Reference

Drug innovation

We share concerns that much research is not “innovative” but focussed on “me too” preparations which seek to gain market share in established profitable markets. The diseases of the developing world which kill many millions prematurely receive limited interest or funding from an industry fixated with the “risk factors” of first world populations.

The conduct of medical research

We echo the widely voiced concerns over “ghost writing”, suppression of results, “Scientific imperialism”, publication bias and the use of editorial “spin”. We question why results from the industry are more likely to show a positive outcome than those sponsored by no profit organisations.

More specifically in the UK we are concerned by the practice of “research for profit”. This is often conducted in General Practice where patients agree to be included in research for altruistic reasons yet the doctors can receive thousands of pounds profit per patient enrolled into the study. This constitutes a direct conflict of financial interest and is widespread in the UK with some practice making £50,000 per year from this work.

The provision of drug information and promotion

A widespread hospitality culture exists in the NHS focussed mainly at doctors but also other health care professionals. The hospitality engenders “goodwill” and allows the industry to gain access to health care professionals. Minor promotion hospitality involves the provision of pens, mugs, lamps and sandwiches. This minor hospitality is a daily occurrence for many doctors.

More troubling and inappropriate hospitality involves expensive lunches (£50 plus) and the use of exclusive hotels (Gleneagles, Turnberry etc). This is common practice. The most important opinion leaders may be involved in hospitality that involves international flights and provision quality hotels abroad. These opinion leaders may in addition be offered lectureship fees and consultancy fees. This hospitality is undeclared and local registers of financial dealing are not kept by hospital or general practitioners.

The ABPI code is broken on a daily basis but both sides have strong vested interests in not reporting these breaches. We argue that doctors are no different from other public servants and these levels of hospitality would not be tolerated in other public sectors. This hospitality culture is highly effective at changing prescribing habits and raising drug costs.

The pharmaceutical industry currently employs “third party” agencies to deliver care widely across the NHS. This might involve drug “switching” on general practice databases or offering direct face review of patients by industry sponsored agents. A potential financial conflict exists with all this activity.

Professional and patient education

“Promotional hospitality masquerading as education” is the best description of the current provision of education by the industry to the NHS. Education is the “foot in the door” pretext of much of the contact and the hospitality between the NHS and the industry. Unfortunately this education for professionals is skewed with agenda setting by the industry and with speakers paid directly by the industry. Quality independent education could be provided at a fraction of the cost through the NHS.
The written material provided by the industry that is relied upon by many doctors is promotional and lacks a strong evidence base.

The pharmaceutical industry directly and indirectly has influence over patient education. Education is delivered through the media either by the use of advertisements in "disease awareness campaigns" or the use of industry friendly journalists. Past examples of industry sponsored campaigns include conditions like depression, anxiety and obesity. Distorted messages bombard the public and serve to undermine our collective sense of well being. The industry and its commercial interests are perhaps the single most powerful force in setting health agenda.

We are concerned about motivation of the pharmaceutical industry involvement with patient advocacy groups.

**Regulatory review of drug safety and efficacy**

No comment.

**Product evaluation, including assessments of value for money**

No comment.

**Summary**

We welcome this opportunity to provide a brief memorandum and would be happy to expand on this if called to give oral evidence. This inquiry is timely as there is a pressing public interest to challenge the relationship between health care professionals and the pharmaceutical industry.

We recommend at the very least a compulsory and open register of contact, hospitality, fees and gifts for medical professionals.

29 July 2004

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**Memorandum by the Consumers’ Association (PI 53)**

1. **Summary**

1.1 Consumers’ Association (CA) welcomes this Inquiry into the influence of the pharmaceutical industry (Industry). This investigation provides a timely opportunity to scrutinise how Industry affects Government, regulators, healthcare professionals and consumers and to assess the effects of this influence on public health. We are concerned that a weak and uncoordinated regulatory system is enabling the Industry to further its own interests without sufficient regard to public health.

1.2 Specifically, CA has identified serious shortcomings in the way that drug promotion is handled by the numerous bodies involved with regulation in this area and in relation to the process for reclassification of medicines. Misleading advertisements to healthcare professionals and more covert promotional campaigns aimed at the public can run unchecked—and proliferate—due to inadequate procedures for monitoring and enforcement. This leads to significant decisions being taken in relation to individual healthcare and prescribing which may impact negatively on both an individual level and on the wider NHS, for example, in relation to unnecessary expenditure or inappropriate treatment.

1.3 Equally, we have serious concerns about the process for selecting and approving medicines for reclassification. The process is driven by inappropriate targets and without due consideration to public health need or a satisfactory level of safety and efficacy data. This exposes the public to potentially serious adverse reactions or, at the very least, to spending money on treatments that are ineffective.

1.4 Fundamentally, medicines policy is not well-coordinated between agencies and the medicines regulatory system is characterised by a lack of clarity, transparency and openness, minimal consumer representation and an approach more geared to the needs of industry than to public health protection.

1.5 We believe that the following actions are essential to ensure that public health is the paramount objective of pharmaceutical policy:

   — The Medicines and Healthcare products Regulatory Agency (MHRA) needs to ensure that all its work is undertaken in the interests of public health protection. This would be facilitated by appropriate involvement of lay representatives and representatives of all key stakeholders, in particular, patients and the wider public. The medicines regulatory system as a whole also needs to be subject to far greater transparency and clarity and communication over roles, remits and responsibilities to ensure accountability and swift and effective action where necessary. Other regulatory bodies, such as the Food Standards Agency, hold Board Meetings in public and make minutes of meetings available on their website. These practices should be adopted by the MHRA. An independent review of the medicines regulatory system would be timely. The Government needs to take action to ensure an integrated medicines policy.
2. INTRODUCTION

2.1 CA is an independent, not-for-profit consumer organisation with around 700,000 members. Based in the UK, it is the largest consumer organisation in Europe. Entirely independent of government and industry, we actively campaign on behalf of consumers and are funded through the sale of our Which? range of consumer magazines and books. We campaign on a wide range of issues relevant to consumers, of which a key example is health. Our health campaign aims to ensure all consumers have access to safe, high-quality and patient-focused healthcare whenever and wherever they need it, and they have the necessary information and support to be able to make informed decisions about their healthcare. This aim is supported through consumer and health policy research, Which? magazine reports and Treatment Notes—a bulletin written in conjunction with Drug and Therapeutics Bulletin (DTB)—which provides patients with independent medicines and treatment information.

2.2 CA has had a long-standing interest in medicines policy. DTB plays an important role in helping prescribers by providing information about the effectiveness and safety of treatments. As part of its role in informing healthcare professionals, DTB has discovered and highlighted instances where promotional material to healthcare professionals is misleading or inaccurate and has also identified concerns with the level and type of information provided through authorised documents, such as the Summary of Product Characteristics.

2.3 CA also deals with broader policy issues about medicines from a public perspective. We have a particular interest in user involvement at all levels of decision-making, from decisions about individual treatment through to involvement in wider policy decisions about which specific treatments are provided on the NHS and why. CA has researched and published reports on the patient information leaflets that are included with all prescription drugs, on the promotion of prescription drugs directly to patients, on the outcome of a CA inquiry into how well NICE works from the patient perspective and on the provision of patient information.

2.4 In the first half of 2004, we conducted research with consumers on their perceptions and attitudes to medicines’ use, and also with general practitioners on their attitudes to promotional material and contact from pharmaceutical companies. This memorandum highlights some of this research, as well as drawing on our earlier relevant research. Additionally, we are continuing to conduct research in this area and will keep the Committee updated on any relevant future work.

2.5 Our research and campaigning activities have centred predominantly on the following three areas, which will provide the focus for our submission:

— the provision of drug information and promotion;
— professional and patient education;
— regulatory review of drug safety and efficacy.

3. THE REGULATORY CONTEXT

3.1 Protecting the public and consumer interest must be at the heart of any regulator’s powers, decision-making and actions. While the MHRA (formerly the Medicines Control Agency; MCA), in common with most regulators, has a public interest/consumer protection objective, this is challenged by objectives relating to protection of the interests of the pharmaceutical industry.

3.2 The MHRA has a dual role: protection of public health and the service it must deliver to industry, for example, in relation to licensing. This was highlighted by the National Audit Office (NAO) in its report on the MCA in January 2003. The original requirement to avoid creating “unnecessary impediments” to the pharmaceutical industry became “to facilitate the development of a successful UK pharmaceutical industry for the benefit of the wider interest of the UK economy” in the Agency’s 2001 Corporate Plan. This

was reflected in its close involvement with the Pharmaceutical Industry Competitiveness Task Force (PICTF) set up by the Government in March 2000. In the 2004 Corporate Plan, this wording refers to supporting innovation “without unnecessary regulatory impediments”, but the challenges of the dual role remain.

3.3 The MHRA must meet clear expectations of Industry to provide an efficient service in return for fees. This is supported by performance targets based on factors such as the speed with which new drugs are assessed. While, in theory, such targets may bring benefits for patients, this is clearly not the case if they are pursued at the expense of a thorough review and an emphasis on safety and public health protection. The pressure on the MHRA to compete in a European regulatory environment is likely to exacerbate this situation. The NAO report states: “Most regulators focus on measuring the efficiency of their operations by reference to the speed with which they assess new drugs …”. In the European Union, where companies can choose where to place their business based on speed and quality of service of the regulator, success in competition for regulatory work can also be used as a performance measure”.2

3.4 The relationship that Industry has with Government is also significant. The MHRA’s Corporate Plan 2004 refers to the “important role to play in ensuring that key ministerial objectives for the health service are achieved, including the wider availability of medicines”.3 This complements the vision within the Wanless Report (2002)4 of a future in which “people increasingly take responsibility for their own health and well-being”. However, while ensuring the wider availability of medicines in this way may benefit the public, it is not necessarily the case. For example, where there are concerns over the safety or efficacy of the medicines being reclassified, where the medicines being selected for reclassification are not those that would most benefit public health needs and/or where the support and monitoring systems are insufficient.

3.5 There is a need for meaningful public scrutiny and input into the setting of the key parameters for the MHRA. Regulatory decisions should take the protection of the consumer as a starting point and be based on cost-benefit analyses which address potential consumer detriment.

**Funding**

3.6 The MHRA is one of only two European medicine regulators fully funded by Industry. CA’s experience with regulators across a range of sectors indicates that the way a regulator is funded does appear to influence the way it operates. Government-funded regulators seem to be better at acting independently of industry or professional interests and to take a more robust approach to promoting the public interest or consumers’ interests. Where funding is provided by those who are regulated, there appears to be greater problems in ensuring the independence of the regulator.

3.7 As the NAO report states, “funding from the pharmaceutical industry can enhance efficiency but reliance is a cause for concern for stakeholders”.5 The MHRA states that funding does not in itself pose a conflict of interest because there are independent committees to act as a safeguard. We have concerns about the extent to which these committees operate transparently and draw on expertise from outside the Industry. If the MHRA is to operate, and be seen to operate, in the interests of the public then transparency and accountability are of the utmost importance.

**Transparency**

3.8 Regulators must command public confidence by operating in a fair, open and transparent way to benefit all consumers. Fundamental to this is ensuring that there is access to information and that most of the information regulators base their decisions on is in the public domain. Consumers should be able to find out easily what the body does, readily access its services and find out what decisions it is taking and how. Currently, it is extremely difficult to obtain information from the MHRA and most of its decision-making remains opaque, for example, in the recent decision to reclassify the prescription-only medicine, simvastatin, as an over-the-counter (OTC) product, Zocor Heart-Pro. The NAO report referred to consultations with patient groups and other stakeholders, concluding that “there was scope to improve the transparency of these consultations”.6

3.9 Greater openness and transparency would be facilitated by:

— Board meetings and key committee meetings held in public (as with the Food Standards Agency).
— Board meetings publicly advertised in advance.
— Publication of Board papers and decisions.
— A requirement to provide all information requested by consumer groups and other parties unless it is genuinely commercially sensitive or personally confidential information.

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4 Wanless, D Securing our Future Health: Taking a long Term View. April 2002.
— Effectiveness on openness and transparency to be regularly assessed and reported on in the Annual Report.

3.10 Access to information concerning any of the regulator’s decisions or policies is vital to ensure openness, transparency and accountability. While CA recognises the legal requirement to protect genuinely sensitive market information, we are concerned that the MHRA adopts a very restrictive approach to sharing information.

ACCOUNTABILITY THROUGH CONSUMER REPRESENTATION AND INVOLVEMENT

3.11 Parliamentary scrutiny is necessary, but not sufficient, to ensuring regulators are publicly accountable. Consumer representation and involvement is part of that process, as is greater engagement with stakeholders through meetings and wider publicity of the role and purpose of regulators. The MHRA has an advisory structure of independent committees. However, these committees are fairly “closed” with very little consumer representation in decision-making. The MHRA Business Plan (2004) refers to the “facilitation and encouragement of lay and patient representation on these bodies wherever it is appropriate” but it is unclear what constitutes “appropriate”. Where lay representatives are currently involved, they are in the minority. CA believes that regulators must seek out and incorporate consumer views at all stages of their work, including development of policy, and that a variety of methods for actively consulting with the general public should be adopted, with views being incorporated into decision-making. While the creation of special interest committees which incorporate consumer representation is a step in the right direction, there nevertheless needs to be independent consumer representation in every aspect of the regulator’s remit.

3.12 More robust promotion of the consumer interest may be aided by a separate body or structure within the regulatory framework that has a clear mandate to promote and protect consumer interests. In order to be truly independent and have sufficient authority, any consumer panel or committee must have:

— The ability to definite its own remit, set its own agenda, decide on its own priorities and which issues to investigate, and appoint its own chair.

— Its own separate funding, which provides adequate resources for the job, including to commission its own research.

— Rights to access any necessary information.

3.13 There is a clear need for an independent review of the MHRA, going beyond the scope of the NAO report. In particular, this review should consider:

— the extent to which the regulator’s public interest objective is undermined by its relationship with Industry;

— ways in which the regulator’s workings could be made more transparent and accountable; and

— means of ensuring effective consumer representation and involvement.

4. The provision of drug information and promotion

4.1 The public and healthcare professionals need high-quality drug information, and the pharmaceutical industry has a legitimate interest in promoting its products. Both information and promotion need to be delivered in a transparent framework which safeguards the public interest and has clear, meaningful sanctions if this interest is undermined. At present, this is not the case. Our research has uncovered substantial use of covert promotional techniques to the public and illegal advertising to healthcare professionals.

THE PROVISION OF DRUG INFORMATION AND PROMOTION TO THE PUBLIC

4.2 While there is a great deal of health information available to the general public, much of this is misleading, inaccurate or simply does not meet individual needs. Where high-quality, independent information does exist, it is difficult for consumers to know where to look for it and whether they can trust it. In our policy report “Patient Information: What’s the Prognosis” (2003), CA called for an overhaul of patient information. This included the establishment of an independent body to oversee the development and implementation of an effective patient information strategy that would meet the information needs of patients and carers for independent, accessible and objective information. Through this work, which involved consultation with patient and carer organisations, we identified ten core principles that we maintain should underpin high-quality standards for information. Information that conforms to these standards would be: accessible, accurate, appropriate, consistent, current, evidence-based, non-biased, timely, transparent and understandable.

4.3 The pharmaceutical industry cannot, by definition, produce this kind of information. However, it does seek a role in providing patient information and education. In particular it has lobbied, to date unsuccessfully, for a relaxation of the laws prohibiting direct-to-consumer advertising (DTCA) of promotion drugs with the intention of “improving” patient information. In the United States of America
and New Zealand, where DTCA is currently permitted, it has led to dramatic increases in the drugs bill; increased unnecessary use of medicines; distorted prescribing behaviour; and exposed the public to numerous misleading and inaccurate advertisements through the popular media.

4.4 CA is continuing to research this area to further evaluate how the patient information environment is developing and will keep the Committee informed of its work.

Patient Information Leaflets (PILs)

4.5 PILs are required by law to accompany all medicines and are the key piece of information that drug companies are legally required to provide patients. They are also likely to be the only information that an individual will have when collecting a prescription or buying an over-the-counter medicine. They contain essential information about how to take the medicine and about potential interactions with other medicines and side effects and what to do if these occur. The PIL must be produced in line with the Summary of Product Characteristics (SPC) which is provided to healthcare professionals and is authorised by the regulatory authority as part of the drug licensing process.

4.6 CA focus group research with patients, published in June 2000, found that patient information leaflets failed to give patients the information they need in a way that is easy to understand. Small print and too much information, combined with poor layout and overuse of medical jargon were the key problems. This was despite a legal requirement that leaflets “should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensive information” and “must be written in clear and understandable terms”. These concerns were echoed in the NAO report on the MCA. The Association of the British Pharmaceutical Industry (ABPI) has argued that legislation which determines the content of the patient information leaflet prevents it from addressing such inadequacies. However, this is not the case. Companies can improve patient information leaflets to make information clearer and more meaningful to users within the legal framework.

4.7 CA has long argued for user-testing to ensure that patients can read and understand PILs and this has now been incorporated into European legislation. However, it is essential that this is carried out in a meaningful way, for example, according to the Australian “gold standard” approach, whereby 20 potential users of a medicine who are given a PIL are asked to find and explain 15 pieces of information. The “gold standard” is a leaflet where 16 out of 20 people can find and explain all the points. Only PILs that reach the gold standard are permitted.

4.8 CA would also like the “black triangle” (a symbol used to denote a drug that is being closely monitored) used on the PIL to help alert patients to the fact that the drug is under intensive surveillance for adverse effects and to increase pharmacovigilance data for these products. The significance of the black triangle will first need to be explained to patients.

4.9 The MHRA has a duty to ensure that PILs are developed that give people important information about medicines in a way that they can understand and should not permit any PILs to be approved that do not comply with this requirement. This should form a key objective on which the performance of the MHRA is assessed.

Direct-to-Consumer Advertising (DTCA) of Prescription-Only Medicines

4.10 DTCA is when drug companies advertise prescription-only medicines (POMs) directly to the public. Currently, DTCA is permitted in only two developed countries: the United States of America and New Zealand. The negative impact of DTCA has been well-documented and includes:

- generating “lifestyle” conditions (eg female sexual dysfunction) which could lead to an unnecessary use of medicines;
- a dramatically increased drugs bill. For example, in the USA, prescription drug sales increased by $20.8 billion between 1999 and 2000. The 50 medicines with the highest advertising budgets accounted for nearly half of the increase, with the top-selling drugs being those that were most heavily DTCA-advertised. A DTCA campaign by Novartis in New Zealand for an oral systemic antifungal called “Lamisil” (for the treatment of fungal nail infections) saw an immediate month on month doubling of prescriptions for this drug.

— source of figures BPAC / PHARMAC c/o personal communication with Les Toop, Public Health Specialist, New Zealand, 17 August 2004.
— distorted prescribing behaviour in response to increased public demand for POMs;\(^\text{13}\) and
— a down-playing of side-effects.\(^\text{14}\)

4.11 There are now calls to introduce a ban on DTCA in New Zealand as a result of its negative impact on public health.

4.12 Proposals by the European Commission that would have allowed the introduction of DTCA into Europe were defeated in EU Parliament in December 2003. As a result, there is pressure upon the pharmaceutical industry to be more creative in its promotional methods to healthcare professionals, prescribers and the public.

**COVERT PROMOTION TO THE PUBLIC—DISEASE AWARENESS CAMPAIGNS**

4.13 CA highlighted a range of methods employed by the pharmaceutical industry to promote prescription drugs which manage to circumvent DTCA in our report “Promotion of Prescription Drugs: Public Health or Private Profit?” published in July 2001. One such method increasingly used is the so-called “disease awareness campaign”. This apparently sets out to raise awareness about a particular condition or disease, such as obesity, erectile dysfunction or toenail fungal infection. It also carries the sponsoring companies’ logo, often an endorsement from an appropriate voluntary organisation, may be fronted by a celebrity and may coincide with a marketing campaign targeted at healthcare professionals for a specific branded product.

4.14 Further information is usually offered, either by way of a telephone helpline or a reply form to post. Respondents’ contact details are then held by the pharmaceutical company sponsoring the campaign. For example, Pharmacia ran an incontinence disease awareness campaign in the autumn of 2003. Using the same imagery for both public and healthcare professional promotion they named their campaign “The Public Health Education Campaign”. The voice of Anna Raeburn (a famous agony aunt) was heard on the helpline and, having registered one’s details, a letter would follow from ‘The Public Health Education Campaign’ announcing to the recipient that it was “Time to take charge”.

4.15 These campaigns are promotional and exist to increase demand for companies’ products. This may be clearer in some cases than others. One example clearly directing people to their GP is Novartis’ longstanding Stepwise campaign on feet and nails. This features a booklet “Feet & Nails—stamping out fungal nail infection and athlete’s foot” which was produced in association with The Society of Chiropodists and Podiatrists promotes Lamisil (terbinafine). Page 6 states: “Although you may find a limited selection available over-the-counter at your local pharmacy, the most effective ones are only available from your doctor . . .”.\(^\text{15}\)

4.16 As with DTCA, disease awareness campaigns tend to focus on what has been termed “lifestyle” conditions and offer drug solutions, albeit more covertly and therefore potentially more dangerously.

4.17 Further examples of covert Industry promotions can be through media editorials. The MHRA confirmed to CA\(^\text{16}\) that while it considers each advertising complaint in relation to reporting individually, it adopts the view that print content is deemed promotional only by intention. The letter from the MHRA states: “. . . where promotion does occur but it is incidental and subordinate to another purpose such as providing the reader with information then the material is not ‘designed to promote’ and is therefore not caught by the Regulations . . . the fact that a positive review of a medicine may encourage readers to seek it out is incidental in our view and does not equate to a finding that the article was written for that purpose . . . balanced information from a patient organisation including the range of medicines available would be considered differently from the situation where a pharmaceutical company provides some of the same information but including only the one product it markets.”

4.18 Advertising is not the same as comprehensive, unbiased information. The media is a popular way of planting advertorials placed by, or on behalf of, Industry through articles that are not based on legitimate assessments of drugs. It is important that the MHRA encourages all health writers and editors to promote and undertake responsible reporting, and for them to be held accountable where there are such breaches of the Advertising Regulations.

**PATIENT GROUP/CHARITY-FRONTED CAMPAIGNS**

4.19 As the public tends to distrust information provided directly by Industry,\(^\text{17}\) using patient organisations to front campaigns can effectively mask drug companies’ involvement and enable them to engage with an audience they may not otherwise have access to.

4.20 The potential benefits to Industry of collaboration with patient groups are immense.

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\(^{13}\) Mintzes, B. Influence of direct to consumer pharmaceutical advertising and patients’ requests on prescribing decisions: two site cross sectional survey, *BMJ* 2002;324:278-279.

\(^{14}\) Charatan, F. Bayer decides to withdraw cholesterol lowering drug. *BMJ* 2001;323:359.

\(^{15}\) see also Jackson, T., *BMJ* 2003;326:1219 (31 May).

\(^{16}\) letter from MHRA to CA 1 April 2004.

4.21 While some (typically larger) charities have a clear and accessible policy on their links with Industry, in general, there is a distinct lack of transparency about such relationships.  

4.22 In 2002, GlaxoSmithKline (GSK) produced, and funded, a Mr Sneeze booklet on allergies (working with the charity, Allergy UK). This targeted children, effectively promoting two of its over-the-counter (OTC) products, Piriton and Piriteze: the last few pages of this document were specifically about the products. Although promotion of OTC products to children is illegal, the Proprietary Association of Great Britain (PAGB) nevertheless approved the Mr Sneeze book. In October 2003, the MHRA upheld a complaint about this underhand tactic of using children for promotional purposes. As a result, GSK was required to separate the promotional pages from the rest of the booklet. However, the MHRA’s action came too late and did not go far enough. It did not prevent the information from finding its target audience, so allowing children to be used as a means to promote GSK products.

4.23 The first Allergy UK, knew of any controversy regarding the illegal promotion within the book was when it was approached by the media. This caused embarrassment by drawing unwanted attention to the charity.

4.24 Drug companies have also been known to use public relations companies to assist with promotional activity. For example, The Observer newspaper discovered that Burson-Marsteller, a public relations firm, managed to persuade various celebrities to support a “sophisticated lobbying campaign” masked as a crusade to introduce a new NHS screening test that could supposedly save the lives of thousands of women. However, celebrities contacted by The Observer said they had no knowledge of the lobby group.

4.25 Other creative techniques have involved using general practitioners as the go-between in eliciting feedback from patients. In the case of Cipralex, an antidepressant, general practitioners were provided with feedback pamphlets and asked to complete “think bubbles”—one outlining the patient experience; the other the general practitioner experience. As a reward for doing so, the drug company pledges a £1 donation to the charity, Depression Alliance.

4.26 Charities, particularly smaller ones that are less well funded, need to be protected from exploitation while at the same time accepting their duty to behave fairly and responsibly. Patient organisations should have accessible, clear and transparent policies for collaborating with corporate sponsors. We understand the Long-term Medical Conditions Alliance is intending to revise its own guidelines.

4.27 Existing disease awareness guidelines are insufficient to address the impact and extent of the covert promotion. Our research with GPs in May 2004 shows that they are concerned about disease awareness campaigns and other covert promotions, but are resigned to them being funded by industry in the absence of alternative funding.

4.28 The GPs expressed irritation at having to rectify misconceptions fostered by inappropriate (lifestyle) disease awareness campaigns. They also reported that they will sometimes prescribe according to patient demand, even when they may not consider such a prescription to be the most appropriate. Doctors referred to it being too complicated to explain the “ins and outs” of other, potentially more appropriate and possibly cheaper medicines. In theory the GPs objected to prescribing upon request, but in reality they admitted to doing so. This finding has also been reported in the USA.

4.29 In short, the influence of the Industry, channelled through individual patients, can mean that patients are prescribed drugs that are inappropriate for them and which may not be the most cost-effective. This pressure towards inappropriate prescribing is complemented by the simultaneous pressure of advertising and promotional activity targeted directly at healthcare professionals.

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21 CA: Attitudes to Medicines’ Promotions to the Public and General Practitioners—a qualitative study with GPs, May 2004 (unpublished).
22 CA: Attitudes to Medicines’ Promotions to the Public and General Practitioners—a qualitative study with GPs, May 2004 (unpublished).
THE PROVISION OF DRUG INFORMATION AND PROMOTION TO HEALTHCARE PROFESSIONALS

4.30 The pharmaceutical industry has considerable influence over the information received by healthcare professionals. Drug companies are allowed to advertise directly to such individuals. However, illegal promotional activity often goes unnoticed or unpunished so providing no real disincentive against repetition.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

4.31 The Summary of Product Characteristics (SPC) for a medicine is written by the holder of the marketing authorisation for that product (typically the drug manufacturer) to provide crucial prescribing information for medicine and complements information contained in the patient information leaflet (PIL). It is essential that the SPC is full and complete and is able to aid the prescriber in anticipating and minimising the risk of preventable side-effects. However, research published by DTB demonstrates how drug companies often fail in this regard.25

DRUG COMPANY REPRESENTATIVES

4.32 Drug company representatives play an essential role in influencing prescribing behaviour. CA’s research with GPs (May 2004)26 revealed that many doctors tend to enter into a symbiotic relationship with pharmaceutical companies. The doctors are aware that pharmaceutical companies do not act altruistically but do offer them a number of perceived benefits. For example, in spite of acknowledging the marketing elements to their relationships, they derive what they consider to be “educational benefits” from being informed of a particular treatment. Furthermore, it is easy to maintain relationships with representatives as it requires little proactivity from the GP.

4.33 Our research highlights the value some GPs place on their relationships with drug representatives, particularly as a source of education and information. What is in reality promotion is perceived by many of the GPs we surveyed to be “educational”. This form of misinterpreted “education” may then become a steady influence on prescribing behaviour. The pharmaceutical industry can ensure a service is “up to the minute” by paying GPs £15 for providing feedback on drug representatives (www.gpreply.net).

4.34 Even a small item, such as a post-it pad or pen from a company representative that offers a prescribing suggestion for a given diagnosis, may have a disproportionate distorting influence on prescribing behaviour while appearing to be a harmless and inexpensive gift.

4.35 GPs are short of time and may find it difficult to keep themselves updated.27 It is unacceptable that GPs should have to rely on being “educated” by drug representatives, whose sole purpose is to influence prescribing behaviour towards their companies’ products.

PUBLIC-PRIVATE PARTNERSHIPS

4.36 Drug representatives are not the only means of contact that doctors have with Industry. Following the Pharmaceutical Industry Competitive Task Force (PICTF) report, there has been an increase in public-private partnerships between Industry and the NHS, with questionable results for the public. An editorial in Pulse magazine28 (a weekly publication for GPs) refers to an example of the “creeping involvement in primary care” whereby Pfizer agreed to reimburse North Staffordshire Health Authority if its drug—atorvastatin—failed to cut cholesterol levels to target. The commentary reports that proponents consider joint working as being “open and transparent” while others recognise it as “another disturbing example of corporate influence on prescribing”. The article concludes that while it “must be right to test schemes with the potential to improve prescribing of effective drugs . . . such a significant shift in the relationship between drug firms and doctors should not be allowed to happen by stealth. It’s time the Government came clean on how much industry influence it wants. It should start by providing a solid ethical framework to guide GPs.”

ADVERTISING: PRE-VETTING, MONITORING, COMPLAINTS AND ENFORCEMENT

“The ‘glittering prize’ (the drug) goes to the marketer who pushes the boundaries of regulations to the point where one micron would be a breach’. . . The Code acts like a speed camera—catching offenders only when the film is operating, making it a risk-taker’s environment’. . . the Code is a collection of random rules that is supposed to protect the vulnerable, but only succeeds in randomly persecuting companies and does not improve real ethical sales environment.”


21 SPCs failing—What DTB found “Failings in treatment advice, SPCs and black triangles”, Vol 39 No 4 April 2001.
26 CA: Attitudes to Medicines’ Promotions to the Public and General Practitioners—a qualitative study with GPs, May 2004 (unpublished).
27 CA: Attitudes to Medicines’ Promotions to the Public and General Practitioners—a qualitative study with GPs, May 2004 (unpublished).
4.37 The current regulatory systems for handling pre-vetting, monitoring and complaints in relation to advertising and promotion are inadequate and, as such, put public health at risk. The MHRA has, itself, confirmed that it cannot vet all promotional material and that the vetting system “in part relies on concerns being drawn to its attention because of the volume of advertising material”.29

4.38 The process of handling complaints about promotion is complicated by the existence of various bodies with responsibilities in this area (each with different powers), for example, the Medicines and Healthcare products Regulatory Agency (MHRA—which has statutory powers), the Proprietary Association of Great Britain (PAGB), the Prescription Medicines Code of Practice Authority (PMCPA), both of which operate Industry self-regulation, and the Advertising Standards Authority (ASA). In addition, OFCOM has statutory powers for broadcast advertising which will be contracted out to the ASA (late 2004). Crucially, there appears to be no coherent relationship between these bodies. For example, the ASA recommends that the MHRA addresses complaints about prescription-only medicines (POMs). Both the MHRA and the ASA can address complaints relating to advertisements for over-the-counter (OTC) medicines. The PMCPA may respond to a received complaint or investigate independently.

4.39 The PMCPA does not communicate with the MHRA in any procedural manner. One consequence is that both the MHRA and the PMCPA may end up investigating the same complaint and reaching different conclusions.

4.40 This occurred, for example, in the case of advertising for the oral contraceptive, Yasmin30 (see paragraphs 4.45–4.54), whereby the, then, Medicines Controls Agency (now the MHRA) and the PMCPA initially took different views about whether the advertisements for Yasmin were in breach of the Advertising Regulations.

4.41 A subsequent difference of opinion between the PMCPA and MHRA arose following concerns raised by DTB about promotional messages on Janssen Cilag’s website for women taking the oral contraceptive, Evra.31 The PMCPA found the company to be in breach of the Authority’s Code of Practice on advertising, but the MHRA took the view that information on the website provided an aid to concordance rather than promoted the product. The MHRA stated that its judgement on whether or not the website content was deemed to be promotional was based on the “overall presentation of the materials”.32

4.42 The time taken for the MHRA and PMCPA to process complaints and deliver final rulings is often unacceptably long.33 Both the MHRA and the PMCPA treat the proceedings of any investigation as confidential until such time that they are published. However, by the time a complaint has been investigated and a ruling delivered, the drug company’s promotional campaign may well have run its course. In the case of Yasmin, around six months elapsed between the time that the advertising was first launched and when it was “voluntarily” withdrawn, as a result of the MHRA’s revised decision to request this.

4.43 A drug company found to have breached Advertising Regulations by the MHRA may be required to issue a corrective statement about any misleading claim. However, delayed publication of such statements obviously reduces their impact, particularly if it occurs several months after the start of the campaign. In the past, DTB has had to urge the MHRA to ensure statements are issued (eg as with an advertisement for Yasmin).34 Where an advertisement has been found to be in breach of the Advertising Regulations, it should be mandatory that prominent publication of a corrective statement is made immediately.

4.44 DTB articles have highlighted a total of seven examples of misleading or inappropriate promotion in the last two years. All examples relate to prescription-only medicines from different companies, perhaps suggesting an Industry-wide tendency to mislead. In six of these cases, the Prescription Medicines Code of Practice Authority (PMCPA) responded to the articles by investigating the relevant promotion and publishing its findings.

4.45 The promotion of the oral contraceptive pill, Yasmin, provides a clear demonstration of various inadequacies in the pre-vetting and complaints system.

4.46 Product:

Yasmin; Drug company—Schering Health Care. Is Yasmin a “truly different” pill? (DTB article published August 2002).

Yasmin advert withdrawn—why and how (DTB article published March 2003).


31 correspondence from MHRA to CA, dated 1 April 2004.
32 MHRA letter to CA, 1 April 2004.
4.47 In April 2002, Schering Health Care (Schering) launched Yasmin in the UK, claiming, in an advertisement to healthcare professionals, that the medicine was “the pill for well-being” and that “Yasmin is different in many ways. It has been shown repeatedly to have no associated weight gain. In addition, Yasmin has a demonstrable effect on PM (pre-menstrual) symptoms and on skin condition... Women feel well on Yasmin. Make a difference to their lives and prescribe Yasmin.”

4.48 DTB published a review of Yasmin in August 2002, which concluded that “we believe that the claim that Yasmin ‘is the pill for well-being’ is unjustified and misleading and should be withdrawn.” In response, Schering threatened (on 9 September 2002) to sue DTB for defamation.

4.49 Prompted by DTB’s article, the PMCPA began an investigation into the promotion of Yasmin and concluded (on 18 September 2002) that Schering had breached the Authority’s Code of Practice on several counts. As a result, the company withdrew its threat to sue DTB. The PMCPA later confirmed its initial findings (after rejecting an appeal by Schering), in concluding (on 22 November 2002) that the company had breached the PMCPA’s Code of Practice on 11 separate counts.

4.50 The Yasmin advertisement had originally been vetted by the MCA (now the MHRA) in late Spring 2002. The MCA told Schering (in a letter dated 13 June 2002) that its promotional claims for Yasmin were acceptable. The findings of DTB (subsequently echoed in the PMCPA investigation) suggest a serious failure in the MCA’s original vetting of the advertisement.

4.51 Although the PMCPA first ruled against the Yasmin advertisement in September 2002, the delayed action by the MCA allowed the company to continue the misleading promotion unchecked for around two months after DTB first highlighted the misleading advertisement (and in total, for around six months from the product’s launch).

4.52 It is also clear that the MCA did not keep in close contact with the PMCPA during their respective investigations of the Yasmin advertisement. For example, the MCA did not know that the PMCPA was investigating DTB’s concerns until alerted by DTB itself. Similarly, the MCA did not know that PMCPA’s rulings had been confirmed (following rejection of the appeal by Schering) in late November.

4.53 As a result of DTB’s August 2002 article, the MCA undertook a second assessment of Schering’s claims for Yasmin. Only on 6 December 2002 were the results of this investigation released in a letter to DTB. On this second occasion, the MCA found Schering’s promotional claims for Yasmin wanting. As a result, the Agency asked the company to withdraw the advertising and to publish a corrective statement in journals that had carried the original advertisement. This correction appeared in late February 2003 (around 10 months after the launch of Yasmin).

4.54 The MCA’s slowness and secrecy in dealing with this issue were wholly unacceptable, particularly in view of the likely effects of the misleading advertisement on prescribing practice.

4.55 Other recent examples of misleading advertising identified by DTB include the following (paragraphs 4.56–4.62):

4.56 Product: pimecrolimus (Elidel); Drug company: Novartis

Pimecrolimus cream for atopic dermatitis (DTB article published May 2003).

PMCPA proceedings: initiated 19 May 2003; case completed 11 July 2003; publication August 2003.

An advertisement for pimecrolimus cream (a treatment for atopic dermatitis) depicted a sleeping child, who appeared to be much younger than two years of age. Since the drug is not licensed for use in children under two years old, DTB considered that the picture could mislead prescribers. The PMCPA agreed that the image and accompanying text gave the impression that the child was less than two years old and concluded that, in this regard, the advertisement was misleading and inconsistent with information in the product’s Summary of Product Characteristics. Two breaches of the Code of Practice were ruled.

4.57 Product: Cerazette; Drug company: Organon

Is Cerazette the minipill of choice? (DTB article published September 2003).


Advertisements for the oral contraceptive pill Cerazette claimed that it had “the efficacy of a combined pill with the reassurance of an oestrogen free pill”. However, DTB disputed this on the basis that there were no published trials directly comparing Cerazette with a combined oral contraceptive. The PMCPA agreed that the claim was misleading and ruled that Organon had committed one breach of its Code of Practice.

4.58 Product: memantine (Ebixa); Drug company: Lundbeck Ltd

Memantine for dementia? (DTB article published October 2003).

PMCPA proceedings: initiated 19 February 2004; case completed 1 April 2004; publication May 2004.
DTB could find no robust scientific evidence to support Lundbeck’s claim that with memantine therapy (a treatment for Alzheimer’s disease) “improvements in activities of daily living help patients to maintain a degree of independence and easier to care for, potentially avoiding the need for nursing home care”. Acting on DTB’s criticisms, the PMCPA ruled that the company had committed four breaches of the Code of Practice.

4.59 Product: Evra; Drug company: Janssen-Cilag:

Evra—a patch on oral contraception? (DTB article published December 2003).


DTB found that Janssen-Cilag’s website for women using the Evra patch was carrying the slogan “Evra The Right Contraceptive Choice”, apparently in breach of Advertising Regulations on promotion of prescription-only medicines. DTB informed the MHRA about this finding and, as a result, the company was asked to remove the slogan. DTB also questioned the claim on the website that Evra was “just as effective as the contraceptive pill”, because it could find no convincing evidence on whether the patch was any more or less effective than a combined oral contraceptive pill. As a result of DTB’s exposure of the use of the slogan “Evra the Right Contraceptive Choice”, Janssen-Cilag “voluntarily” admitted this use to the PMCPA. The PMCPA ruled that the company had breached the Code of Practice on two counts. The PMCPA also initially concluded that the claim “just as effective as the contraceptive pill” was “not factual or presented in a balanced way”. However, the PMCPA later reversed this latter decision following an appeal by Janssen-Cilag.

4.60 Product: voriconazole (Vfend); Drug company: Pfizer

Caspofungin and voriconazole for fungal infections (DTB article published January 2004).


Promotional claims for the antifungal medicine voriconazole included that it “significantly improved survival in invasive aspergillosis compared with amphotericin B”. However, on reviewing the relevant data, DTB concluded that “there is no convincing evidence to justify the claim that voriconazole is superior to amphotericin B at increasing survival rates in patients with invasive aspergillosis”. Subsequently, the PMCPA reached a similar conclusion in ruling that Pfizer had committed three breaches of the Code of Practice.

4.61 Product: Symbicort (budesonide plus formoterol); Drug company: AstraZeneca

Are Seretide and Symbicort useful in COPD? (DTB article published March 2004).


Promotional claims for Symbicort (a medicine licensed for treating chronic obstructive pulmonary disease) included benefits in “reducing symptoms” and “improving quality of life”. However, DTB concluded that Symbicort did not appear to improve symptom scores any more than did formoterol (one of Symbicort’s two component drugs) when taken on its own. It also concluded that there was conflicting evidence about whether Symbicort improved quality of life. These findings seemed at odds with the advertising claims. The PMCPA subsequently agreed with DTB’s view, concluding that AstraZeneca had committed 10 breaches of the Code of Practice.

4.62 Oral moxifloxacin (Avelox) is an antibacterial medicine marketed by the drug company Bayer plc, with the promotional claim that if offers “rapid relief from chest infections”. A recent DTB review of oral moxifloxacin (Moxifloxacin—a new fluoroquinolone antibacterial) has concluded that “In our view, claims that oral moxifloxacin provides ‘rapid relief from chest infections’ are unsubstantiated, may mislead prescribers and should be withdrawn.”

4.63 In relation to another promotional concern, CA complained to the MHRA in November 2003 about invitations being distributed to the public inviting them to attend Botox parties. We were informed in that month that an investigation would be conducted. Having received no further correspondence thereafter, we again contacted the MHRA and were subsequently sent a letter in August 2004 that apologised for the fact that we had not been notified in January 2004 of the outcome of the investigation and that the advertising had been withdrawn. This example provides further evidence of the MHRA failing to effectively monitor and sanction the promotion of prescription-only medicines.

4.64 The advertising complaints system needs to be harnessed and simplified, with a clearly stated protocol.
MEANINGFUL SANCTIONS

4.65. While the MHRA has strong powers in this area, even to the point of prosecution, it appears to underuse these powers, preferring to treat breaches as administrative matters.

4.66. This suggests that the interests of Industry are put before those of patients and public health, particularly since issuing of corrective statements is not mandatory for all breaches, so prescribers may be completely unaware they have been misled. Publication of complaints on websites is not an adequate substitute. The current sanctions are no disincentive for drug companies pushing the legal boundaries.

4.67. The PMCPA’s Code of Practice pamphlet13 states: “In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling.”

4.68. It also states that “Additional sanctions [are] imposed in serious cases.” The failure to appropriately enforce these sanctions reflects how the PMCPA fails to take breaches of the advertising Code of Practice by Industry seriously.36

4.69. Furthermore, what should be considered a minimum standard of conduct has even been commended by the PMCPA. For example, one reported case in 2004 of a drug company employee “inadvertently marketing a drug on a local radio station”, was registered as a “voluntary admission” in the PMCPA Code of Practice Review May 2004. Although the company was found to be in breach of the Code, the PMCPA panel nevertheless “commended” it for reporting the breach.37

4.70. In another case a “voluntary admission” to the PMCPA was recorded even though the “admission” was made only once the matter had already been raised by DTB (see paragraph 4.59). Furthermore, there was no reference to this fact in the PMCPA report.

4.71. As CA has found with the PMCPA, it would appear that the MHRA also takes a lenient view with regard to breaches of the Advertising Regulations, given its reluctance to “resort to formal procedures”.

4.72. A complete revision of the sanctions and penalties used for addressing breaches of Advertising Regulations38 needs to be undertaken as a key priority.

4.73. Redress should involve contrite corrective advertising, payment of the regulator’s legal costs and other relevant financial elements, such as a substantial fine or bearing the cost of running an Industry training seminar for the benefit of others in the Industry.

4.74. In a letter to CA of 7 January 2004, Lord Warner, Parliamentary Under-Secretary of State for Health, said that making complaints transparent via the MHRA website should prove to serve as a disincentive of bad practice.

4.75. While any such increase in transparency is welcomed, on its own it adds little value because the enforcement system and penalties are weak or expensive and complicated to operate. Publicising breaches of advertising regulations and codes is not a new phenomenon. Complaints about advertising of medicines have been published by both the PMCPA and the Advertising Standards Agency (ASA) for some time and yet illegal practice is still occurring. A combination of an effective penalties and enforcement system and subsequent publication of case investigations and outcomes is needed urgently.

4.76. The MHRA, together with other bodies in this area, has failed repeatedly to protect the public from misleading and inappropriate advertisements. The responsibility for monitoring advertising and promotion should be co-ordinated in a new, independent body with a single public interest objective, armed with meaningful sanctions and, crucially, the will to use them. An independent pharmaceutical industry advertising and information regulator is urgently needed.

5. RECLASSIFICATION OF MEDICINES FROM PRESCRIPTION-ONLY MEDICINE (POM) TO PHARMACY (P) STATUS

5.1. The medicines reclassification process illustrates the conflicts of interest, lack of transparency and lack of accountability prevalent in the regulatory system. Reclassification is driven by Industry demands and produces clear benefits for the Industry. The benefits to the public are often less certain. We are concerned that insufficient regard is paid to the public interest and that the efficacy and long-term safety of reclassified drugs is not sufficiently evaluated.

5.2. The MHRA website states that: “New medicines are usually authorised for use as prescription only medicines (POM). After some years’ use, if adverse reactions to the medicine are rare and minor, it is possible that the medicine may be safely used without a doctor’s supervision. If there is sufficient evidence of safety, a medicine may be reclassified for sale or supply under the supervision of a pharmacist (P). Pharmacy medicines which have been safely used for several years may be suitable for general sale and may be

36 See Annex A—Prescription Medicines Code of Practice Authority Code of Practice on Advertising.
38 See Annexes A and B for further details in relation to the PMCPA and MHRA.
reclassified as general sales list (GSL). Reclassification of a substance normally follows a request from the company which holds a marketing authorisation for it. However, requests can be made by any interested party, such as a professional body, or be initiated by the MHRA. Applications to reclassify medicines are evaluated by the MHRA, with advice from a suitable expert committee (currently the Committee on Safety of Medicines (CSM)), as necessary. Where it is considered that the proposed reclassification may safely be made, wide public consultation, via the MHRA website takes place. Interested organisations will be notified when a new consultation has been added to the website. Responses to the consultation are evaluated by the MHRA and advice is sought from the CSM only if a new safety issue is raised during consultation. Following a successful reclassification proposal, the change of legal status will be conferred on the product that is the subject of the application for switching. All other products with the same active substance will need to make a separate application to follow suit.

5.3 The Government encourages wider availability of medicines as soon as there is adequate evidence of safety in use.\(^{39}\) As part of its “Choice” agenda, in the Building on the Best Report (2004), the Government makes a commitment to doubling the rate of medicine reclassifications (“switches”)\(^{40}\) from five per year to 10 per year. Companies will receive 12 months’ exclusivity on trial data for products that are reclassified, thereby preventing other companies from switching similar products based on the data of another company.\(^{41}\) An additional incentive for Industry to switch products is that over-the-counter (OTC) products can be advertised to the public, enabling companies to communicate directly with a wider market. Applying for a reclassification of status is particularly attractive to companies when a product’s patent is due to expire because of the potential commercial opportunities associated with a switch. Switching should be driven by proven safety and efficacy data and not predominantly to boost Industry’s profits or to shift the cost of treatment from the NHS to the consumer.

5.4 The PAGB’s briefing paper “POM to P in a changing NHS” (www.pagb.org.uk) refers to “ambitious switches” which “will not advance without substantial cooperation between industry, health professionals and other stakeholders”. As such, a broad list of selected therapeutic targets for POM to P reclassifications has been generated. This includes obesity, erectile dysfunction, urinary incontinence, anxiety and migraine.

5.5 The decision to make the statin, simvastatin, available in a 10 mg dose over-the-counter (OTC) in July 2004 did not fully take into account the potential consumer detriment and uncertainties surrounding the potential benefits as a consequence of that reclassification. In particular, no clinical trials have been conducted in people deemed to be at moderate risk of coronary heart disease (CHD) in OTC conditions. This effectively means the public are being subjected to a world-first experiment given that there is no evidence on the safety and efficacy of a 10 mg daily dose of simvastatin in OTC conditions. The public has not been alerted to this. Instead, simvastatin (brand name Zocor), is promoted as being of definite public benefit whereby it is assumed that the low dosage of 10 mg will not give rise to the rare, but dangerous, side-effects reported in higher prescription-only medicine (POM) doses.

5.6 Pharmacists supplying reclassified medicines over-the-counter can end up having to choose between potentially confusing protocols on such provision. This is because the manufacturer produces one protocol pertinent to the switched drug (in this case, Zocor), while the Royal Pharmaceutical Society of Great Britain (RPSGB) and other relevant bodies (see below) may produce another. In addition, further guidance on the treatment area more generally may also be supplied to pharmacists by such bodies.

5.7 The MHRA states that the drug manufacturer’s protocol should be agreed with stakeholders such as the Royal Pharmaceutical Society of Great Britain (RPSGB), the National Pharmaceutical Association (NPA) and the Centre for Postgraduate Pharmacy Education (CPPE),\(^ {42}\) but these stakeholders do not need to have approved the protocol for the switch to receive its authorisation for sale as OTC from the MHRA.

5.8 Moreover, anecdotal evidence suggests that as a result of receiving various guidelines, pharmacists collate the information and draw up personalised/local versions of protocols.

5.9 It is essential that effective monitoring and evaluation takes place as part of the reclassification process. However, it is unclear to what extent this occurs.

5.10 CA was not alone in opposing the Zocor switch and yet the decision had all the appearances of a foregone conclusion as there was no clear evidence that the concerns expressed to the MHRA during the consultation process had been addressed.

5.11 While safety must be paramount, a possible consequence of meeting safety criteria, by, for example, lowering the dosage of a drug, could undermine that treatment’s efficacy. In the absence of demonstrable evidence of efficacy, public trust in the regulator’s ability to ensure drugs are effective before they become available OTC could be undermined.

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40 Building on the Best: choice, responsiveness and equity in the NHS, Department of Health, December 2003.
41 “Switches” refer to reclassification of status from Prescription-only Medicine (POM) to Pharmacy (P) or P to General Sales List (GSL) (“POM-Over the Counter—OTC”). An application to switch requires the approval of the Committee for Safety of Medicines (CSM); Once a medicine is awarded OTC status it can be advertised to the public. A key driver to switching can be when a medicine’s patent is due to expire.
42 Article 74a of Directive 2001/83/EC.
5.12 The conflict of interests inherent within the reclassification process demands that there is greater transparency in the process than at present to ensure this is carried out in the public interest and that public health is protected.

5.13 The reclassification process needs to be urgently reviewed. Government targets for the number of reclassifications are inappropriate and the public interest should be the sole criterion for approving a reclassification. It cannot simply be assumed (as appears the case currently) that reclassification in and of itself produces benefits to the public. Similarly, the MHRA’s efficiency should not be measured by the speed with which it handles reclassifications but by its effectiveness in ensuring that reclassified drugs are sufficiently safe and effective for OTC use.

5.14 Consultation periods should follow Cabinet Office guidelines as a minimum and attempts should be made to elicit views from all relevant stakeholders. Decisions must be based on proven adequate safety and efficacy data, and these data must be made publicly available. Reclassifications from prescription-only medicine (POM) to pharmacy (P) status should be supported by the development of one pharmacy protocol, approved by the Royal Pharmaceutical Society of Great Britain, which should also be open to adequate consultation before any decision is taken about reclassification.

5.15 Following reclassification, there should be a period of close monitoring and evaluation to ensure that the public is not being put at unnecessary risk and swift action should be taken to address any problems.

August 2004

Annex A

PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY CODE OF PRACTICE ON ADVERTISING

The Prescription Medicines Code of Practice Authority Pamphlet January 2004 states:

“These can include:
— the carrying out by the Authority of an audit of a company’s procedures to comply with the Code;
— requiring the recovering of a promotional item from those to whom it has been given;
— requiring the publication of a corrective statement;
— a public reprimand by the ABPI (Association of the British Pharmaceutical Industry) Board of Management;
— suspension or expulsion of a company from the ABPI.

Thereafter, notwithstanding the annual levy charged to Members, administration charges are payable by pharmaceutical companies in relation to complaints made under the Code of Practice. The charges are assessed per matter ruled upon. A charge of £1,250 per matter is payable where a company accepts the Code of Practice Panel’s ruling that it had breached the Code or where a company complainant accepts the Panel’s ruling that there had been no breach.

A charge of £5,000 per matter is payable where a company ruled in breach of the Code by the Panel appeals that ruling and its appeal is rejected or where a company complainant appeals against a ruling of no breach by the Panel and its appeal is rejected.

Where a complainant appeals against a ruling of no breach and the appeal is upheld by the Appeal Board, the company then ruled in breach pays £1,250 per matter. Where a company ruled in breach appeals and its appeal is upheld by the Appeal Board, then a company complainant pays £1,250 per matter.”

44 Promotion of Medicines CA Omnibus Survey 1,053 adults aged 15+ were interviewed, weighted to a total of 1,030 adults representative of the adult population of Great Britain. Fieldwork took place between 16 and 22 April 2004 using CAPI (Computer Aided Personal Interviewing). (unpublished).
THE MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)
BREACH OF ADVERTISING REGULATIONS

The MHRA website states:

“The MHRA website states: (still referring to its former name, the MCA):

“5.6 Breach of Advertising Regulations

Where the assessment of advertising material identified under paragraphs 2, 3 or 4 above indicates a potential breach of the Advertising Regulations, the person responsible for the advertisement will be advised that the MCA considers that the advertisement is potentially in breach of the Advertising Regulations.

Although the Regulations clearly set out the powers available to the MCA, the Agency is not intending to extend its role. It is expected that, in the majority of cases, companies will work with the MCA to issue acceptable advertising without the need to resort to the formal procedures laid down under the Schedule to the Monitoring Regulations. However, once the formal procedures have been invoked they will continue until the matter is resolved.

In the small minority of cases where we are unable to reach a satisfactory result by negotiation the advertiser may be issued with a notice under paragraph 3 of the Schedule to the Monitoring Regulations advising him that:

the MCA is “minded to” determine that the advertisement, if published, would be in breach of the Advertising Regulations and the reasons why they are minded to make such a determination; if such a determination is made, that person may be required to refrain from publishing that advertisement by a notice served under paragraph 5 of the Schedule; and the person on whom the notice is served has 21 days from the date of the notice in which to make written representations that the proposed determination should not be made.

The notice may require that person to refrain from publishing the advertisement until the notice has been withdrawn by Health Ministers. In deciding whether to include such a requirement, the MCA will take into account all the interests involved and, in particular, the public interest.

If the advertiser agrees that the advertising material may be in breach and agrees to amend the material before issue, or withdraw material already in issue, any revised material should be submitted for assessment before it is issued.

If the advertiser considers that the advertising is not in breach of the Advertising Regulations, he may submit a written representation that the proposed determination should not be made. The representation will be passed to an Independent Review Panel for advice before a final decision is made by the Licensing Authority. Full details of the operation of the Review Panel are available from the MCA.

5.7 Issue of decisions and determinations

If an advertiser has provided written representations in response to a notice under paragraph 3 of the Schedule to the Monitoring Regulations, the advertisements in question will be reconsidered in the light of that representation. The MCA will refer the advertisement and written representation to an Independent Review Panel for advice before making a final determination.

If, following consideration of that advice, the MCA decides that the advertisement would not be in breach of the Regulations, a notice under paragraph 4 of the Schedule will be issued informing the advertiser of that decision and withdrawing the notice served under paragraph 3.

Alternatively, the MCA may, in the light of advice received from the Independent Review Panel, make a determination that the advertisement, if published, would be in breach of the Advertising Regulations. In this case, a notice under paragraph 5 of the Schedule will be issued stating the reasons for the determination, withdrawing the notice served under paragraph 3 and which may require the advertiser to refrain from publishing the advertisement.

Where the publication of an advertisement has been prohibited under paragraph 5, and that advertisement has previously been published, the person may be required to publish the reasons for the determination (as notified to him by the notice under paragraph 5a in full or in part) and a corrective statement within a specified time and in an appropriate form (paragraph 6 of the Schedule refers).

Once the Licensing Authority’s final decision has been given, any further disagreement must be settled in the Courts. A company which is unhappy about the decision will continue to have the opportunity to request a judicial review of the Authority’s executive decision.

5.8 Sanctions

Paragraph 7 of the Schedule creates offences where the addressees of notices under paragraphs 1, 3 or 5 of the Schedule fail to comply with the requirements imposed. Paragraph 8 makes it an offence for a person to fail to comply with any requirement imposed on him under paragraph 6 of
the Schedule. The provisions of the Monitoring Regulations make it an offence to fail to comply with the MCA’s determination of the matter and the MCA will consider enforcement action where any breach of the Regulations has taken place and where the legislation makes that breach a criminal offence. In addition, the MCA is entitled to seek an injunction in the courts as part of its investigation of a complaint or of its own motion.”

**Supplementary documents provided to the Committee**


**Supplementary memorandum by the Consumers’ Association (Which?) (PI 53A)**

Since we submitted written evidence to the Committee and are due to give oral evidence to the Committee on 14 October, new information has come to light and we would like to bring this to the Committee’s attention.

1. **Promotion of Oral Moxifloxacin**

1.1 Paragraph 4.62 of our written evidence outlines concerns raised by *Drug and Therapeutics Bulletin (DTB)* about the promotion of the oral antibacterial drug moxifloxacin. The pharmaceutical company Bayer launched the drug in April 2003 with the claim that it offered “rapid relief from chest infections”. This claim appeared on all of the promotional materials produced by Bayer to support the product, as well as in journal advertisements.

1.2 Having assessed the published evidence on the drug, *DTB* published an article (in August 2004), which concluded that “In our view, claims that oral moxifloxacin provides ‘rapid relief from chest infections’ are unsubstantiated, may mislead prescribers and should be withdrawn.”

1.3 *DTB* circulated a pre-publication draft of its article, including the concerns about the promotion of oral moxifloxacin, to the Medicines and Healthcare products Regulatory Agency (MHRA) on 17 June 2004. To date, as far as we know, the Agency has not taken any action with regard to this claim.

1.4 On 12 July 2004, Jeremy Booth from Bayer Health Care rang the *DTB* office and sought to persuade Ike Iheanacho (then acting editor) that publication of the *DTB* article on moxifloxacin should be delayed pending the results of an MHRA investigation into the advertising claim. In response, Ike Iheanacho made it clear that he would not delay publication of the article.

1.5 Publication of *DTB*’s article prompted an investigation of the advertising claim by the Prescription Medicines Code of Practice Authority (PMCPA), the results of which have recently been sent to *DTB*. The PMCPA concluded (on 16 September 2004) that “the strapline [‘rapid relief from chest infections’] was ambiguous and thus misleading as alleged and had not been substantiated.” As a result of the PMCPA investigation, Bayer Health Care has had to withdraw the advertising claim from all promotional materials.

1.6 The current regulatory systems had allowed the misleading promotion of oral moxifloxacin to continue unchecked for around 17 months.

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45 Not printed.
2. **Promotion of Zocor Heart-Pro**

2.1 Paragraph 5.5 of Which’s written submission outlines our concerns about the move to make the drug simvastatin available over the counter as Zocor Heart-Pro. Since submission of our evidence, advertisements for the medicine have started to appear in newspapers. We believe that these advertisements contain information that may mislead potential purchasers of Zocor Heart-Pro.

2.2 One advertisement depicts a man and quotes him as saying “Once I turned 45, I found out my risk of a heart attack was increasing. I had a chat with my pharmacist, who told me my risk could be as much as 1 in 7 and that’s too much for me. Now I’m using Zocor Heart-Pro(r) and eating a healthy diet to reduce my risk, and keep it down.” The advertisement also includes the following message to potential users:

   “Could your risk be as high as 1 in 7? If you’re a man 55 or over, then it may well be.
   “It’s the same if you’re a man aged between 45 and 54, or a woman 55 or over with an additional risk factor such as a family history of early heart disease, if you smoke, or are overweight”

2.3 A second advertisement depicts a woman, who is quoted as saying “Because I’d turned 55, my risk of a heart attack was increasing. I had a chat with my pharmacist, who told me my risk could be as much as 1 in 7. Now I’m taking Zocor Heart-Pro(r) and eating a healthy diet to reduce my risk, and keep it down.” The advertisement also includes the following message to potential users:

   “Could your risk be as high as 1 in 7? If you’re a woman 55 or over with an additional risk factor such as a family history of early heart disease, if you smoke, or are overweight, then it may well be.”
   “It’s the same if you’re a man aged between 45 and 54, with one of these risk factors, or just by being 55 or over.”

2.4 Neither advertisement states that the “1 in 7” risk represents the chance of having a heart attack within the next 10 years. The omission of this crucial piece of information could mislead people into believing that they could be at a much greater risk of having a heart attack than they actually are (for example, that there is a 1 in 7 chance that a heart attack is imminent or could happen within days, weeks, months or even a few years). In our view, therefore, the advertisements are misleading and should be withdrawn.
Thursday 14 October 2004

Members present:
Mr David Hinchliffe, in the Chair
Mr David Amess
John Austin
Mr Simon Burns
Mrs Patsy Calton
Dr Doug Naysmith
Mr Jon Owen Jones
Dr Richard Taylor

Witnesses:
Dr Des Spence, UK Spokesperson, No Free Lunch,
Mr Graham Vidler, Head, Policy, Consumers’ Association,
Dr Ike Iheanacho, Editor, Drug and Therapeutics Bulletin
and Dr Peter Wilmshurst, Consultant Cardiologist, Royal Shrewsbury Hospital, examined.

Q87 Chairman: Can I welcome our witnesses to this session of the Committee and express our thanks for your written evidence and your willingness to come and speak to us today. Could I ask you briefly to introduce yourselves to the Committee.

Dr Wilmshurst: I am Peter Wilmshurst. I am a consultant cardiologist at the Royal Shrewsbury Hospital.

Dr Iheanacho: My name is Ike Iheanacho. I am Editor of Drug and Therapeutics Bulletin, which is published by Which?

Mr Vidler: I am Graham Vidler, Head of Policy at Which? For the sake of clarity, I should explain to the Committee that since we submitted written evidence, we have changed the name we campaign under from “Consumers’ Association” to “Which?”

Dr Spence: I am Dr Des Spence. I am a GP, and I speak for the No Free Lunch organisation in the UK.

Q88 Chairman: Can I begin by asking a broad, general question, probably to you, Dr Spence, and some of the other witnesses, as to how you feel our approach to health care in this country is shaped by the role of the pharmaceutical industry.

Dr Spence: We certainly feel that the industry has a major influence over health care policy and that the influence of the industry is across the board, so it is not just a question of impacting upon doctors and nurses but it is the involvement with patient organisations and with government agencies. The industry is active in all these spheres and has a very clear agenda. Our perspective is that the agenda of the industry, which is predominantly that of profit—and they are responsible to their shareholders—is in some ways in direct conflict with the responsibilities of the NHS.

Q89 Chairman: If I were to put it to you in a different way, if we did not have the industry working as it currently does and as you and the other witnesses have described, and the influence it has, which comes over pretty clearly in your evidence, how might our approach to health care be shaped differently? Would we do things differently to the way we do them now?

Dr Spence: We probably have different priorities, in the sense that if you have an industry that is worth £9 billion a year, that has enormous clout over the priority setting. We certainly feel that health care is not merely about drugs. Health is not about what medications you take. It is a much broader brush than that. We would seek a much broader discussion about health in its global sense. One of the issues that I feel very strongly about as a day-to-day general practitioner is the amount of health anxiety and health neurosis that has been generated, often through things like disease awareness campaigns. We certainly feel that is undermining people’s sense of health and wellbeing. To put it bluntly, the reason for that is because it is in the commercial interests of the pharmaceutical industry to promote new conditions and different conditions.

Q90 Chairman: Can you give any specific examples?

Dr Spence: We certainly feel that the industry has a major influence over health care policy and that the influence of the industry is across the board, so it is not just a question of impacting upon doctors and nurses but it is the involvement with patient organisations and with government agencies. The industry is active in all these spheres and has a very clear agenda. Our perspective is that the agenda of the industry, which is predominantly that of profit—and they are responsible to their shareholders—is in some ways in direct conflict with the responsibilities of the NHS.

Q91 Chairman: Was this an industry campaign?

Dr Spence: It was a campaign promoted through the Royal College of General Practitioners and the Royal College of Psychiatrists, but with industry backing it with money. That led to us being told that a third of people were depressed, that we should screen for it, that we should start using antidepressants early, and we did. If I think back five or 10 years ago, we were diagnosing large numbers of people with depression, and we were prescribing many antidepressants. As time has gone on, I have certainly begun to realise that in some ways yes, there are many people who do have depression, but lots of people are just unhappy and that is a part of life. So there is a whole generation of people coming up who almost feel that being unhappy is an abnormal state, which, of course, it is not. That is part of the backlash against the use of antidepressants. The public as a whole are beginning to realise that.

Dr Iheanacho: I would like to echo a lot of what Dr Spence has said. Your question related to how things might be different if the industry were not active in
the way that it is. The plain answer to that is that there would be a lot more focus on things that the industry does not do so well or is not so interested in, such as non-drug measures and so on. It would be a mistake, I think, for anyone to equate the activities and interests of the industry with necessarily promoting public health.

**Dr Wilmshurst:** There would also be a major impact on medical education. There is a requirement for people to undertake a certain number of hours of medical education, 50 hours a year, and most of that is funded by industry, directly or indirectly. Whenever I go to a lecture at the postgraduate institute in my hospital, the room hire is paid by a drug company, as are the meals that you get, and the NHS would have to find the funding for that because there is inadequate funding, and government is tied in with it. Next week there is a conference at the Royal College of Physicians, at which the key speaker is the Deputy Chief Medical Officer, and industry sponsors that meeting: it is £2,000 a time to experience about change in influence comes from the time? impact?

Q93 Mr Jones: Has that influence changed over time?

**Dr Spence:** Certainly in surgeries much of my experience about change in influence comes from the pharmaceutical industry and from the use of drug representatives, and their contact with the doctors can almost be on a daily basis. Certainly my contact with the industry via pharmaceutical reps five years ago was on a daily basis. That can lead to very wide variations in a local area in the prescriptions of drugs. Taking the situation of Vioxx recently, in our local area, within a very short space of time, within three or four years, that class of medication became 40% of the particular group of medicines that we were using, and there was a very wide variation between different practices on how that was conducted. That is despite the recommendations.

Q94 Mr Jones: Can I ask a naıve question? GPs are very busy people. We hear constantly that they have no time for more than five minutes per patient. Why are they wasting all their time seeing pharmaceutical companies?

**Dr Wilmshurst:** It is not a naıve question. The reason is that that influence has weakened over time. If in with it. Next week there is a conference at the Royal College of Physicians, at which the key speaker is the Deputy Chief Medical Officer, and industry sponsors that meeting: it is £2,000 a time to experience about change in influence comes from the time? impact?

Q95 Chairman: Has the advent of primary care trusts changed these practices in any way?

**Dr Spence:** No.

Q96 Chairman: That is interesting because obviously there is a much greater degree of monitoring of prescribing practices of individual GPs within PCTs. What you are saying is that the practices we have all heard of over many years of the kind you have just described continue without any impact?
Dr Spence: Yes.

Q97 Mr Jones: Can I move on to a different though again a fairly general question: what is the connection between the development of new drugs and the improvement in therapy? How well-connected or not are these two processes?

Dr Wilmshurst: I do not know if they are really. It relates in part to the previous question, because I think the pharmaceutical industry also influences the research that is published. I know from experience. One reason I am here is that I was offered a bribe of two years’ salary not to publish research which was counter to the interests of the company making the drug. I know other people were influenced because of that not to publish—not because of bribes but pressure was put on other researchers working on the same drug.

Q98 Mr Jones: I think other questions will begin to explore that particular area but can I ask you more generally. One might again take a naïve view that every time a new drug comes into the marketplace, there is a new cure being proposed. Can you broadly explain what the relationship between new drugs and new cures is.

Dr Iheanacho: There is an uncoupling in the relationship you have described. The advent of new drugs often has very little to do with new cures. If you look at all the drugs that are licensed in a particular year and critically assess whether these actually constitute genuine innovations for patients, you would be surprised, I think, to find that relatively few of them do, and a decreasing proportion do. That is the important thing. The ability of industry to produce genuine innovations is going down—there is no secret about that—partly because it is expensive and difficult to do. When you see a new drug, you always have to ask yourself the question which we do: what does this actually offer as an advantage compared to what I have already, or what my patient has access to already? They are not coupled at all.

Q99 Dr Naysmith: I was interested in what Dr Spence was saying in relation to depression and how people were being encouraged to think they are depressed and you can have a drug treatment for it. When I discussed this matter, as I have before, with general practitioners, they tell me that they know that some kinds of talking therapies would be a lot better for their patients than giving a pill, but you just do not have the time to do that. Is it compensating really for not having the time to talk and try and sort problems out, or is it just a way to get patients out of the practice more quickly?

Dr Spence: It goes back to agenda setting. It goes back to saying, “What is the priority when it comes to treatment?” From the point of view of talk therapies, that could come from the primary care trust. The resources that are spent or used for, say, antidepressants, which can be up to £80 a month worth of antidepressant medication, could be freed up to provide talk therapies, but it is because the industry are very effective at drilling their line of intervention. It is treatment first. The people involved in talk therapies do not have the same levels of influence and access to the people who make those decisions.

Q100 Dr Naysmith: So how do we achieve the switch? Do patients like the talk therapies better than being given pills and shoved out the door?

Dr Spence: I do not know how you do that, but it goes back to what this general argument and discussion is about, which is looking at the current relationship between the industry, health care professionals and government as a whole. It is that close relationship that gives them an undue sway over the health agenda.

Q101 John Austin: This is a question for Dr Iheanacho and Mr Vidler. In your evidence you have actually said “a weak and unco-ordinated regulatory system is enabling the pharmaceutical industry to further its own interests without sufficient regard to public health.” That is a fairly damning indictment. What do you mean by “a weak and unco-ordinated regulatory system”?

Mr Vidler: We noted in our evidence two specific examples, one of which was around the reclassification process, where our concern is that the process is being driven by targets imposed by government, so that the assumption is that a reclassification is a good thing in its own right because the government believes that more people should have access to medicines over the counter and more people should take control of their own treatment. What this leads to is a situation where drugs are being reclassified without due consideration given to whether or not they are actually bringing public health benefits. We have a situation where drugs are reclassified and there are clear benefits for the company whose drug it is in terms of profits, but the benefits to the public are much less clear. The most recent high-profile example is the statin Zocor, where we know that the drug works at a particular dose for high-risk patients. To speed up the reclassification process, it is being allowed to be sold over the counter at a lower dose and to patients at lower risk. We simply do not know if it will be effective for that group, but what that group is being asked to do is spend £13 a month to participate in a clinical trial, to see if the product works in those conditions. That was the first key area we flagged up: reclassifications. It might be better if Ike spoke about advertising and promotion.

Dr Iheanacho: From the experience of Drug and Therapeutics Bulletin, the clearest example of weak regulation comes in the promotion of prescription-only medicines. A large part of our workload is assessing new medicines, and in the course of that we occasionally look at the advertising that accompanies those medicines. Our experience, which echoes that of others, is that often those products are promoted misleadingly. There is something in the regulatory system that allows that to happen, and it is worrying.
Q102 John Austin: Can I ask you as well about the monitoring of side effects and adverse reactions, and whether the regulatory control there is sufficient? In some of the evidence we received which referred to the early detection of safety hazards, there is the use of the black triangle labelling that doctors; nurses and other medical staff are then asked to record adverse reactions to those medicines. My understanding is that that is a voluntary system, not mandatory. Does it work as a voluntary system?

Dr Iheanacho: If you mean does it identify every adverse reaction it should do, the answer to that is no. The system is voluntary from two aspects really. It is voluntary in the sense that it relies on companies to put the triangles on all of their products. In the past, from our own work, we know that two or three years ago that was a problem, because we identified several cases where companies, for whatever reason, had not been doing that. I think that has been tightened up now, so you can expect a new product which should have a black triangle on it to have it.

Q103 Dr Naysmith: Is it mandatory on the drug companies to notify the MHRA if there is a potential...

Dr Iheanacho: Absolutely. It is mandatory for drug companies but it is not mandatory for health care professionals. If you are a doctor and you are told about an adverse reaction by your patient, it relies on you to fill in a yellow card and submit that to the Committee on the Safety of Medicines. That is voluntary.

Q104 Chairman: Can you explain to us why it is voluntary? It does seem rather odd.

Dr Iheanacho: That is a good question. It is not voluntary everywhere. It is not voluntary throughout the world. I cannot answer for it. It is not my policy. I think at the time it came about there must have been a genuine feeling that doctors would report adverse reactions, would be keen to submit to a system which would collect all these data and make them available for future prescribers and eventually patients. Do not forget that a lot of this grew up in the wake of the thalidomide scandal in the Sixties, and at that time I guess there was a genuine feeling that if this kind of thing could happen again, people would be very keen to report adverse reactions but the reality is that often it does not happen, I suspect for a number of reasons: there are other things to do, doctors are busy.

Q105 John Austin: Has it worked, for example, with Seroxat? There has been a lot of concern about side effects.

Dr Iheanacho: I think witnesses after us will give you a lot more background to what has happened in terms of that, but the short answer is there is a problem with yellow cards in relation to Seroxat in terms of how that information was collected and dealt with by the regulator and made available to people who might be in a position to prescribe the drug. So yes, there has been a problem with that particular drug, but others can say a lot more about that.

Q106 John Austin: Do you or the CA have a view as to how the public interest may be better served by a different regulatory system?

Dr Iheanacho: I think ultimately it is difficult to get away from the idea that, difficult though it may be, the best person to tell you about an adverse reaction is the person who is suffering it. That raises a lot of problems for regulators because they say “It is very difficult; patients will not be able to understand what a serious effect is, or what a minor effect is; it is going to produce a lot of data; there will be a lot of noise in the system”; but ultimately, if you want a pure account of what happened and you want to be able to tie that to the taking of a particular medication, the best person to tell you that is the patient. If you rely on a third party to tell you that, diligent though he or she may be, you start to erode some of the experience. In fact, you may not get the experience if you rely totally on the yellow card system.

Q107 John Austin: Dr Iheanacho has just told us that it is mandatory on the part of the drug companies to report all adverse drug-related events to the MHRA. You have just indicated in a fairly stark statement that there were inducements to you to not publish certain information, but in your evidence you have actually suggested that drug companies knowingly submit fraudulent material when negotiating with the regulatory authorities. Would you like to comment further on that?

Dr Wilmshurst: I have documented in publications the fact that, for example, in the case that I was involved in, the drug amrinone, when I published a paper on the side effects of the drug in the British Medical Journal, I was contacted by a regulator in the Netherlands, the Netherlands Committee for the Evaluation of Medicines, who pointed out that he did not understand our paper because on our clinical record cards the side effects were not reported. I had a copy of my clinical record cards, and the documents he had were a forgery from the company. The company had altered our clinical record cards, omitting side effects. I have also published an example where the same company got at the New England Journal of Medicine to try to suppress a publication from Stanley Rubin and colleagues in Los Angeles about the side effects of amrinone. So there are lots of examples where that occurs.

Q108 John Austin: How commonplace would you think it is now?

Dr Wilmshurst: I suspect it as common now as it ever was, and I think it was very common. In my experience, there were a number of people influenced by the company to withhold data in one way or another. Sometimes they withheld data because they were influenced by opinion leaders within the profession, who were paid consultants to the company who went along and spoke to them and persuaded them not to publish. They told them their data was aberrant and we were told by a very eminent professor of cardiology that our results were aberrant, it would be very embarrassing for us when we published. We went ahead and published and I presented data at the American Heart
Association, and when I did, three professors of cardiology contacted me, came up to me and said, “We got data like yours but the company persuaded us not to publish.” They got opinion leaders in, who were well paid to persuade them not to publish.

Q109 Dr Naysmith: I wonder if we could return for a moment to Mr Vidler and Dr Iheanacho and the reclassification of drugs from prescription-only medicines to other categories. You were suggesting that this might lead to safety problems, and we have probably dealt with this a bit, but is it possible, do you think, that this can mean that not very effective medicines or even ineffective medicines get much wider circulation and promotion? Really, what I am saying is, in the reclassification process, should there be an attempt to look at whether the medicines are effective or not?

Dr Iheanacho: Yes. As things stand at the moment, that is specifically excluded by law from the process of reclassification if you are seeking reclassification of a product for a use which is identical to the use that it previously had as a prescription-only product. If you want your drug to be reclassified for disease X as an over-the-counter drug—exactly the same disease, exactly the same patient categories—the evaluation process does not ask the question “Is it effective?” because the assumption is that, if the drug has a licence and has been relicensed repeatedly, one can take it as read that it is effective in the indication which is being proposed. The only way to refuse a reclassification is if you think that use of the drug in the way that is proposed in the new use raises safety concerns. That might be a reason for refusing reclassification but you cannot refuse reclassification on the basis of efficacy at that stage. The only way you would be able to stop a drug being reclassified is if somebody during the relicensing process, which should happen every five years, says for example, “Hold on a minute. We have had this drug for 10 years now. Look at all the data. Actually, on the whole, it doesn’t look that effective. Why has it got a licence?” That does not happen all that often.

Q110 Dr Naysmith: Presumably, you would expect it to be less effective than other drugs on the market being sold on prescription because one assumes that there will be better products coming along and they will be the ones which have their patents still in existence, and almost by definition these drugs should be less effective.

Dr Iheanacho: Possibly. One has to be careful about tarring the whole of the OTC market as being ineffective. That is clearly not true. There are many drugs which are available over the counter which do bring great benefits to patients, but to go back to your specific question, could the reclassification process as it stands lead to ineffective or less effective medicines being promoted to patients without their knowing, yes is the answer.

Q111 Dr Naysmith: Do you agree, Mr Vidler?

Mr Vidler: Entirely, yes.

Q112 Dr Naysmith: What can we do about it? What should we do about it? At that stage it would not be sensible, would it, to ask for efficacy tests on these medicines all over again medicines?

Dr Iheanacho: As the system stands at the moment, that could not happen. It would need a fundamental change in the way that we think about reclassification, or the way the regulator thinks about reclassification. The only mechanism at the moment is greater critical analysis of in the relicensing process, so that when a drug comes up for relicensing, to ask the question again “Does it still deserve its licence?” which should happen; that is part of the system.

Q113 Dr Naysmith: It is meant to happen now, but it does not?

Dr Iheanacho: It does happen, in inverted commas, but you see very few drugs actually having their licences revoked on the grounds of efficacy. There is a very good example. Possibly it would help to give a specific example. I suppose the most prominent example of a product for a use which is identical to the use that it previously had as a prescription-only product, or Buscopan, which is a treatment for a condition known as irritable bowel syndrome, and in particular, relief of spasm in irritable bowel syndrome. If you want an example of a drug which is ineffective, or at least appears to be ineffective for the reason its reclassification is being proposed, that is a very good example.
to do with the industry, government, the Prime Minister’s involvement, and there is a big 70-page document where the Task Force set out lots of proposals to try and improve the competitiveness of the drug industry in this country. I do not want to go into all the details of it, but since lots of you have mentioned it in your evidence, (a) do you think it is working and (b) is it working to the benefit of patients and health care in this country, or is the benefit totally to pharmaceutical firms?

Dr Iheanacho: I think it is working in the terms that it is meant to work, which essentially is to promote the business interests of industry, which is a perfectly legitimate thing for government to be interested in. If you look at the reports produced annually and you see the targets which are set and measure up whether they are being met, in those terms it is a very successful collaborative. With most of the targets that PICTF sets itself, it is much clearer to see what the benefits are for industry than they necessarily are for patients. I am not saying that it is a wholly useless collaborative that cannot possibly do any good, but when you read the documents, when you see how the collaborative works, you sometimes have the feeling, “Well, OK, I can see why they are doing this. It is a big industry, it pays a lot of tax, it is very important, it does a lot of research. These things are all very important, but actually, what is the spin-off going to be for patients in the long term?”

Q116 Dr Naysmith: Do you think the Department of Health and the Government should play a stronger part in trying to decide what the industry does in terms of benefits to patients and the population in general?

Mr Vidler: Certainly, yes. We quite understand the Government’s desire to have a competitive pharmaceutical industry contributing to the economy and contributing to employment, but that needs to be in second place to public health benefits. As Ike was saying, PICTF does a good job in its own terms. Where is the public health balance to that, and is it strong enough? Those are the questions we are asking.

Q117 Mr Amess: I am going to ask you a couple of straightforward questions. Gentlemen, do you welcome the influence of the industry in the promotion of newer drugs? The other point that I wanted to raise with you: how corrupted are doctors by the pharmaceutical industry in the promotion of these new products? Here we have a witness telling us all about free lunches. If these free lunches are as rife as perhaps you are going to share with us, it is not going to do this Committee’s campaign on obesity much good, is it?

Dr Spence: I can only give you a personal perspective of 10 years’ experience. I can tell you that I know hundreds of doctors and I know what the industry is like on the ground. The industry on the ground is unbelievably vociferous and active in promoting its own message, and there is a widespread hospitality culture in medicine. Whether the profession want to accept that or not is open to debate. The amount of hospitality received by the medical profession compared to other public services is, in my view, a complete disgrace. If you had other public servants, like civil servants or teachers or policemen, receiving that level of hospitality, there would be a public outcry. There is this idea that doctors are somehow different from other people, that we are anointed by God and made of a different moral fibre. That simply is not true. Doctors share the same failings as the rest of humanity. They are just representative of society as a whole. You cannot blame doctors, because this is what they have been used to. I always say talking about these things is rather like playing Father Christmas. “Oh, Father Christmas, you gave me too many presents this year!” It is that sort of relationship. That is what we are going to move away from. That is why it is difficult for doctors to hear this. It is so ingrained in them that they do not see it as being a problem, but it is a problem because it affects directly the medicines and health care that is delivered to patients in this country, and we have a professional and moral obligation to protect them.

Dr Wilmshurst: I think there are the issues around the influence on doctors, but there is also a more important influence, and that is the influence on government. When I did work with amrinone years ago, the fact is that we discovered we had been lied to about the clinical trial certificate. There was no clinical trial certificate for the oral drug, and we had conducted trials at St Thomas’s and others at the National Heart Hospital, Hillingdon Hospital, the Freeman in Newcastle and in Birmingham.

Q118 Mr Amess: Who lied to you?

Dr Wilmshurst: The pharmaceutical company. They told us they had a clinical trial certificate for the drug, and we conducted trials, and when we discovered that there was no clinical trial certificate, we went back to the Medicine Control Agency, or CSM, as I think it was called then, and they conceded that there was no clinical trial certificate, but the senior vice president of the company, Dr Trout, came over from America and said that the company would not be prosecuted for the breach of the Medicines Act—a serious breach—because he was going to tell the Health Minister that if they were prosecuted, they would shut down all manufacturing of drugs in this country, which would include their large manufacturing plant near Newcastle Upon Tyne. The company was not prosecuted although there was a clear breach of the Medicines Act.

Q119 Mr Amess: When was this?

Dr Wilmshurst: This was in the mid-Eighties.

Mr Amess: I will not question you any further on this point. You had me mildly interested if it was since 1997.

Q120 Dr Naysmith: Who would have authorised the certificate and how could it be possible that you thought there should be a certificate and there was not one?

Dr Wilmshurst: Because the company sent us a letter saying they had got it.
Q121 Dr Naysmith: Who should they have applied to to get it?
Dr Wilmshurst: The Committee on the Safety of Medicines.

Q122 Dr Naysmith: Had they not been asked at all or had they refused to give one?
Dr Wilmshurst: They had not been asked. However, if I had suspected initially that they had not got one and asked them, they would not have told me anyway. It did not occur to me that they would not have one when they said they had, but if I had asked the Committee on the Safety of Medicines, they would not have told me anyway because it was confidential between them and the company.

Q123 Chairman: You have got to be of a certain age to remember a Conservative government. Some might say that your evidence here is a little bit out of date. How would you say the current practices are similar? Have you evidence that is more up to date?
Dr Wilmshurst: I had a meeting with the Chief Medical Officer two years ago and gave him other examples of serious research misconduct. I have written to him repeatedly since then asking what he has done about it, and I get a postcard acknowledging my letter.
Mr Amess: This is much more interesting!

Q124 Dr Taylor: Can I go back to Dr Spence. We are led to believe that generic prescribing is being used more and more. We are led to believe that general practices have their own drug formularies more and more. Are these not lessening the effect that the drug companies can have?
Dr Spence: I reflect the question back to you: has that had an impact upon the drug costs to the NHS, which still stand at £9 billion per year, rising at an annual rate of 8–10%? Evidently not. The greatest cost to the NHS are not the generics but the branded drugs. You are probably aware of the issues about accusations of manipulation in the generic industry a few years ago anyway, and I think a number of companies were fined over that. As for the use of formularies, these are not compulsory formularies and there is a huge variation from practice to practice. Within a certain area there may be even a twofold difference in what GPs prescribe, and there is no way of controlling that.

Q125 John Austin: You mentioned the prescribing habits of doctors. If I could pick out an example, there has been an enormous explosion in the cost of prescribed drugs for indigestion and the use of proton pump inhibitors. There is some concern that they are being prescribed indiscriminately when there are more traditional and cheaper methods which might be effective. To what extent do you think that the alleged over-prescription of PPIs is as a result of pressure from the pharmaceutical industry?
Dr Spence: It is all about pressure. In fact, I wrote the complaint to the ABPI about the promotion of a PPI known as Zoton Fas Tab. What was happening there was the industry were using a third party to come into general practice to switch patients from Zoton to Zoton Fas Tab because Zoton was coming off patent. The PPI market is huge and the representatives were very effective at persuading practices to allow the switch to happen.

Q126 Dr Taylor: Going back to drug formularies, would it be feasible to have PCTs producing standard drug formularies for their particular area and in some ways getting them enforced? Hospital formularies seem to be much more widely used and accepted.
Dr Spence: It is certainly my experience that that is not the case. In our area we have something called the Glasgow Formulary, which is produced jointly between the hospitals and the PCT, and there are great variations between which hospitals use which medications and which medicines consultants use. The problem is that the authorities are very reluctant to take on the medical professions because the medical professions tend to hide behind this idea that we are professionals and we know best, so it is very difficult to enforce a formulary upon hospitals and doctors and general practitioners.

Q127 Dr Taylor: Should that be one of our recommendations?
Dr Spence: Absolutely. If you assume that the drug costs in the UK over the next year or two will go up by £1 billion, which is a likely projection, you have an enormous financial responsibility to contain this. I do not want to quote the Leader of the Opposition, but apparently £1 billion would put an extra 40,000 police officers on the street. That might be something worth considering. You might be better off putting 40,000 regulators into the drugs industry and find out what doctors are actually doing.

Q128 Dr Taylor: Is it fair to ask you whether there is any move among doctors to be less receptive to the freebies?
Dr Spence: Yes, I think there is. I can quote a survey, an online survey in the BMJ of 1,500 respondents. I think they were largely doctors. Ninety-six per cent of them said there should be transparency in the relationship between the industry and doctors, and what we are calling for is a compulsory register, in the same way as Members of Parliament have, of contacts and hospitality received from the industry. If there is not a problem with the industry, let your peers and let the patients decide. It will be important for the NHS to take that lead, because no other country has done that, and the onus of responsibility should rest with the industry because they know who they are seeing and they know how many contacts there are.

Q129 Dr Taylor: So another of our recommendations should be that doctors should report in detail their contacts?
Dr Spence: Yes, but the problem with self-reporting goes back to the problems with the yellow cards. Rest it with the industry. They have the
infrastructure and they know who they are seeing at the moment. If the industry has nothing to hide, let them publish this information.

**Dr Taylor:** Certainly when we get them before us we will want to ask them about their expenditure on advertising and drug reps.

**Q130 Mr Jones:** I just want to intrude in this discussion between the two doctors and say there might be another way of looking at the problem. The problem that you are describing is a problem of undue influence of the industry over GPs in their prescription practice.

**Dr Spence:** Not just GPs but hospital doctors as well.

**Q131 Mr Jones:** Largely GPs in terms of the prescription of pharmaceuticals, I think. Instead of looking at it from one end of the spiggy glass, looking at how we regulate the industry in order to reduce the undue influence, you might look at it the other way around and say that perhaps we should look at the gate keepers. If we remove a great deal of the control from the gate keepers, i.e. the GPs, have over which drugs they prescribe, that might be a more effective way of dealing with the problem.

**Dr Spence:** Yes. There is a problem. You have to seek to resolve it. Our perspective is that we want to use resources like the Drug and Therapeutics Bulletin to deliver effective and cost-effective treatments to patients. How do you deliver that? There are lots of different models, but you need to tackle this problem.

**Q132 Chairman:** That thought was behind my question some time ago, when I asked you about any changes to these practices through PCTs, where there has been a more collective discussion about prescribing practice at a local level. You said that might be happening, but the practice of inducement through the lunches side is still there.

**Dr Spence:** I suppose if the PCT were more prescriptive to the doctors who work for them—notionally they are independent contractors but in fact they actually work for the PCT—the industry’s influence would be much less, but they would exert that influence at the PCT level rather than the medical level. There are lots of different threads to this, but certainly a more prescriptive formulary would be one end, but I do believe very strongly that there has to be some register.

**Mr Vidler:** Can I just add that it is important that we do not lose sight of the fact that the industry also has a direct influence on consumers, and in those circumstances it is not feasible to imagine that we can quickly build up consumers’ knowledge and understanding to a level where they can cope with it, and in those circumstances we do very much need to focus on regulation of the industry.

**Q133 Mrs Calton:** Dr Spence, could you say whether you think that doctors who actually resist contact with the pharmaceutical industry and reps actually prescribe more appropriately?

**Dr Spence:** That is a difficult thing. I suppose the reverse is true: there is some evidence that if you see more pharmaceutical represents, you prescribe more of the new drugs, so conversely I guess that is true. Again, it is slightly anecdotal, but in my experience, those people who distance themselves from the industry do practise in a more effective and cost-effective way.

**Q134 Mrs Calton:** If promotional activity is severely curbed, it seems highly unlikely for economic reasons that any major pharmaceutical company could operate with acceptable levels of profit. Do you believe that that is so?

**Dr Spence:** What does “acceptable levels of profit” actually mean, seeing as the pharmaceutical industry has been the most profitable industry throughout the 1990s, and despite the downturn in the market has still maintained enormous profits throughout? Reasonable profits? They are unbelievably profitable already.

**Dr Wilmshurst:** I just wanted to mention the point that there is a lot of discussion about the interaction between pharmaceutical reps and GPs, but in fact, the companies influence GPs I think rather more because GPs are sceptical about what reps tell them. They are influenced more by opinion leaders, which is why the pharmaceutical industry pays opinion leaders so much. The senior people can get £5,000 plus for one hour’s talk to their colleagues in cardiology, and that is obviously because that is how much the pharmaceutical industry rates those people.

**Dr Spence:** That happens at a local level, with local specialists coming in and giving messages to local GPs, and these guys are being paid very handsomely for delivering their message—an independent message but . . .

**Q135 Mrs Calton:** I accept absolutely and from the evidence that you have been giving that an enormous amount is going on. The question is, what would happen if you withdrew all of that, or if you regulated it so heavily that it did not happen?

**Dr Spence:** My view is you would have a much more appropriate and better health care system.

**Q136 Mrs Calton:** Can we move on to consumers, the public. What is your view on the part the pharmaceutical industry has to play in informing the public about the medicines they make and how they might be used? We touched on this earlier.

**Mr Vidler:** We believe it potentially has an important role to play, and clearly, the industry has widespread experience of marketing and great skills to bring to bear in translating that into education. The problem with what is happening at the moment through disease awareness campaigns is that people are not being given a holistic view of the situation. They are being given a view which leads down a fairly narrow track to a drug-based solution, where that may not be appropriate. That sort of information and that sort of awareness-raising has its place but it needs to be part and parcel of a holistic approach.
Dr Iheanacho: I obviously echo a lot of that.

Q137 Mrs Calton: In a sense what you are saying is that it is more of the nature of propaganda than it is of true information in the round?

Mr Vidler: We would need to distinguish. There is obviously a spectrum of disease awareness campaigns and promotional activity. At one extreme of that spectrum, you are fairly close to propaganda. There are some less bad examples as well.

Q138 Mrs Calton: Could you give us a broad view of the effectiveness of self-regulation in drug promotion? I think from what you have said already you feel it is not particularly effective.

Dr Iheanacho: No. I suppose it is being generous to say it is not effective. I would say that the self-regulatory bits that we come across in terms of promotion of particular medicines to doctors, for example, are very weak indeed. In some sense, their activities are so questionable in terms of actual regulation that you have to ask why they are there at all. The conclusion that I think I have reached is that they are there because they need to be there, so that if somebody asks “What is the regulation?” people can point to them and say “There is the regulatory system.” But if you were looking for evidence that this is a system which acts in a way that I think most reasonable people would want a regulatory system to act in terms of advertising, that is, it can spot misleading advertising quickly or react when misleading advertising is brought to its attention; can investigate it quickly and stop it happening if necessary; effectively punish whichever company is doing it and be seen to have done that; and crucially, inform the people who have been misled quickly and as widely as possible that they have been misled, and act as a deterrent to that company or someone else doing it again; if those were the standards that you wanted to see in a regulatory system, they are, in my view, largely absent from the present regulatory arrangement.

Mr Vidler: We have suggested for that reason that the current web of regulation and self-regulation over advertising and promotion needs to be replaced by one single independent advertising unit.

Q139 Chairman: Can I conclude by picking up a couple of points that have come out in the session so far. Dr Wilmshurst, you mentioned a few moments ago the way drug companies will pay eminent cardiologists £5,000 for an hour’s session to talk about their products. How widespread is this practice, and do people not see through what is going on? Surely, people can make up their own mind as to the merits of this practice.

Dr Wilmshurst: People do not always know, because people do not always declare their conflicts of interest.

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Dr Wilmshurst: People do not always know, because people do not always declare their conflicts of interest.
afterwards, and they really had no experience of use of the drug but were prepared . . . . I did not ask them how much they earned.

Q146 Mr Burns: Did you ask them though that they were earning something?
Dr Wilmshurst: I am sure they were.

Q147 Mr Burns: But did you ask them?
Dr Wilmshurst: No, I did not. OK. I will have to check my records. There is another company—I just have to remember which company.
Chairman: It might be helpful if you came back to us in writing.
Mr Burns: I would quite like an answer to my question first.
Chairman: He is not able to on specific examples.
Mr Burns: He has made the allegations, so surely he can back them up.
Chairman: Of course, but what I am asking is for him to follow up in writing with detail that he probably cannot give at the moment.
Mr Burns: If it is a very common practice and well known and he has submitted written evidence, surely, given the seriousness of it, Dr Wilmshurst should be able to give us at least one oral example for the record.
Chairman: He has just given you one.

Q148 Mr Burns: He has not actually. He tailed off. Dr Wilmshurst: If I might finish, I will just tell you about the Posicor, if I might. The doctors that I spoke to I assumed were earning money because I knew—

Q149 Mr Burns: That is an assumption, not necessarily a fact.
Dr Wilmshurst:—because I knew that one of the two I spoke to was in fact also employed by another pharmaceutical company, Rhone-Poulen Rorer, and he was a member of what I have described in the literature as the “roadshow” and would earn between £2,000 and £5,000 a time for speaking plus travelling expenses in this country. He spoke about once a fortnight with one of his colleagues for the company. I have this from a representative of the company. The company called the pair of them “the roadshow” and they travelled around, talking about a drug made by the company. Also afterwards I spoke to a colleague who had done similar work for a company making Captopril, and in fact his experience was quite bad. He had gone off message, and unfortunately he was in Amsterdam at the time, and they refused to bring him back, so he then had to find his own way back. That is what happens if you go off message. So there is an incentive. If you are getting a large amount of money from the company, there is an incentive to keep on saying it because one, the money will dry up if you say the wrong things, and of course, there is also the danger you will embellish it because you are trying to make it sound even better.

Chairman: Can I ask on behalf of the Committee that you follow up in writing to satisfy the concerns that Simon Burns has, and give as much evidence as you can of the examples you are referring to, because obviously this is a key issue from our point of view.
Mr Burns: So as not to delay things any longer, can I just add to what the Chairman has just said that when you do come back, we are looking for specific examples of eminent cardiologists getting up to £4,000 plus expenses for an hour-long talk on their products. Specific examples. That is the allegation you make, and I am not questioning whether it is true or not; I just want the evidence, because it is a very serious matter if the evidence exists.

Q150 John Austin: Earlier on you were talking about the importance of listening to the patients on issues of adverse reactions etc, and I think all of us would agree that the voice of the patients and patient organisations has to be listened to. It has also been suggested that in some cases there is a very cosy relationship between the pharmaceutical industry and some patient organisations, whereby patient organisations may be used by pharmaceutical companies to pursue their own ends. Do you have any evidence of that?
Dr Iheanacho: I have a clear example. The example I would suggest is GlaxoSmithKline’s involvement with a small charity called Allergy UK. That involved producing a book, a little “Mr Men” book based on the children’s characters—here it is—and it appears to be a very ordinary Mr Men book until you get to the back, where you find some advertising for some of the company’s products. This book was in fact illegal and is no longer available; it had to be withdrawn. The law makes it very clear that children cannot be used as a promotional vehicle in this kind of way. The charity did not know about the problem, that this was bad behaviour, until they were alerted by the media, who pointed out: “What is going on here? This isn’t the done thing.” So the charity was in a very embarrassing position because they had been acting in good faith but essentially they had been taken in by the company.
Dr Wilmshurst: I should have thought of this. I travelled expenses in this country. He spoke about once a fortnight with one of his colleagues for the company. I have this from a representative of the company. The company called the pair of them “the roadshow” and they travelled around, talking about a drug made by the company. Also afterwards I spoke to a colleague who had done similar work for a company making Captopril, and in fact his experience was quite bad. He had gone off message, and unfortunately he was in Amsterdam at the time, and they refused to bring him back, so he then had to find his own way back. That is what happens if you go off message. So there is an incentive. If you are getting a large amount of money from the company, there is an incentive to keep on saying it because one, the money will dry up if you say the wrong things, and of course, there is also the danger you will embellish it because you are trying to make it sound even better.

Q151 Mr Burns: On what?
Dr Wilmshurst: About drugs, and about their drugs, but I only talk about drugs that influence me. I am also a consultant—this is slightly different—for a device manufacturer. It is covered by the Medicine Device Agency, so it is slightly different but it is a medical device. I have been asked to be a consultant for them, and it is difficult for me to do so because I
am a specialist adviser to NICE, so I have agreed with them that they pay the money to a charity so that I cannot receive it. It is an overseas charity in Africa for kids with AIDS. I thought that would be a way that no-one could ever say I had a conflict of interest. But the sums involved for my few hours of work with them will be £22,000. That is the sort of level that they pay a DGH cardiologist. If you are a professor of cardiology somewhere else, you can earn considerably more.

Chairman: Can I thank our witnesses for an excellent session. I am sorry we have had to somewhat curtail it but it has been very helpful and we are most grateful to you.

Memorandum by Mind (P127)

THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY: SUMMARY

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References

Mind’s contribution to this inquiry is based on the organisation’s extensive information, policy and campaigning work on medication issues. The chief executive’s recent participation in the Committee on Safety of Medicine’s expert group on SSRI antidepressants provided an insight into the industry.

Drug innovation: the innovation that takes place is not necessarily driven by health needs. Drugs are manufactured that differ very little from others on the market, and new conditions are defined that provide a new use for an existing drug thus extending its market and patent-life.

Conduct of medical research: most published drugs research is industry funded, and recent analyses of clinical trials have shown how company-sponsored trials are more likely to produce results that favour the experimental drug. Companies are free not to publish trial results and some SSRI research has been shown to exaggerate the drugs’ benefits and downplay the risks.

Provision of drug information and promotion: information produced by pharmaceutical companies is mostly marketing, and the Medicines and Healthcare products Regulatory Agency (MHRA)’s information is generally aimed at professionals. Research with users of medication consistently shows a demand for information, which is often not met by prescribers.

Professional and patient education: industry activities such as sponsorship of medical educational events and patient campaigns, and ghost-writing of clinical journal articles, promote particular drug treatments and also promote drug treatment over other approaches.

Regulatory review of drug safety and efficacy: the ability of the MHRA to safeguard public health is compromised by its secrecy, industry links and its licensing role which is a service to industry. The review of SSRIs showed the MHRA slow to put important information into the public domain, and to act on information from clinical trials and consumers. It has little involvement with consumers and is only now about to accept consumer reports of drug side effects. From our recent involvement, the MHRA fails to understand basic elements of effective communication and involvement with consumer groups.

Product evaluation, including assessments of value for money: shortcomings in drug regulation inevitably affect product evaluation. There is little or no consumer input to the process, and the basis on which licensing decisions are made are not public so that professionals and consumers can make informed decisions about marketed drugs.
Recommendations

— full publication of trial data and adverse drug reactions;
— comprehensive reform of the MHRA around consumer interests, with resources and powers to fulfil its responsibilities;
— separation of pharmacovigilance from licensing and independent testing of drugs;
— requirements for good practice in trial design and reporting;
— independent information service to consumers of medicines;
— national task force to develop a strategy for health research which involves the public, balances drug and other treatments and funds priority needs.

INTRODUCTION

1. Mind is the leading mental health charity in England and Wales. We work for a better life for everyone with experience of mental distress by:
— advancing the views, needs and ambitions of people with experience of mental distress;
— promoting inclusion through challenging discrimination;
— influencing policy through campaigning and education;
— inspiring the development of quality services which reflect expressed need and diversity;
— achieving equal civil and legal rights through campaigning and education.

2. Mind’s contribution to this inquiry is based on the organisation’s extensive work on medication issues, and links with a wide-ranging network of individuals with experience of mental distress, Local Mind Associations and other local mental health organisations. The organisation believes in providing people with information with which to make their own decisions, and publishes information booklets about the drug treatments used for mental health problems. Through the organisation’s information service we are in regular touch with the questions people have about medication. Enquiries about depression and antidepressants are the most frequent calls we receive. Drugs have a key role to play in alleviating serious mental distress; Mind’s concern is that they are used in the safest, most effective way possible, alongside other options and on the basis of informed choice.

3. We have drawn attention over many years to the damage psychiatric drugs can do, and in the late 1990s ran a yellow card scheme for people to report the side effects they were experiencing. This was repeated in 2001 and was part of continuing efforts to have people’s own accounts of side effects taken seriously. This work demonstrated the demand among people being prescribed drugs for impartial, accurate information about their effects. Mind carried out a similar survey with Panorama following their first programme on the antidepressant Seroxat, “Secrets of Seroxat” (October 2002). This highlighted serious side effects, including suicidal feelings, and withdrawal effects.

4. Richard Brook, Mind’s chief executive, participated in the Committee on Safety of Medicines’ (CSM) expert group reviewing the safety of SSRI antidepressants until he resigned in March 2004 because of the Medicines and Healthcare products Regulatory Agency’s slowness to publicise important information about dosage. This experience provided an insight into the processes involved in medicines regulation and failures to protect public health. Mind is represented on the CSM’s working groups on patient information and direct patient reporting of suspected adverse drug reactions. Mind has a policy of not accepting funds from the pharmaceutical industry.

5. Whilst a mental health charity, we believe our experience, past and recent makes us able to determine some common aspects of drug regulation which we believe are wider than just our specific interest.

6. In addition to the references in the text of this submission we should like to draw the Committee’s attention to the important work by Dr David Healy in identifying and exposing the links between SSRI antidepressants and suicidality, and to the work of Charles Medawar of Social Audit in describing and challenging the operations of the industry and regulator, most recently in his book “Medicines out of control?”.

Drug innovation

7. Drug innovation is clearly an important role for the pharmaceutical industry but the innovation that takes place is not necessarily driven by health needs. Drugs are manufactured which differ very little from others on the market, and new conditions are defined that provide a new use for an existing drug thus extending its market and patent-life. In her paper “Is psychiatry for sale?” Joanna Moncrieff shows how Smith Kline Beecham (now GSK—GlaxoSmithKline) identified a new use for its antidepressant paroxetine (sold as Seroxat in the UK, Paxil in the US). The manufacturer created a market for Seroxat as a treatment for social anxiety disorder or social phobia by shaping public and medical opinion through a disease awareness campaign. Roche ran a similar campaign about its antidepressant moclobemide (Moncrieff, 2003).
8. As evidence for these strategies, we are taking the unusual step of submitting the internal fact file of Seroxat, sourced from the Panorama programme in the research it has done for a pending third programme. Unlike our other references, this document is not in the public domain. Such types of documents are rarely available to the general public or consumer groups, although we suppose that regulatory agencies do see them. (They could be submitted to the agency or seen by appointees to bodies such as the Committee on Safety of Medicines because of their own pharmaceutical interests.) Initially produced in 1998 and subsequently updated, it is an internal document relating to the marketing of Seroxat.

9. GlaxoSmithKline (GSK), manufacturers of this heavily marketed and promoted blockbuster antidepressant drug, revealingly title a major section (section 1) of it as “Towards the second billion—all SSRIs are not the same”. The driver is obvious—greater profitability—and the strategy involves making the case that the drug fits a whole new number of “diseases” and providing arguments why Seroxat should be used as the “anti-depressant of first choice”.

10. These industry strategies make the case, in Mind’s view, for a stronger, and better resourced, regulatory framework that is transparent and in turn requires openness from the industry. Greater transparency of industry research would make it harder for misleading claims to be made or to go unchallenged. There is also a case for improved provision of information and education to the professions and public which is independent of the industry. Recommendations on medicines regulation, and other relevant sections of the evidence, are set out below.

11. Drug innovation is important but should be seen in the wider context of health and medicines research, and led by need. A discussion paper published by the Kings Fund (Harrison, 2003) points out that the pharmaceutical industry is the active driver in an implicit public-private partnership, in which the industry develops the products that it considers likely to be profitable and the Government is generally a passive purchaser. The weaknesses identified in this situation are that research areas other than new medicines are neglected, the needs of some groups of people—particularly children and older people—are not sufficiently taken into account, and the public is not involved.

12. Consideration should be given to setting up a task force as set out in the paper which would address pharmaceutical research, within a broader strategy for health research generally, and include independent reviewers, consumers and other research users. For example through the process of reviewing clinical evidence for National Institute for Clinical Excellence (NICE) guidelines and treatment appraisals, research needs are identified. NICE should equally be able to specify at an earlier stage in the development of treatments what kind of data is needed in order to assess effectiveness in clinical practice.

13. Involving citizens and service users in the governance of pharmaceutical research could result in significant changes in priorities. This approach could also be a way to create equality between the opportunities for researching different therapies, not only medicines. Setting priorities in this way could provide a basis for expanding and/or redirecting the funds available for health research.

**Conduct of medical research**

14. The pharmaceutical industry is a massive part of the UK economy and exerts a pervasive influence over the research into and use of medicines. Virtually all research on drugs—70% of trials reported in major medical journals—is funded by the industry (Smith, 2004). By virtue of doing most of the research, the industry has a hugely disproportionate effect on what gets researched, and also how it is researched, how the results are interpreted, and how—and crucially whether—the results are reported.

15. There is bias in research design. Several reviews of trials have shown that results are more likely to show a positive result for the experimental drug if the trial is funded by the company (Smith, 2004, Kjaergard and Als-Nielsen, 2002, Wahlbeck and Adams, 1999). Experts in the subject have shown how aspects of clinical trial design can favour the experimental drug. These include:

- comparison with placebo rather than other drugs;
- comparison with other drugs that are prescribed at ineffective or excessive doses;
- trials that are too small;
- using “categorical outcomes” which can exaggerate small differences between groups (eg two points in a depression rating scale can make the difference between “response” and “non-response” to a treatment). (Smith, 2004, Moncrieff and Double, 2003, Jureidini et al, 2004.)

16. Selection of people for clinical trials who are most likely to benefit from the drug, or least likely to have adverse reactions, can also present a more favourable picture than when the drug is in general use and prescribed more widely. This is one factor in the better results obtained for SSRIs than for tricyclic drugs in older trials.

17. The way trial results are interpreted and reported may also exaggerate the drug’s benefits and play down the size of the placebo effect and/or the adverse reactions. A case in point is that of the SSRI class of antidepressants as used in children and adolescents (Jureidini, 2004). We are also aware of research in progress that shows atypical antipsychotic drugs may have been oversold.
18. Pharmaceutical companies and others conducting clinical trials are free not to publish the results at all. The recent controversy over the safety of SSRI antidepressants for children and young people centred on the results of unpublished trials. A review (Whittington et al., 2004) of published and unpublished trials of SSRIs in children and young people shows that the published trials suggested that the drugs were effective, but once the unpublished data were built into the analysis the indications were that risks outweighed the benefits. In developing a guideline on depression in children for the National Institute for Clinical Excellence (NICE) reviewers had contacted all pharmaceutical companies that made antidepressants requesting unpublished data, but none were forthcoming. NICE was able to access the information obtained by the MHRA for its review, but without this NICE would be likely to have issued harmful guidance.

19. An internal GSK paper that was dated 1998 and revealed by the press in February 2004, indicated that trials of the antidepressant Seroxat (generic name paroxetine) in children showed this drug was no better than placebo in alleviating children’s depression. The report stated “it would be commercially unacceptable to include a statement that the efficacy had not been demonstrated, as this would undermine the profile of [Seroxat]”. When the company pooled the trial data it also discovered a “safety signal”—more of the children on the real drug than the dummy drug had suicidal thoughts. The Medicines and Healthcare products Regulatory Agency issued guidance effectively banning the drug (along with other SSRI antidepressants) for under 18s in the UK in September 2003 (other antidepressants in February 2004).

20. The New York State attorney Elliot Spitzer has taken this issue to the courts, suing GSK (GlaxoSmithKline) and claiming that by “concealing critically important scientific studies on Paxil [US brand name of paroxetine], GSK impaired doctors’ ability to make appropriate prescribing decision for their patients and may have jeopardized their health and safety”. GSK subsequently announced that it would publish summaries of all its clinical trials of a new product once it has been launched. However this is still a voluntary arrangement and leaves control in the hands of the company. Regulatory agencies at least need full data before that point.

21. Under the EU Clinical Trials Directive, which came into force in May this year, all clinical trials must be registered on an EU database. However, only national regulatory agencies have access to this information, and although the conclusion of a trial must be notified, including reasons for early termination where relevant, this does not include the results.

22. The degree of control exercised by the industry in determining what research is carried out as part of product development is also illustrated by the SSR1 expert group’s work. In the course of the group’s work, Richard Brook was struck by the number of times that it was acknowledged more research was needed on the issues under consideration. On several occasions of raising the issue, it was clear that whilst there was almost universal agreement work was needed, sometimes of an urgent nature, there was no way of making pharmaceutical companies undertake or fund it, and neither was it possible to find an accessible independent source of funds that could do this. It was thus accepted that on the issues identified, there were unlikely to be any useful additional facts coming forward, and nothing further could be done.

23. The interpretation and evaluation of research would be greatly assisted if all clinical trials, whether sponsored by pharmaceutical companies or not, complied with CONSORT guidelines (consolidated standards of reporting trials, www.consort-statement.org). CONSORT is a research tool, developed by international collaboration and continually evolving, that provides a checklist and flowchart on what to include in trial reports. For example there is guidance on reporting the eligibility criteria for trial participants, methods for random allocation, and the reporting of adverse events experienced by trial participants.

24. Improvements in reporting should have an effect on the conduct of the research itself; if information has to be reported it has to be collected. However, Mind’s view is that more requirements about the conduct of research should be built into the drug licensing process. Individuals’ own assessment of the treatment they have received, its efficacy and adverse effects are rarely included in clinical research, but should be. Research in the field of ECT (electroconvulsive therapy) shows how research by clinicians and research by consumers comes to different conclusions (Rose, 2003). Improvements to clinical trials should include user, and where appropriate carer, assessments of treatment efficacy and adverse effects, optimal doses of comparator drugs, and better collection of data on adverse effects.

25. Biased reporting of drug trials may unfairly advantage drug treatments in relation to safer non-drug approaches, not just one drug over another. However, simply by virtue of its size and economic power the pharmaceutical industry advantages drug treatments over other types of treatment. Clearly drug treatments are the industry’s business, and pharmaceutical companies are not responsible for other sectors. There is a need for a national strategy for health research that balances drugs with other treatments, with public funds directed to non-pharmaceutical treatments research (see 11–13).

Provision of drug information and promotion

26. There are several problems with drug information as provided or influenced by the pharmaceutical industry. As shown above it may be partial, and potentially harmfully so. The foundation for information about drugs is the clinical trial data; it provides the basis for licensing medicines, advice to prescribers, the development of clinical guidelines, and information to consumers. The lack of independent research and the
biases in the system make it more likely that this information will be partial or inaccurate. This in turn means that people will not be able to make properly informed choices, and prescribing may be at best less than optimal, and a worst harmful. It may also lead to distorted allocation of NHS funds.

27. Much information from pharmaceutical companies is in fact marketing. Pharmaceutical companies exert extensive influence through promotional activities including:

- highly visible sponsorship and products;
- sponsoring conferences and other medical training;
- payments to speakers and opinion leaders;
- ghost-writing clinical journal articles;
- sponsoring patient groups/campaigns to support and market medicines;
- creating new, and expanding existing, problems to treat;
- pressing for direct to consumer advertising;
- heavy marketing of new products/uses despite the caution that is needed before a full side effect profile begins to emerge.

28. The Seroxat file is highly illustrative of using marketing information as facts, in particular in relation to the arguments over discontinuation. Prozac manufacturer, Eli Lilly, raised the issues of discontinuation and Seroxat’s relatively short half-life as a issue to try and defend its failing market share in 1998. The Seroxat fact-file sets out strong arguments about why Eli Lilly’s arguments are wrong and how the half-life is a major advantage even allowing “treatment holidays”. Original trial data submitted to the UK regulators from the licensing of Seroxat show at best this was naive and at worst, seriously misleading. It was clearly an emerging theme in the SSRI working group prior to Richard Brook’s departure that discontinuation of Seroxat was probably influenced by its short-half life and was likely to be the major reason why it has been experienced as the most problematic of the SSRI’s. The fact file minimises the therapeutic considerations and maximises those of commercial success to the detriment of the consumer.

29. Another example of this approach is the failure of GSK to issue a “dear doctor” letter to physicians in the US warning about paroxetine use in children at the time that it did amend labelling in the UK in line with the MHRA’s requirement.

30. Again, these strategies reinforce the case for a strong regulator (see 39–64). Full publication of trial results could also strengthen the capacity of the Prescription Medicines Code of Practice Authority to challenge misleading claims by companies.

31. There is a real gap in independent specialist information provision for the public. Research with users of medication consistently shows a demand for information, which is often not met by the prescriber. For example, 61% of respondents to Mind’s Yellow Card survey about drug side effects (Cobb, 2001) said they did not receive enough information when they were prescribed medication. People wanted information about what drugs do (benefits and risks), withdrawal effects, alternatives, and new ways of using drugs. They identified numerous ways in which information could be improved, including its independence; more detail; clearer, more understandable language and large print; information based on others’ experience; and information as of right.

32. In a more recent survey by the Scottish Association for Mental Health (Bradstreet and Norris, 2004) 29% of respondents had not been given written information at the time when a drug was prescribed. The report comments; “This is of some concern given that a Patient Information Leaflet (PIL) should be included with every prescription. While our findings may demonstrate inadequacies in prescribing practice they may also be due, in part, to survey respondents not being aware of a PIL.” The authors also comment that patients may not be given PILs and that the issue requires investigation. For example people may not have been given a PIL on receiving a generic drug, a depot injection of antipsychotic medication, or when they are in hospital.

33. In the course of the SSRI review the MHRA has provided more information for consumers, for example question and answer sheets, but most of the Agency’s communication is with prescribers.

34. Therefore there is a real need for a consumer information resource about medication. There is a useful helpline providing information on psychiatric medication to consumers, which is run by the UKPPG (UK Psychiatric Pharmacists Group) with funding from the National Institute for Mental Health in England. However we believe that a service that can meet wide scale demand needs to be developed and publicised.

Professional and patient education

35. Several of the activities listed in the section above relate to professional and patient education. These activities not only favour one drug over another, they also have the effect of promoting drug treatment over other approaches.

36. The predominance of pharmaceutical company research means that other treatment options do not get comparable resources, and the position of medicines as the effective treatment is reinforced (11–13).
37. There is also a responsibility on the medical professions to examine their links with the pharmaceutical industry and the use of industry funding. However aware a doctor is of their exposure to marketing, the volume of material and the blurring of clinical and promotional information mean it is difficult to believe that doctors and other health care professionals are not influenced in their day-to-day practice.

38. However this evidence is most concerned with the statutory regulation of the companies and their products.

Regulatory review of drug safety and efficacy

39. This section summarises concerns arising from the SSRI review, and then looks at the regulatory process in more detail, drawing on the SSRI review for evidence.

40. SSRI review: The Committee on Safety of Medicines’ review of the safety of SSRI antidepressants revealed major failings in the regulatory process, relating to the two sets of guidance issued so far as a result of the group’s work.

41. Children and young people: As discussed above (18–20) there was a failure either to obtain full trial data, or to interpret and act on information received, such that some 10,000 under 18s in the UK were prescribed paroxetine before it was eventually warned against in 2003. The European Agency for the Evaluation of Medicines has recommended that paroxetine (Seroxat) be prescribed with extra caution to people aged under 30 because of a possibility of increased risk of suicide-related behaviour in young adults. However the MHRA has not significantly publicised this warning to doctors and the public.

42. Dosage: as a result of the review group’s work, guidance was issued in March 2004 reminding doctors that the maximum effective dose of paroxetine for depression is 20mg. However the information on which this guidance was based formed part of the manufacturer’s licence application and was therefore held by the regulator. As recently as 2003 an estimated 17,000 people were started on doses above that at which there is no additional benefit although the risk of side effects continues to increase. Either the Agency did not understand the full implications of the data when the drug was licensed, or it did understand but failed to act. In Mind’s view this is extremely negligent and a dereliction of duty and has led to many individuals suffering side effects or worse that they did not need to experience. It is also Mind’s view the current advice still falls short of what the Companies’ own trial data warrants.

43. Medicines regulation: The pharmaceutical industry’s relationship with the Medicines and Healthcare products Regulatory Agency includes:

   — controlling the data supplied to the MHRA;
   — funding the MHRA through fees;
   — financial and employment links with MHRA and Committee on Safety of Medicines personnel;
   — commercial confidentiality assured by the MHRA (at least until the Freedom of Information Act comes into force).

44. Other limitations on the MHRA to provide an adequate safeguard are:

   — lack of research that is independent of the industry;
   — lack of consumer input;
   — lack of public profile;
   — possibly inadequate powers and resources;
   — organisational culture that fails to recognise the importance and centrality of the consumer;
   — a legal framework that prevents full and frank disclosure.

45. The next paragraphs look at these links and limitations in more detail.

46. Reliance on company data: When it is deciding whether to license a drug for sale in the UK, the MHRA depends on the company’s own dossier on the drug. It does not analyse the raw data independently and only in recent times has had in-house statistical staff able to undertake such reviews of the data. The SSRI review shows there was at least one occasion in the past when the Agency either failed to interpret the “top-level” data a company submitted or else failed to communicate its meaning effectively to prescribers (see 42). This failure, as far as Richard Brook knows, remains unacknowledged and no action has been taken on it or considered for other drugs where the same situation may apply.

47. Lack of independent research: Clinical research is largely what the pharmaceutical companies want to fund, rather than what serves a wider interest. The MHRA does not in general commission research apart from limited research it carries out through its General Practice Research Database. It has no powers or funds to have specific work done as might be indicated by, say, adverse effects reports.

48. No duty to report new efficacy data: Although they must report adverse drug reactions within 15 days, and supply periodic safety reports, there is no obligation on pharmaceutical companies to provide new efficacy data once a drug has been marketed, other than in the five yearly licence renewal applications. It
appears from the SSRI review that companies would not report a trial that showed no efficacy to the Regulator, often explaining away adverse effects or safety issues arising in trials as not relevant in their view. The Regulator has no access (or capacity) to examine these types of events.

49. Overt relationship with the industry: Facilitating the development of a successful pharmaceutical industry in Britain was until recently an objective of the Agency. Licensing medicines is a service to the industry, as well as a safeguard for the public; it is an inherently reactive process and the MHRA is funded by industry fees. It can be argued that this makes too close a relationship with the industry (at least for pharmacovigilance work), or that it is right that this successful industry—and not the public—should bear the costs of regulating it. With respect to new licence applications, centralisation and mutual recognition in Europe mean that there is more competition between regulators for less work. Essentially the scale, size and status of the MHRA’s work, including pharmacovigilance, is determined by the level of industry activity funding it and to some extent the “general” view of how successful it is.

50. Other industry links: The approach to the holding of pharmaceutical interests by those involved in medicines regulation is in urgent need of review. It is quite untenable that regulatory advice and decision-making should be the responsibility of people with close links with the industry. Many members of the MHRA’s committees have extensive interests in the pharmaceutical industry, such as shares, consultancies and fees (details of which are published in the Medicines Act 1968 Advisory Bodies Annual Reports). These interests have to be declared, and depending on their status—personal or non-personal (eg funding for the member’s research department), specific to a product under discussion or not—the member may or may not take part in proceedings. A proposal to stop members of committees holding interests is part of the MHRA’s recent consultation on its advisory committees.

51. The extent of company interests inevitably raises concerns about the independence of decision-making. It also raises questions about the effectiveness of committees where several members are disqualified from a discussion (for example in the 2001 annual report six out of 36 members of the Committee on Safety of Medicines had a personal interest in GlaxoSmithKline and a further seven had a non-personal interest.). This is especially heightened if such members have any involvement or contact with material such as that in the Seroxat Fact File.

52. Lack of consumer input: There is lay representation on the Committee on Safety of Medicines which advises the MHRA and runs the Yellow Card scheme for reporting suspected adverse drug reactions. Indirect consumer reporting of adverse drug reactions—via NHS Direct—was piloted in 2003, and the Government has now announced that direct consumer reporting is to be piloted. However consumer representation and championing of robust consumer rights are not built into the MHRA’s structures and processes. Indeed the MHRA appears to be extremely inept at handling consumer involvement. Some examples from many from Richard Brook’s involvement in the SSRI expert group are:

— Seating arrangements at meetings that are intimidating and conflictual.
— Undermining comments from MHRA staff about the usefulness and expertise of consumer representation.
— Suggestions by a working group member—unchallenged by MHRA officials—that a few consumers may have made up the 1,600 plus Panorama emails following their most recent programme on Seroxat.
— Use of email for numerous and extensive papers, making participation harder for a consumer representative.

53. A further concern is that despite pressure from Mind and other groups and parties for Richard Brook’s place on the group to be filled, to date we are not aware that an additional consumer representative has been announced or appointed.

54. Whilst undoubtedly, there have been recent efforts to improve communication with patients and health professionals much is still needed to be done as a matter of urgency. During the SSRI review, some of these changes occurred—such as giving more raw data, simple Q&A sheets, etc. However, the handling of consumer involvement in the release of information about the dosage of Seroxat suggests a lack of expertise and knowledge within the MHRA over communicating with the public and users of medication. It clearly has never been a major strand to their work and despite recent attempts to improve this area they remain at a very fundamental stage of development.

55. Lack of public profile and impact: In its report on the then Medicines Control Agency, the National Audit Office stated that the Agency needed to strengthen its public profile in order to fulfil its mission to provide information to contribute to the safe and effective use of medicines (National Audit Office, 2003). The Agency does not for example have a high public profile as the Food and Drug Administration in the USA does. This limits its ability to get safety messages across to the public, and to engage with the public as a source of information on the effects of medicines.

56. Despite recent announcements that the MHRA is addressing this, it still remains a low priority in terms of action. For instance, the MHRA does not comment or present its view of events such as the controversy over the SSRI issues. It places a low priority on communicating with the public and even health
care professionals. One example of this is the very limited publicity over the EMEA (European regulator) decision to advise that Seroxat use in people aged under 30 should be undertaken with extra caution despite this being European advice to which the UK contributed.

57. **Secrecy:** There are legal constraints set out in the Medicines Act 1968 on what information the MHRA can make public. Pharmaceutical companies are free to withhold unpublished data from such bodies as the National Institute for Clinical Excellence, which is responsible for developing guidance for the NHS on effective treatments. This prevents independent scrutiny of MHRA decisions, and undermines public safety. The legal basis for giving and withholding information by the MHRA will change with implementation of the Freedom of Information Act but any attempts to thwart the thrust of this Act must be prevented.

58. The other issue is that any consumer groups or representatives involved in regulatory processes are restricted by the legislation and the MHRA’s view of the legislation. During Richard Brook’s involvement with the SSRI Expert Group there was an ongoing emphasis on this legal framework which seemed to work against consumer’s interests and in favour of the pharmaceutical companies.

Examples are:
- Concerns of litigation if certain public health decisions were made and announced;
- Due process potentially allowing facts about pharmaceutical companies being hidden or never exposed;
- Requiring consumer representatives to forgo any level of moral or ethical responsibility to their stakeholders whilst involved in drug regulatory processes.

59. **Resources:** The capacity of the MHRA to properly evaluate the risks and benefits of medicines, both pre-and post-licensing, and to act promptly on the outcome, depends on its being adequately resourced. In its report the National Audit Office stated that the Agency needed more resources for its pharmacovigilance strategy and that with more resources it could make fuller use of the General Practice Research Database which it holds. It also remarked on the amount of information with which the Agency has to deal. The amount of available information will increase with the recently established EU-wide clinical trials database and adverse drug reactions database. There is also a pressure to carry out the licensing process within specific timeframes. Mind considers that a greater amount of audit work by the MHRA is also needed with more active visiting of companies.

60. There is clearly, in terms of at least the SSRI work, an inability to effectively predict work-load, resources required and work-plans that match the two. Despite receiving absolute assurances in September 2003 from the Chairman and the Acting CEO of the MHRA that there was no resource issue in terms of the SSRI review work, the work has consistently been behind schedule and additional staff were recruited to match the ever increasing demands on a few key staff.

61. **Need for reform:** Mind considers that consumers have a right to expect full and impartial information about the potential risks and side effects of prescription medicines. This requires a robust regulatory framework to ensure that this information is not only publicly available but also acted upon promptly.

62. **We need a drug regulatory system:**
- that puts consumer safety before commercial pressures and cost;
- whose membership and operation is transparent and accountable;
- that has sufficient legal powers to ensure access to all drug trial information and adequate funding to verify the accuracy of this information;
- that gives comparable weighting to consumer experience of drugs as it does to information from drug trials.

63. **Public views obtained in an NOP poll carried out in March 2004,** support a shift in the balance in favour of legal powers and regulatory action:
- The majority of the public thought the following people ought to be able to see the findings of pharmaceutical companies’ research: Government bodies responsible for medicines safety (79%), doctors and other health professionals (84%), independent health researchers (72%), patients and the general public (76%).
- Only one third of the public trusted pharmaceutical companies to pass the information on voluntarily. Indeed 17% of the public did not trust the companies to pass the information on even if legally required to do so.
- Only 13% of the public believed that companies themselves should be in charge of deciding how they carry out research into the safety and effectiveness of medicines and how they report the findings. Fifty per cent thought this should be the responsibility of Government bodies responsible for medicines safety, and 33% thought it should be independent health researchers.

64. **Recommendations for reform of the MHRA are made in more detail in the recommendations section,** but in summary, Mind considers that the agency should be reformed around consumer interests with strong consumer representation and a commitment to make full use of consumer intelligence. The MHRA should have access to all clinical trial results in full and be able to make this available to independent reviewers.
Pharmacovigilance should be separated from the licensing process. The MHRA should have the powers and resources it needs to safeguard public health. Its operation should be transparent and accountable with key personnel free of industry interests.

**Product evaluation, including assessments of value for money**

65. The industry’s influence on research and the shortcomings in drug regulation inevitably affect product evaluation. The yellow card scheme and other pharmacovigilance activity need to be strengthened, and recipients’ own assessments of treatments’ effectiveness measured. Drop-out from clinical trials is a useful indicator but it is hardly an adequate measure of a drug’s acceptability to the person taking it, yet is generally the only one available.

66. Work on the safety of SSRIs has underlined the importance of consumer reporting of suspected adverse drug reactions. There was a huge public response to Panorama’s “Secrets of Seroxat” programme and analysis of emails sent to the BBC revealed patterns of experience of side effects which are not identified by the filtered and coded data collected through the yellow card scheme (Medawar et al, 2002). Consumer reports are to be accepted through the yellow card scheme and Mind welcomes this, having argued the case for some time. However this analysis indicates that narrative reports give a quality of information that it is essential to capture, and we believe the MHRA needs to make fullest use of consumer intelligence through the extended yellow card scheme and other methods.

67. The authorities’ decision-making on the balance of effectiveness and risk needs to be transparent — for example on what basis is fluoxetine tacitly approved for under 18s when there is only limited evidence of efficacy and this is for a short-term only? Despite requests from the SSRI Expert Working Group to the MHRA to emphasise this, it has not occurred. It is also extremely worrying to learn from journalists that Eli Lilly’s press office confirmed they were directly approached by the MHRA to seek a licence for Prozac (fluoxetine) without any need for further trial data. If this is correct, it is another example of the inappropriate relationship of the MHRA and pharmaceutical companies.

**Recommendations**

68. A minimum level of safety requires access by the MHRA to all trial results, in full, regardless of whether they have been published and whether the results are negative, equivocal or positive. It in turn should be able to put such information into the domain of researchers and reviewers, and once a drug has been licensed, make the information available in suitable format to all.

69. The quality of research and its interpretation would be improved if all clinical trials, whether sponsored by pharmaceutical companies or not, complied with CONSORT guidelines (consolidated standards of reporting trials, www.consort-statement.org).

70. There should be more requirements on companies as part of the licensing process. This should include that user, and where appropriate carer, assessments of treatment efficacy and adverse effects are built into trials, that optimal doses of comparator drugs are given, and that there is better collection of data on adverse effects.

71. Pharmacovigilance work should be separated from the licensing process, and there should be independent testing of drugs, not just reliance on companies’ own data.

72. The MHRA should make a commitment to full use of consumer intelligence in its pharmacovigilance work, and do this through the yellow card scheme and other approaches. It should proactively engage with the public both to get intelligence in and send information out.

73. The MHRA should have all necessary legal powers and resources to obtain the information it needs in order to safeguard public health and the resources to audit companies, use the information fully, act promptly on it, and publicise any safety messages effectively.

74. The MHRA should champion consumer safety and have strong consumer representation. There should be a well-supported consumer committee on a par with other MHRA committees, as well as a “critical mass” of lay people in those other committees, including consumer representatives, and legal and ethical expertise.

75. The operation of the MHRA should be transparent and accountable. Members as well as chairs of advisory groups should hold no personal interests, and preferably no interests at all, and the most senior personnel should have a complete break from the industry.

76. The MHRA should only keep confidential information that absolutely needs to be—confidentiality should be an active and justifiable decision. There needs to be a clear process for putting full trials data into the domain of researchers/reviewers both pre-and post-marketing and making it publicly available in suitable format after licensing.

77. An independent information service to consumers about medication should be developed.
78. There should be a national task force to develop a strategy for health research which involves the public, balances drug and other treatments and directs funding towards priority needs.

August 2004

REFERENCES


Memorandum by Professor David Healy (PI 77)

1. INTRODUCTION

2. In response to the select committee’s call for comments, I wish to offer an analysis that may help explain how companies can engineer a clinical consensus that will favour their product—even in the absence of a scientific basis for claims for superiority for the new and usually much more expensive product—and how this process can feed through and shape even disinterested assessments of the evidence undertaken by NICE. These processes appear to many to underpin a relatively recent “capture” of regulatory and other professional domains.

3. I will also comment on how the safety of pharmaceutical products might be better ensured under current arrangements and on how current arrangements may be changed to produce a safer framework for healthcare.

4. I bring to this commentary a background in consultancy work with pharmaceutical companies, access to company archives through medico-legal work, (as outlined in the accompanying conflict of interest statement—appendix 1), and 10 years of work on mapping the history of the development of psychotropic drugs and pharmaceutical companies in their present form as published by Harvard and New York University Presses.
5. **Commentary**

6. **Clinical Consensus**: The main point of note is that the scientific literature is being managed to an ever increasing extent, the most visible sign of which is that an increasing proportion of the scientific literature on aspects of therapeutics with pharmacological agents (over 50%) is now ghost-written. This is associated with a demonstrable failure to report important safety data on drugs, or with the reporting of such data in terms that mislead. The risks from ghost-writing stem from the fact that the data that ghostwriters purport to represent remain inaccessible to outside scrutiny.

7. As a consequence of the ghost-writing of articles, efforts to establish clinical consensus in the form of guidelines and algorithms, which depend on a review of the entire literature on a drug are compromised and can be shown to produce outcomes indistinguishable from the outcomes that would be produced by having a group of employees of the pharmaceutical company write the guidelines. Even though there may in fact be no evidence of superior efficacy or safety for newer agents, they will end being written up as superior to older agents and to be used in preference to older agents.

8. The effects of ghost-writing and other literature management strategies feed through into a process of pharmaco-economic modelling undertaken for new drugs, which can demonstrate that not only is a drug that is not proven to be in any way superior its predecessors better than its predecessors but is better to the extent that it should be in replace older agents, even though the costs of the new treatment may be 50 times greater than the older agent.

9. The details of how these processes work are laid out in appendix 2. Of note here is that I have been a participant in these processes and party to the generation of views favouring newer over older agents, unaware that pharmaceutical companies were keeping key safety data hidden from the scientific community and that they would refuse to produce such data on request.

10. **Safety Data**: Current procedures to manage the entry of drugs onto the market favour the detection of drug effects and set a higher threshold for safety effects. This shows up in two ways.

11. First, in order for a drug to be licensed it has to show superiority to placebo in two controlled trials. Companies however can run ten or more trials in carefully selected samples using instruments carefully designed to pick up any effect in order to demonstrate this, and even if the results show the drug failing to beat placebo in the clear majority of trials, this is not held against them. These other trials are commonly termed failed trials rather than drug failures.

12. In contrast, the demonstration of a safety issue is not handled in this way. In this case regulators will only act if the overwhelming preponderance of the data show a hazard.

13. This issue has at its heart unresolved philosophical issues about the nature of statistics. Safety data is typically presented in terms of Confidence Intervals, so that for instance in recent antidepressant studies the rate of suicides on drugs compared to placebo is typically of the order of two times greater but what is termed the confidence interval surrounding this figure of 2.0 might be for example 0.9 to 4.4.

14. There is a deep philosophical divide between two ways to interpret such a finding. First according to a school of thought stemming from R A Fisher is the view that nothing has in fact been shown unless the confidence interval does not include 1.0, thus for instance a confidence interval of 1.1 to 4.4.

15. Second, the Neymann-Pearson school of thought argues that the best estimate of the effect is 2.0, in this case. This is the figure regarding which we can be most confident.

16. In practice regulators, adopt the Fisher approach. This cannot be viewed as a rigorous approach to safety. Epidemiologists or a drug regulatory process on the other hand, concerned with safety, would argue that in this case the figure of 4.4 is potentially consistent with the data—that is the hazard in question may well happen up to 4.4 times more often on the drug than on placebo or non-treatment, and that therefore if the hazard is serious patients and doctors should be warned about this possibility.

17. **Safety Procedures and Informed Consent**: At present when patients enter clinical trials they are asked to sign informed consent forms, which contain ever longer lists of potential problems a treatment may cause. These consent forms though never inform patients or others that neither patient, nor physician nor any other third party will ever have access to the raw data from this trial, particularly data on safety issues. They are not told that pharmaceutical companies may choose only to “market” the bits of the data that suit them.

18. Changing informed consent forms to make this explicit might have salutary effects. Alternatively transforming informed consent forms into contracts between patients and companies that provided rights of access to experts in the event of safety concerns might make a big difference.

19. Requiring companies to permit access to the raw data, given for free by patients as part of a “gift” arrangement with the rest of the community, would simply require companies to conform to the norms of science under whose banner they claim they sell their products.
21. Until some arrangement is put in place to ensure access, then every patient who enters a clinical trial in the United Kingdom (or anywhere else) is putting every Member of Parliament and all the constituents those Members represent in a state of legal jeopardy. This follows as the absence of publicly available data on hazards will be used by pharmaceutical companies to argue that the hazard does not exist, even when the datasets available to industry establish clearly that the hazard does exist.

22. Regulators, who typically read study summaries prepared for them by pharmaceutical company employees, rather than scrutinise and analyse the raw data themselves, can miss these issues.

23. This evidence is being submitted on an individual rather than a corporate basis. I would be willing to give oral evidence on these issues, and can bring some benefit to any hearings by virtue of being an active participant in the processes described above and below.

24. I am a Reader in Psychological Medicine in the University of Wales College of Medicine (as of August Cardiff University).

20 July 2004

APPENDIX 1

COMPETING INTERESTS

25. In recent years, I have had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for or been in receipt of support to attend foreign meetings from Astra, Astra-Zeneca, Boots/Knoll Pharmaceuticals, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, SmithKline Beecham, Solvay, Zeneca.

26. I have also been an expert witness for the plaintiff in seven legal actions involving SSRIs, as well as for the defendant in four cases of assault involving SSRIs, but otherwise has not implicated in approximately 100 other cases. I have been an expert witness for the defendants (the British National Health Service) in a large series of LSD and ECT cases.

APPENDIX 2

MANUFACTURING CONSENSUS


BACKGROUND

27. Consider this excerpt from the 1993 FDA medical review of Janssen Pharmaceutical’s application to market the antipsychotic drug, risperidone (Risperdal): “We would consider any advertisement, promotion or labeling for Risperdal false, misleading or lacking fair balance under Section 502 of the Act if there is a presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness” (Mosholder 1993).

28. The clinical trials undertaken by Janssen with Risperdal prior to marketing had compared it to an older antipsychotic, another Janssen drug, haloperidol. In a similar way, all recently released antipsychotics, including olanzapine (Zyprexa), quetiapine (Seroquel) and ziprasidone (Geodon), were compared to haloperidol in key pre-marketing trials. All companies used much the same dose of haloperidol—a dose that was no more efficacious than lower doses of haloperidol but which did cause more side effects. The company rationale for using haloperidol was that haloperidol was supposedly the market leading antipsychotic agent. Whatever the real rationale, it was generally accepted at the time these trials were conducted that newer agents stood their best possible chance of looking better in terms of key side effects—or at least no worse (if compared to the doses of haloperidol used in these trials).

29. The role of a drug regulator in addition to gate-keeping the entry of a new drug to the marketplace is to regulate any claims a manufacturer might make as regards a new product in its advertising or in any statements its personnel might make to doctors afterwards. This assessment by the FDA would appear to produce problems for any company that might wish to market Risperdal.

30. But regulators have no control over what academics say in lectures, report in medical journals or elsewhere. FDA in addition have no control over what assessments these academics might make in their roles as experts called on to contribute to an expert consensus on new versus older drugs. Shortly after Risperdal was launched, it was being widely touted by academics as superior to older antipsychotics on the market.

31. Aside from the perennial need to market the product, the 1990s brought a new hurdle for drug companies to vault. It was increasingly necessary to persuade clinicians and pharmacists that a new drug should be listed on hospital formularies. These formularies were created to ensure new agents would not be
used without good evidence of cost-benefit returns. The formularies are notionally meant to be evidence based and cost-sensitive. A certain amount of trade-off was likely—if a new drug cost more but could show a real benefit over older agents it would be included.

32. No convincing evidence has ever been forthcoming that any of the new “atypical” antipsychotics are superior to the older “typicals” in either safety or efficacy. A study completed in 2003 by the VA hospitals compared olanzapine (Zyprexa) and haloperidol both in terms of efficacy and tolerability and found no difference between them; olanzapine in this study, however, cost approximately 80 times as much as haloperidol (Rosenheck, Perlick, Bingham et al 2003). Despite this lack of greater efficacy, olanzapine has won a place on formularies since its launch in 1996 to the extent that it has become the most profitable antipsychotic in the world.

33. In the absence of clear evidence from clinical trials sufficient to warrant claiming a new drug was superior to an older drug, it would appear difficult to make the extra step to advocating that the newer agent is more effective to the point of warranting a potential 80-fold increase in expenditure. Nevertheless, shortly after their launch, Risperdal and other recently released antipsychotics were available on most hospital formularies in both the United States and Europe.

34. Pharmaceutical companies have clearly found methods of circumventing these difficult areas of marketing terrain. Circumvention is achieved by recruiting senior academics and institutions to their cause, by means of three stratagems: consensus conferences, pharmaco-economic modeling, and ghostwriting.

Consensus Conferences

35. Consensus conferences aimed at producing guidelines for clinical practice came into existence in the late 1980s (Sheldon and Smith 1993). A range of bodies took up this apparently academic development. Within psychiatry, groups such as the British Association of Psychopharmacology and the European College of Neuropsychopharmacology, for example, produced guidelines on the treatment of a range of conditions from depression through to schizophrenia. This may have happened in part in an effort to establish a political profile. In a number of the organizations that produced guidelines, the influence of key individuals with links to pharmaceutical companies is apparent.

36. At the same time pharmaceutical companies began to sponsor meetings aimed at producing expert consensus on issues such as the appropriate use of medication in schizophrenia. These company sponsored meetings have often resulted in products that may appear almost indistinguishable from non-company sponsored guidelines or algorithms. While this might be thought as an exercise designed to confound the recommendations of independent committees, in fact committees that should be independent have come up with recommendations that barely differ from explicitly company-sponsored exercises.

37. Given the lack of evidence-base for the superiority of the new antipsychotics, just how have all these guidelines ended up endorsing newer, more costly agents over older, less expensive, but equally effective ones? One such guideline system, the Texas Medication Algorithm Project (TMAP), offers one set of answers (Petersen 2004)46.

38. Risperdal was launched in 1994. TMAP was instituted in 1995, initially funded by Janssen Pharmaceuticals (Johnson & Johnson), the makers of Risperdal. Soon afterwards it had attracted funding from all major pharmaceutical companies. TMAP drew up a panel of consultants to produce an expert consensus on the use of antipsychotics, and later on the use of antidepressants and mood-stabilizers (Gilbert, Althüler, Rego et al 1998). Most had prior links to Janssen and the other major pharmaceutical companies operating in the mental health field.

39. The first set of TMAP guidelines concluded that the atypical antipsychotic medications Risperdal, Zyprexa and Seroquel were the drugs of choice for the management of schizophrenia (Chiles, Miller, Crismon et al 1999). A second set concluded that newer patented antidepressants, such as the SSRIs, Prozac, Paxil and Zoloft, were the drugs of choice for the treatment of depression rather than older agents such as the tricyclic antidepressants. Subsequently mood-stabilizers such as Depakote and Lamictal have been endorsed over other treatments for bipolar disorder. In all these instances, the claims have been that the new drugs were safer, more effective and better tolerated than the older agents. The expert panels then formulated a set of algorithms or care pathways for the treatment of schizophrenia, depression and bipolar disorder based on these guidelines.

40. In a number of US states, legislators have the powers to rule that algorithms and guidelines such as these must be applied in the care of any patients receiving treatment in public facilities. The logic here is that evidence based guidelines and algorithms, if they really do reflect reality, can be expected to be cost-effective over time. The legislators faced with the question of adopting the algorithm and guideline proposals in Texas meet infrequently, are poorly paid and are intensively lobbied. Not surprisingly perhaps, TMAP was administratively endorsed in Texas, and as a result state hospital doctors were required to follow its algorithms and use these newer drugs first.

46 Note: In connection with TMAP, this article has benefited hugely by work undertaken by Allen Jones, Special Investigator in the United States OIG Office of Special Investigations, detailed in Dwight McKee and Allen Jones v Henry Hart, Sydmi Guido, Wesley Rish, Albert Masland, James Sheehan and Daniel P Sattele, CIVIL ACTION No: 4:CV-02-1910, in the United States District Court for the Middle District of Pennsylvania.
41. Researchers linked to TMAP were also able to access the records of patients in state facilities, including prison hospitals and mental hospitals, and report on the cases that appeared to do favorably. These surveys produced data supporting the selection of Risperdal and Zyprexa, for instance, as first line treatments for schizophrenia, and later the selection of SSRIs or other newer antidepressants over older treatments for depression. On this basis, the TMAP guidelines and algorithms began to be referred to as evidence-based guidelines and evidence-based best practices.

42. A related panel formulated a set of medication algorithms for children, which recommended new antipsychotics and antidepressants, such as Paxil (paroxetine), for the management of children’s problems (Hughes 1999). In this case, not only was there a lack of evidence for the superiority of the newer over the older agents; there was essentially no evidence base for the recommendations other than a set of then unpublished clinical trials.

43. The TMAP algorithm and guidelines were subsequently marketed to other states on the basis of the Texas precedent and instituted by administrative decision in a number of these other states also. In this way a very few people had effectively paved the way for the acceptance of these guidelines and algorithms in many states, and produced a situation in which a growing cohort of patients treated in the public sector end up being put on and maintained on these drugs. It will probably come as no surprise that within Janssen there was a special unit aimed at maximizing the effectiveness of the companies marketing in the public sector.

FROM TMAP TO NICE

44. While the TMAP process appears close to egregious, something very similar happened within the socialized system of medicine in Britain. In the first place, opinion leaders in Britain were recruited to panels to produce evidence-based guidelines for antipsychotics. The experts invited to such meetings will have had no pressure put on them to come to a particular point of view. All of the publications of clinical trial data for antipsychotic drugs will have been made available to them on request, and they will have been encouraged to be evidence based.

45. Again as with TMAP, the results, despite the assessment of the FDA, which will have been unknown to any of the participating experts, must have been gratifying to the sponsoring company (Mortimer, Healy, Gray et al 1998). The process involved no overt selling of named medications, but rather a set of positions endorsing the use of antipsychotics in monotherapy regimens, and in doses consistent with British National Formulary recommendations, and in a manner that would avoid precipitating acute treatment related side effects. These positions along with exhortations to adhere to an evidence based approach were considered by the company as an effective marketing tool.

46. Subsequently, a National Institute of Clinical Excellence (NICE) was set up in Britain with a brief to make recommendations as to the most clinically effective and cost-effective treatments for both physical and mental illnesses. The NICE guidelines for psychiatric treatment are an essentially similar creation to TMAP, and earlier UK based industry sponsored guidelines: a consensus of expert views rather than evidence based views. The process involves a small number of psychiatrists, psychologists and other stakeholders in mental health such as psychiatric pharmacists collating evidence, preparing draft reports and then sending these to selected experts for comments. Decisions are reached not by experiment or evidence but by agreement. The process will also have to take into account prior algorithms, guidelines and Delphi panel recommendations (see below). And finally, as has been pointed out publicly by the World Health Organisation, the process operates within the constraints of the unwillingness of pharmaceutical companies to share the raw data arising from clinical trials (WHO 2003).

47. The upshot of this in the case of the antipsychotics has been a set of guidelines indistinguishable from the ones drawn up by TMAP, or by other guideline groups linked closely to pharmaceutical companies (NICE 2003). NICE recommends the use of the new antipsychotics over old, even though it acknowledges it does so without having any evidence base for this. In fact, the NICE guidelines fly in the face of evidence that new antipsychotics compared in clinical trials with the older antipsychotics and placebo produce significantly higher death rates from a variety of causes and significantly higher suicide rates, as well as a range of physical problems, from cardiovascular to endocrine disorders, that were not linked as frequently to the older antipsychotics.

48. In a public health system such as the NHS, NICE guidelines are implemented in a very similar way to the TMAP guidelines. The medical directors of hospitals will ordinarily seek to ensure that their clinical staff adhere to NICE guidelines. As a direct result of NICE then a much larger number of patients will end up being given new rather than old antipsychotics than would otherwise have been the case, with a probable resulting detriment in the collective patient health, brought about at vast cost. It is all but impossible for individual clinicians to opt out of the system as the public health system endorses adherence to these guidelines and practicing outside the guidelines may not be regarded as evidence based.

47 As of 2004, these guidelines had been adopted at some point by Pennsylvania, California, Colorado, Nevada, Illinois, Kentucky, New Mexico, New York, Ohio, South Carolina, Maryland, Missouri, and Washington DC, or by jurisdictions within those states.

48 It is important to note that the author participated as a guideline panel member in this Risperdal exercise.
49. The critical influence here lies with the clinical trials that supposedly form the basis for the guideline process. Newer agents almost invariably have more and larger trials than older agents, especially if this is for indications that have been “created” since the older drugs went off patent. A great number of older agents may in fact have minimal trial data. Those constructing the guidelines rarely appear to take into consideration the fact that the larger the trials needed, the weaker the drug must be, and that in general trials are only needed when there are some doubts as to whether the drug actually works or not. But, even more critically, the underlying data that might reveal increased deaths from suicide and other causes that might occasion a different set of conclusions are never available to those constructing the guidelines.

50. While the data that might have led NICE to a different conclusion were not available in the reports of randomized trials of these agents, a good deal of relevant data was in fact publicly available in reviews published by the Food & Drugs Administration (FDA) for each of the new antipsychotics at the time of licensing. In the case of suicides, a great deal of the data was available in a paper on rates of suicides and suicidal acts in clinical trials with novel antipsychotics.

51. These published data show high rates of suicide on Risperdal and perhaps the highest rates of suicide in clinical trial history on Zyprexa (see table 1). But the most surprising thing is that the paper offers no figures for suicidal acts on Zyprexa, while it does offer figures for suicidal acts in the clinical trials programs for the other new antipsychotics. Against a background of possibly the highest suicide rates in clinical trial history, this absence of data on suicidal acts for Zyprexa is striking. Eli-Lilly, the makers of Zyprexa, have since refused to answer questions as to what the rate of suicidal acts on their drug might be. Despite this, this drug has become the best selling antipsychotic on the marketplace.

52. NICE guidelines however as mentioned endorse the use of both Risperdal and Zyprexa over older agents, although given the absence of these key data and public knowledge about this key absence, it is difficult to see how any patient taking Zyprexa can be taking it on the basis of informed consent. While NICE guidelines do not have the force of law, it would be difficult for clinicians in the UK to flout this guidance. Thus, there are good grounds to think that the availability of NICE, TMAP and other guidelines has resulted in a vast increase in the expenditure of drugs in the mental health domain at a presumptive cost to the development of other services, and this increase has also taken place without any reasonable expectation of health gains at either the individual or systems level.

**Pharmaco-Economics**

53. In the case of these newer agents, another method resorted to by companies has been a set of pharmaco-economic procedures. Pharmaco-economics as a discipline began in the 1970s, heavily subsided by the pharmaceutical industry (Healy 1998). It basically involves estimating and comparing the costs of leaving a condition untreated against the costs of treatment. The original view of the first pharmaco-economists was that the complications of establishing treatment effects and outcomes for psychotropic drugs across a range of domains of value in mental health meant it would be impossible to apply the procedures of pharmaco-economics to psychiatric conditions and treatments.

54. Nonetheless the emergence of a set of SSRI antidepressants and atypical antipsychotics that could not be distinguished from older agents in terms of efficacy or tolerability, but which were associated with greatly increased costs, led to a flurry of pharmaco-economic exercises. This is exemplified nicely by the emergence of supplements to major journals detailing a range of pharmaco-economic approaches that probably did a good deal to smooth the marketing path of the SSRI antidepressants (Eccleston 1993).

55. One of these methods involved the establishment of Delphi panels of experts. Delphi panels invite experts to consider clinical trial data and estimate the likely translation from the actually published randomized trial evidence to possible outcomes in clinical practice if the drugs are adopted widely. These outcomes are then costed by economists working to the manufacturing company.

56. The participants in these exercises will again be unaware of assessments such as those made by the FDA, or the data on suicide or death rates from trial programs. The invariable outcome of these proceedings has been sets of models indicating that treatment with newer agents costing ten to eighty times more than older agents would in fact lead to savings in either for profit healthcare systems such as that of the United States, or socialized medical systems such as the UK mental health system (Guest et al 1996).49

57. No one seems prepared to say what the original exponents of pharmaco-economics realized, namely that short-term trials cannot be used for this purpose. This issue is now further complicated by something that would once have been all but inconceivable, which has been hinted at above and is developed below, namely, the fact that in a growing number of cases critical aspects of the raw data are substantially at odds with the published data.

49 It is important to note that the author also participated as a Delphi panel member in this Risperdal exercise.
"Ghost-writing"

58. In the 1980s, pharmaceutical companies began to outsource a range of functions, such as the running of clinical trials and medical writing, to other companies. Medical writing was outsourced to medical communication agencies. With this development, the practice of ghost-writing academic articles picked up pace. Ghost-writing involves medical writers writing articles, which subsequently appear under the apparent authorship of academics who might or might not have reviewed the piece before publication; the ghost traditionally is the medical writer who receives no credit for her input. For some time it was believed that this form of medical communication was largely confined to journal supplements or peripheral journals (Healy 2003, & 2004). The first hints that the picture might be somewhat different came in the mid-1990s. Flanagan and colleagues for example reported in 1998 that up to 11% of articles published in six mainstream peer reviewed journals involved the use of ghostwriters (Flanagan, Carey, Fontanarosa et al 1998).

59. Recently a document became publicly available covering the co-ordination during the course of 1998 of medical articles on Pfizer’s antidepressant Zoloft (sertraline) by a medical communications agency, Current Medical Directions (CMD). This has permitted the comparison of published articles written for Pfizer with other articles on Zoloft in terms of the impact factor of the journals in which they appeared, prior publication history of the respective authors and subsequent citation rates of the respective series of articles.

60. The analysis showed the journals in which Pfizer’s articles were published had an impact factor three times greater than the journals in which other articles on Zoloft were published. The authors on Pfizer’s articles had nearly three times more previously published articles, as cited in Medline and Embase, than the authors of articles not linked to Pfizer. Of greatest importance was the subsequent citation rate. It might be thought that, despite publication in the most prestigious journals and under the apparent authorship of the most distinguished academics, clinicians and researchers would find this literature too obviously industry linked and would not be influenced by it. However, the subsequent citation rates for the Pfizer-linked articles were three times greater than that of the non-Pfizer articles (Healy and Cattell 2003).

61. The profile of this so-called scientific activity suggests that Pfizer ended up with a set of authors whose background increased the possibility of the company’s publications appearing in the most prestigious journals. The combination of distinguished journal, distinguished author, an efficient distribution system and sponsored platforms appears to have led to an impact on the therapeutics domain greatly in excess of 50% of the impact of the rest of the literature on Zoloft. At present roughly three-quarters of all randomized trials appearing in JAMA, NEJM or the Lancet are industry funded.

62. The impact of this literature on third party payers is at present unquantifiable, but authorship by perceived opinion leaders with minimal company representation and non-declaration of other authorship inputs increase the likelihood that these articles will be influential with purchasers as well as prescribers.

63. Academics become opinion leaders in a therapeutic field because they have their names on a larger proportion of the literature appearing in the most prestigious journals than their colleagues, and because they get asked to international meetings to present this data (with which they may not, in fact, have first hand acquaintance. This, allied to the volume of industry-linked authorship, is arguably leading to a situation in which the dominant figures in therapeutics actually have little first hand research experience and may have no raw data that they can share with others and probably have simply never seen the raw data. This is a situation in which, in contrast to the traditional perception of who the ghost authors are in the medical literature, our leading academics have become ghosts or ciphers.

64. It is in fact a situation in which ghost-writers increasingly have to take on ghost-acting as part of their repertoire. This happens because the apparent authors of a study will often now have so little familiarity or association with the basic data, that they either cannot present it at major meetings or are not inclined to do so in for instance poster form. As a result it is becoming increasingly common to find medical writers presenting posters at academic meetings, where they will in all probability often be assumed to be doctoral students linked to the research being presented.50

65. The situation that has developed underlines the significance of the proprietary control of raw data. The raw data from one trial of Zoloft compared to mianserin or placebo in the CMD series, for instance, shows that one patient on Zoloft committed suicide and three others had their treatment discontinued because of increasing suicidal ideation. In contrast there was just one case of emergent suicidality on the comparator drug mianserin and no problems on placebo. But the final published article makes no reference to any patient becoming suicidal in any way (Malt, Robak, Madsbu et al 1999).

66. Second, within the CMD series of articles on Zoloft, there were six that dealt with the use of Zoloft for children. Of these six articles, only one mentions suicidality—one single suicidal act. There were in fact six suicidal acts on sertraline in the trials that these articles report: a rate approximately six times higher than the published rate in adults.51 The rate of suicidality in depressed children taking sertraline was in fact nine per cent. However the article dealing with the hazards of treatment in children who are depressed only reported on the side effects that occurred at a ten per cent rate or more (Alderman, Wolkow, Chung et al 1998).

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50 This claim is based on the personal experience and discussions with ghost-writers/actors.
The consensus on treating children with psychotropic drugs

67. The consequences of these developments came to a focus in 2003 on the issue of treating children with psychotropic drugs. The TMAP children’s algorithm project outlined above endorsed the use of SSRI antidepressants for treating childhood nervous disorders, largely on the basis of a series of unpublished trials. Although unpublished, the experts formulating algorithms for TMAP and the experts running these trials and appearing as authors on the few published trials were in many instances the same people. These experts therefore had a better opportunity to know what the raw data looked like than anyone else. As a result, the issue of treating children with psychotropic drugs offers a good case example to bring out a number of features of the new world of manufactured consensus.

68. There has been a long-standing awareness that it is difficult to show in clinical trials that antidepressant drugs offer benefits for children. Despite this there were grounds for using psychotropic drugs for children, and guidelines on the treatment of children who were depressed endorsed such usage (Healy and Nutt, 1998). The advent of the SSRI antidepressants offered some hope that these agents might be shown to be effective for children where efforts with older agents had failed.

69. In the early 1990s, regulatory authorities approved the use of the SSRIs Paxil and Zoloft for the treatment of depression for adults. They had previously approved Prozac and subsequently approved Celexa and Effexor. From the 1990s, standard letters of approval to companies noted that as these drugs were likely to be used to treat children studies to establish the safety of the drugs in these populations would be helpful. This encouragement led to a series of studies of SSRIs in children during the early to mid 1990s. A further incentive was put in place in 1998 with an FDA Modernization Act (FDAMA) (Sharav 2003), which offered patent extension on the basis of testing for rather than proving safety; if the drugs showed hazards, the company still got patent extension but had to incorporate this information in the label.

Prozac

70. In the case of fluoxetine an early series of clinical trials failed to establish efficacy for this drug in treating childhood nervous problems. This work led to a study that started in 1990, which involved extensive pre-screening of patients so that less than one-fifth of those screened entered the study, and those who did were put through a placebo washout phase in an effort to reduce the high rate of placebo responsiveness found in SSRI trials in children. Using these procedures, an article that appeared in 1997 claimed that Prozac could produce beneficial effects for children and adolescents (Emslie, Rush, Weinberg et al 1997). However, in fact on the primary end-point measure, Prozac was no better than placebo and on secondary measures benefits were apparent on physician-based ratings but not on patient or carer ratings. In addition, there was a 29% drop-out rate on Prozac and the rate of behavioral side effects was greater on Prozac than on placebo.52

71. This Prozac study had been run under the auspices of the NIMH. Subsequently another study funded by the makers of Prozac, Eli Lilly, led to a comparable result (Emslie, Heiligenstein, Wagner et al 2002). The second study, in contrast to both the previous Prozac study and studies of other SSRIs and in contrast to clinical practice, showed no greater rate of adverse events on Prozac than on placebo. This combination of studies led to a license for Prozac for the treatment of depression in children and adolescents in 2003.

72. A further study had been undertaken on Prozac for obsessive-compulsive disorder (OCD). This showed somewhat more clearly positive results for Prozac over placebo, but equally an excess of suicidality over placebo.

Paxil

73. The first study undertaken with Paxil, protocol 329, was conducted in the early to mid-1990s. The published report from 2001 pointed to mixed benefits of Paxil on the primary endpoints of the trial, with apparent responsiveness on some measures accompanied by non-responsiveness on others, concluded that Paxil is effective, safe and generally well-tolerated (Keller, Ryan, Strober et al 2001). But in this study there was an increased rate of suicidal acts on Paxil (5/93, a 5.4% rate) compared with either imipramine (1/95) or placebo (0/89). The difference between Paxil and placebo was close to significance at the 95% level (p = 0.06), and the difference between Paxil and comparators (1/183) was significant.

74. These figures were not apparent from the published the paper, where suicidal children were coded as having had emotional lability. Hostility was also a reported side effect in 6.5% of Paxil patients in this study versus 1.1% on placebo. While the published paper does outline that emotional lability might include suicidal acts, this is not a common meaning of the term for most clinicians, who will be unaware that dictionaries for coding side-effects, such as the ADEC’s system, offer the possibility to code suicide, suicidal acts and suicidal ideation under the heading of emotional lability. The same dictionary codes homicidal acts, homicidal ideation and other aggressive acts under the heading of hostility.

52 Food and Drug Administration Review.
75. A second, protocol 377, and a third protocol 701, and a fourth trial protocol 716 failed to demonstrate efficacy for Paxil for depression, and also seems to have returned an increased frequency of suicidality on Paxil. The first two of these studies, which appear to have been completed by 2000, were presented in part in abstracts in 2001 and 2002 that concluded that Paxil was effective, safe, and generally well-tolerated (Wagner, Wetherhold, Carpenter et al. 2002). The fourth apparently remained unscrutinized by FDA, when FDA undertook a review of SSRI agents in children in 2003.

76. At much the same time studies of Paxil in obsessive-compulsive disorder (OCD) were instituted, protocols 453 and 704. Reports of these studies in abstract form also claimed that Paxil was effective safe and generally well tolerated (Geller, Wagner, Emslie et al. 2002). However, company data on file point to an increased rate of side-effects on Paxil compared to placebo, in the domains of hostility, agitation and hyperkinesis. In 453, 6.3% of children taking Paxil (n = 97) became hostile compared with 0% on placebo (n = 100). In 704, 9.2% of children became hostile on Paxil (n = 98) with 1% becoming hostile on placebo (n = 105). There was also an increased frequency of suicidal acts on Paxil (1/195) compared to placebo (0/205).53

77. Finally, a study of Paxil was conducted in social phobia, protocol 658. The unpublished results indicate that Paxil might in some cases produce a beneficial effect in children, but as with depression and OCD there was a higher rate of adverse events in the behavioral domain on Paxil compared to placebo. In this case there appear to have been three suicidal acts in 165 children on Paxil compared to 0 in 157 on placebo.54

**Zoloft**

78. In the case of Zoloft, in the mid-1990s, a double blind placebo controlled study was undertaken in OCD, which reported that Zoloft can have a greater beneficial effect on core features of OCD than placebo (March, Biederman, Wolkow et al 1998). This paper, which was one of the CMD series, noted one suicidal act on Zoloft compared with one that might have been on placebo.55 In the absence of the raw data, it is not clear whether this suicidal act on placebo actually occurred during the randomized phase of the trial, as in the case of Pfizer’s clinical trial program in adults suicidal acts that occurred during the washout phase of trials were coded under the heading of placebo (Healy 2003).

79. At the same time, Pfizer initiated open trials of Zoloft in children who were depressed. In the first of these, also reported in the CMD series of papers, 44 children were given Zoloft of whom four became suicidal, a 9% suicidality rate. The article reporting these results portrayed Zoloft as likely to be effective, and generally well-tolerated; this article also restricted itself to reporting on the side-effects that occurred at a 10% rate or more (Alderman, Wolkow, Chung et al 1998). A further open study of Zoloft in depression, also in the CMD series, reported that there were three suicidal acts among 53 children who were depressed, a 5.6% rate (Ambrosini, Wagner, Biederman et al 1999).

80. The expert report on these early OCD and depression studies undertaken for Pfizer commented, “Clinical studies in pediatric patients with OCD (aged 6–17 years) have shown that sertraline is well tolerated. The adverse events which led to discontinuation were generally psychiatric in nature, and there were no discontinuations due to laboratory safety data following administration of sertraline”56

81. Subsequently, Pfizer conducted two randomized controlled trials on Zoloft in depression. These were both negative; combined, however, they were reported as showing Zoloft as effective and well-tolerated (Wagner, Ambrosini, Rynn et al 2003). In fact, 59% of children on Zoloft showed a change of 5 points on a Clinical Global Impression scale against 49% of children on placebo showing comparable changes, a finding that only reached statistical significance when both studies are combined. In the case of the side-effect profile, there was a doubling of the rate of behavioral problems, including suicidal acts, suicidal ideation and aggression in children on Zoloft (6/189) compared to children taking placebo (2/187), and a 9% drop-out rate on Zoloft versus 3% on placebo for adverse events, but in fact 46 of 189 children on Zoloft, 24%, dropped out for one reason or another (Garland 2004).

82. The actual drop-out rates on Zoloft contrast with a lower rate of reported behavioral problems in this study compared to earlier studies on both Zoloft and Paxil. In addition it can be noted that the design in this study did not encourage detection of adverse events. In SSRI studies where side effects are more actively sought, the rates are higher. For example, in a study of fluvoxamine in anxiety, increased motor activity was found in 27% of children compared to 12% of placebo patients (p = 0.06) (Walkup, Labellarte, Riddle et al 2001). This study in contrast to the Zoloft studies above used side effect checklists.

Efexor

83. In the case of Efexor, two studies have been undertaken in depression and two in generalized anxiety disorder. One study published in 1997 suggests venlafaxine was safe, and well-tolerated, but that efficacy had not been established (Mandoki, Tapla, Tapla et al 1997). However it now seems that in the combined depression studies there was an increased rate of children becoming hostile (2% v < 1% on placebo) and suicidal on venlafaxine compared to placebo (2% v 0%) (Kuslak 2003). There seems no prospect that the full findings from these studies will be published.

The Unraveling of the Consensus

84. In addition to a small number of publications (six full articles with three abstracts) from approximately 15 randomized trials in children, there were approximately 70 publications of open studies or case reports with Celexa, Prozac, Paxil, Zoloft, Luvox and Efexor. The open studies and published double blind trials universally portrayed these drugs as safe, well-tolerated and effective when given to children.

85. In 2002, the issue of Newsweek coinciding with World Mental Health Day carried a cover feature of a depressed teenage girl (Newsweek 2002). The inside story outlined that there were three million depressed teenagers in the United States, and that if left untreated this would lead to high toll in substance abuse, failed marriages and careers and deaths from suicide. The article noted that there were a number of new antidepressants, such as Paxil, Zoloft and Prozac, which could help. Such articles commonly have input from PR companies working to pharmaceutical companies. The expectation in this case would appear to have been that a number of SSRIs would shortly have a license to treat teenage depression.

86. It is important to understand what licensing means in this context. It does not mean that physicians would thereafter be enabled to treat children who were depressed in a way that they had been unable to do before. It means rather that Pfizer, Lilly and Glaxo SmithKline would be enabled to convert the vicissitudes of teenage angst into an illness, one supposedly stemming from a chemical imbalance, and one that it was appropriate, indeed almost morally necessary to detect and treat.

87. There are no grounds to believe that NICE would have come to any different conclusions to TMAP on the issue of how to treat depressed children, when they in due course had gotten round to considering this issue, as they would have been called on to do had the drugs been licensed in the United Kingdom. Fate and the media intervened to ensure this never happened.

88. As a result of a Glaxo SmithKline application to the regulators for a license for Paxil to treat childhood nervous disorders, the raw data from clinical trials were lodged with a number of national regulators. Within a fortnight of seeing the raw data in response to queries as to the events behind the term emotional lability, in May 2003 the regulators in the United Kingdom issued a warning against the use of Paxil (Seroxat) for minors. A few weeks later, Glaxo SmithKline wrote to all doctors noting that Paxil use was linked to suicidality and that withdrawal from Paxil was also linked to an apparent doubling of the rate of suicidality. Three months later, Wyeth recommended against the use of Efexor in children, in similar terms. Later that year in December, the British regulators issued a position statement in which they stated that none of these drugs, bar Prozac, had demonstrated efficacy in depression.

89. These developments led to a projected FDA hearing for 2 February 2004. Ten days before this hearing, a working group for the American College of Neuropsychopharmacology reported that after reviewing the evidence it was the task force’s view that SSRJ drugs were safe and effective and well-tolerated by children (Emslie, Mann, Beardslee et al 2004). The authors of this report included Emslie, Wagner and Ryan who had all been authors on study 329, and between had been authors on most of the randomized trial literature on SSRIs given to children. These three authors and their co-authors however noted that they might not be correct in their conclusions that there were no problems with SSRIs in that they had not seen the raw data.

90. Despite this move which was widely seen as a pre-emptive strike, in February 2004, an FDA hearing on the use of psychotropic drugs for children recommended strengthening the warnings on these drugs, against a background of regulatory assessments that at least 13 of the 15 studies undertaken of antidepressants in children failed to show efficacy for the drug, and panel views that there appeared to be an activation syndrome on these drugs.

57 This was initially only available through GYMR, a Washington based public relations company, who specialise in translating the language of science and medicine into the more understandable language of health. From GYMR.com, GYMR was “founded in 1998 by a team of experts in healthcare and social change . . . [i]t offers clients marketing and communications expertise that strategically support public policy goals . . . [clients] include many of the nation’s most respected associations, government agencies, pharmaceutical companies, philanthropic organizations and health initiatives.” “Whether it’s provoking action on a national health issue or crafting an organizational image that appeals to internal and external audiences, GYMR excels at designing and implementing issue and image campaigns.” “Our media events are successful because we have a nose for news. We know how to take the language of science and medicine and transform it into the more understandable language of health. We advise clients of the best dissemination strategy for their news and make sure that the message they deliver is compelling, documented and contributes to other national dialogues in a real and meaningful way.”

58 www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.htm
91. It transpired that in 1998, a SmithKline Beecham assessment of the Paxil studies, which had been completed at that time, 329 and 377, indicated that the drug did not work for depressed children, but that the data would not be submitted to the regulators, as a statement to the effect that the drug had not been shown to work for children would have a negative commercial impact. Selected positive data, however, would be progressed to publication.

92. What lessons can be drawn from this situation which probably offers the greatest divide in all of medicine between the raw data on an issue on the one side and the published medical accounts purporting to represent those data on the other?

93. First, this divide gives the lie to a body of close to 100 papers and abstracts universally reporting the benefits of these drugs. These open and randomized trials would seem have the appearances but not the substance of science. The discrepancy between the papers and the underlying data may stem from the possibility that many if not close to all of the key studies have been ghost-written. It is difficult to avoid such a conclusion when even the notional authors of the key papers claim not to have seen the raw data.

94. It follows from this that it is almost impossible to accept that these are scientific papers. What the field would appear to need is a new term with which to designate such infomercials, and a set of criteria that might reliably identify this new genre of marketing product that aims at manufacturing a clinical consensus. This it should be noted is the aim of all good marketing—to own the market, not just to sell the product (Applbam 2004).

95. A second point is that while pharmaceutical companies know exactly how many prescriptions have been issued and just what each physician writes, almost no-one knows how many children or adults are on any psychotropic drugs. When this fact is allied to the fact that serious adverse events are reported by physicians to regulators in no more than one in one hundred cases, a picture emerges in which Americans and others track the fate of parcels put in the post 100 times more accurately than they track the occurrence of adverse events on these drugs. The quality of the information reported by patients on adverse events indeed would appear to be much better than that reported by physicians (Hersheimer and Mintzes 2004). This is a situation that could not have been tailored better to maximize the consensus building capacities of pharmaceutical companies.

96. There would appear to be reasonable grounds to state that there must be some fundamental opposition between marketing and science in that the former explicitly operates to build consensus, while the latter supposedly moves forward by fracturing consensus. When we have arrive at a situation in which the mental sets of clinicians have been captured so that it is difficult for them to conceive of alternatives to those being sold to them, there are reasonable grounds to state that such a field is no longer scientific. When there is almost no possibility of discrepant data emerging to trigger a thought that might be unwelcome to the marketing department of a pharmaceutical company, these marketing capabilities would seem appropriately described as totalitarian.

REFERENCES


137. WHO Technology appraisal programme of the National Institute for Clinical Excellence. Geneva: WHO Available at www.nice.org.uk

154. Table 1:

<table>
<thead>
<tr>
<th>INCIDENCE OF SUICIDES AND SUICIDE ATTEMPTS IN ANTIPSYCHOTIC CLINICAL TRIALS DRAWN FROM REGULATORY LICENSE APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Risperidone</strong></td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Sertindole</strong></td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>New Antipsychotic</td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

The data here comes from FDA medical and statistical reviews of risperidone, olanzapine, quetiapine and ziprasidone and from Lundbeck pharmaceuticals in the case of sertindole. Analyzing the data on suicides using an exact version Mantel Haenszel procedure and a one-sided test for significance yields an odds ratio with a Confidence Interval of (1.0825, Infinity), \( p = 0.03955 \), for new antipsychotics compared to placebo.
Personal Statement

I have taught clinical pharmacology and therapeutics at London University from 1960 to 1991, most recently at Charing Cross and Westminster Medical School. I founded Drug and Therapeutics Bulletin, published by Consumers’ Association, in 1962 and edited it until 1992. I chaired the International Society of Drug Bulletins from its foundation in 1986 till 1996, and the Health Working Group of Consumers International. I have many times been a consultant to the World Health Organization. I am interested in all aspects of providing independent, unbiased, clear and concise information about therapeutic interventions to professionals and the public, and have long experience of observing the pharmaceutical industry at work.

Since 1992 I have worked in the Cochrane Collaboration and am now Emeritus Fellow of the UK Cochrane Centre in Oxford.

If the Committee wishes, I would be willing to give oral evidence.

This memorandum focuses on the following main issues, the first three of which contribute substantially to a systematic over-estimation of drug benefit and underestimation of harm:

1. The influence of the industry on medical practice and on the regulation of medicines is pervasive, overpowering and relentless. The problem of undue and unhelpful influence is, arguably, related much more to the extent and volume of industry influence, rather than to outright malpractice.

2. The industry takes little pro-active interest in adverse effects of drugs; only legal or commercial concerns move it to do more than the regulators require. The drug regulatory framework encourages this complacency by relying excessively on pre-marketing clinical trials in defining drug safety profiles.

3. The nature and extent of drug marketing is worrying, not least because of the intensity of promotion at and soon after a drug is launched—ie when relatively little is known about the performance of a drug in clinical practice. A conspicuous example of the negative impact of drug marketing relates to recommended drug dosage, which is often inappropriately uniform. It is not true that one size fits all, as marketing often demands; industry and the regulators need to take much more account of important differences among users.

4. What might be the most effective ways of containing undue industry influence in the future?

1. The Industry’s Influence

The development of drug regulation in the UK that followed the thalidomide disaster has been described in detail by John Abraham (1995). From the beginning in 1962, when Lord Cohen’s Committee reported on the testing and regulation of new drugs, the industry has greatly influenced what was to be done. Close collaboration between industry, ministers and civil servants on the principles and details of regulatory policies has continued, albeit with a marked shift towards international regulation since the 1990s. During all this time the Ministry of Health and its successors, the DHSS and the DoH have been the sponsoring Department for the pharmaceutical industry, responsible for its welfare—while also of course being its biggest customer. The industry’s exports were then and still remain important to the national economy, and might be threatened by strict regulation.

Government and industry have strived for and largely achieved a family atmosphere of cooperation and trust—hardly dimmed by some adversarial episodes—and reinforced by the blanket secrecy guaranteed by s 118 of the Medicines Act, 1968. Over the years many personal relationships have grown between regulatory officials and the staff of pharmaceutical companies, helped by a “revolving door” and frequent meetings to address regulatory matters. The argument has been that experience of working in the industry is highly desirable, if not essential, to understanding the practical implications of regulatory issues. Similarly comfortable contacts have existed between many of the members of the Committee on Safety of Medicines and industry, and this continues.

These close working relationships over decades have meant that industry views have been much more prominently represented—and to a notable extent internalised—in drug regulation than the interests of patients and consumers, or of clinicians.

The influence of the industry on medical practice is enormous, but largely intangible and unseen. It is mediated by its internationally and nationally dominant position in determining the agendas of therapeutic research and providing funding for it, by the huge volume of pharmaceutical promotion, direct and indirect

This trend was underlined by the founding of the European single market and the setting up of the European Medicines Evaluation Agency, and the establishment of the International Conference on Harmonisation (on technical requirements for registration of pharmaceuticals for human use).
Ev 90  Health Committee: Evidence

... (including its scientific publication policies and its selective support of continuing medical education), and intense public relations activity. Competition in the industry is based far more on innovative marketing methods and public relations than on the effectiveness and safety of its products.

The industry tries its considerable best to control information about its products and its work. It naturally wishes to guard all unfavourable information, claiming commercial and proprietary rights, and ceaselessly pushes the positive aspects at all its target constituencies—prescribers, patients, consumers, health service managers, politicians. This is called “Providing information”.

One seriously harmful result of these frenetic activities, which governments have ignored, is that drug treatments are uppermost in the minds of doctors and the public, and non-drug treatments (including non-intervention) are very often not adequately considered. There is much less money to promote these.

Recommendations

1.1 The sponsoring Department for the pharmaceutical industry should be the Department of Trade and Industry instead of the Department of Health. Similarly, responsibility for regulation of the pharmaceutical industry in Europe should rest primarily with the Directorate-General for Health and Consumer Protection, rather than the Commission’s departments for Enterprise and Trade.

1.2 Policies should be developed for reducing the potential for conflicts of interest in medicines regulation, including complete transparency about the conflicts that may exist.

1.3 The NHS, which pays for the promotion of medicines as an important part of their cost, should thoroughly investigate the health impacts of promotion, including the benefits and harms of various forms of medicalisation of common problems, and of disease awareness campaigns aimed at the public. It would be logical to fund such research through a small levy on promotional spending by companies.

1.4 If self-regulation of pharmaceutical promotion by the industry is to continue, independently chosen representatives of the public interest should play a substantial if not dominant part in it.

2. **Adverse Effects of Drugs**

All medicines have unwanted effects, which prescribers and users must understand and be able to manage. They need to know what may happen and what to do if it does. They have to use the drug in ways that minimise the chance of unwanted effects and their intensity.

The task of medicines regulation is to assure their “safety, quality and efficacy”. This work is done mainly before products are licensed. The regulators have to satisfy themselves about these before approving a product, and for this purpose require detailed data from the company, including “safety data” from studies of pharmacology and toxicology in animals, studies in healthy volunteers and in patients. These studies are primarily intended to demonstrate the harmlessness (“safety”) of the drug. Companies themselves undertake and commission the large amount of work needed to meet all the regulators’ requirements. They do not usually investigate how various adverse effects are produced.

After a licence has been issued and the product marketed the Post-Licensing Division of the MHRA is in charge of continuing surveillance of safety; companies must report to the MHRA all adverse events they become aware of. This is the mainstay of what is called pharmacovigilance, but the scope of pharmacovigilance is, in practice, quite limited. Lack of transparency has proved an obstacle to assessing its quality and impact overall, though there are obvious grounds for concern (Medawar & Herxheimer, 2003). Companies rarely do more research on safety aspects unless they need to defend the product when a serious adverse effect is alleged or suspected, or to show that it is safer than a competing product. The design of studies performed in these circumstances is liable to be much influenced by legal and commercial considerations.

It is unusual for regulators to require (as opposed to request) companies to do further studies of adverse effects on a licensed product; they may not have the power to do so, nor can they check that such studies are adequately designed and performed. It is no-one’s job to undertake or to fund such work. What little work is done tends to be done by interested independent researchers without specific funding.

Since the Inquiry focuses on the impact of the industry on the regulatory review of drug safety and efficacy, it may be necessary to discuss some aspects of pharmacovigilance in detail, and I have therefore tried to put these briefly into context in Appendix A.

Recommendations

2.1 Research on the natural history, mechanisms, prevention and clinical management of adverse drug reactions (ADRs) should be encouraged and publicly funded. It should be independent of industry and of drug regulatory agencies. Consideration might be given to organising the funding of such work through a modest levy on pharmaceutical sales.
2.2 Adverse drug reactions represent only one (the most visible) aspect of the ill-effects of drugs on health. The impact of drug use on communities, including the medicalisation of personal problems and the drawbacks of "disease awareness" promotion need also to be addressed.

3. Doses

The doses to be recommended for new drugs are decided by the manufacturers, on the basis of their experimental dose-ranging studies in healthy volunteers and patients. These studies are submitted as part of the licensing application, but few are published. Many recommended drug doses are higher than is medically necessary, for two reasons (Herxheimer 1991; Cohen 2001).

The first is that manufacturers aim for a dose that will be effective in the great majority of people given it. A simple dosage scheme, one-size-fits-all, appeals to prescribers and so helps market penetration. Complicated dosage regimens tend to inconvenience doctors and to create practical difficulties for many patients. Also, doctors and patients will not wish to use the drug if it is ineffective in a substantial proportion of people. So drugs are typically introduced at a dose that will be effective in the highest proportion of the target population. But patients vary quite widely in their sensitivity to various drugs, and the standard "recommended" dose is too high for many, causing unwanted effects that range from transient unpleasantness and inconvenience to serious harm, while a lower dose would have been effective and much less likely to cause trouble.

The second reason for doses being higher than necessary or desirable is that manufacturers prefer doses rounded up to "convenient" numbers, especially those ending with the digits 1, 2, 5, and 0. The dose excess due to such digit preference may be as much as 70% of the correct dose and on average is probably 25% (Herxheimer 1991).

Drug regulators have traditionally paid little attention to dose and generally accept the doses proposed when drugs are first marketed. One reason for this may be that all the clinical trials that prove the drug’s effectiveness have been performed at those doses: to require new trials at lower doses would cause long delays and high costs, which would be hard to justify. About one in six drugs have had dosage recommendations modified (generally downwards) at some time after licensing.

Recommendations

3.1 Companies should be required to submit evidence on the lowest effective dose for all drugs for any significant minority of users, and regulators should require that this dosage will be in the range of doses to be marketed.

3.2 Companies should be required to submit, and after licensing to publish, dose-effect data for all the intended beneficial effects, and the most important unwanted effects of the drug.

4. What might be the most effective ways of containing undue industry influence in the future?

Many factors complicate the Health Committee’s task in assessing the impact of the pharmaceutical industry’s influence, and addressing the problems it creates. The major factors include: the extent of acceptance and complicity among other stakeholders; the increasingly international character of the pharmaceutical industry; the introduction of supranational regulatory mechanisms and standards; and the traditional and pervasive secrecy in this field, in particular relating to drug risks and harms.

The options available for proposing reform seem limited, other than in relation to the last of these factors. Transparency seems all the more critical because of the rapidly waning influence of national authority in drug control. I believe there would be overwhelming support from all concerned about the adverse impacts of industry influence, for recommendations from the Committee that might lead to greater transparency in this field. Freedom of information—including freedom of expression and protection for whistle-blowers—is a prerequisite to the planning and implementation of reform. Without this it is unrealistic to suppose that pernicious influence can be contained. In the absence of transparency, it would seem much more likely to grow.

References


APPENDIX A

The relationship between pharmacovigilance and drug safety

1. To equate drug safety with pharmacovigilance in its present form is a dangerous delusion: Pharmacovigilance makes only a modest and partial contribution to drug safety.

2. Accidental and avoidable harm is nowhere near revealed by pharmacovigilance. Mishaps involving medicines are a leading cause of death in hospitals in the UK. To assure the public about drug safety on the grounds that we have a well developed pharmacovigilance system is misleading.

3. The gross underreporting of ADRs in all countries means that we cannot conclude that a lack of reports even about a widely used drug means that it does no harm.

4. Neither in the UK nor as far as I know in any other European country has there ever been any public enquiry into any mishap with drugs (unless TV programmes count).

Table—Professional tasks relating to adverse drug effects

<table>
<thead>
<tr>
<th>Task</th>
<th>Is it done?</th>
<th>With what results?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Preclinical animal toxicology</td>
<td>Always done</td>
<td>Results secret</td>
</tr>
<tr>
<td>B. Preclinical human toxicology, including adverse effect monitoring during clinical trials</td>
<td>Always done</td>
<td>Results often secret</td>
</tr>
<tr>
<td>C. Gather and analyse spontaneous reports of suspected ADRs</td>
<td>Done</td>
<td>Crude summaries accessible</td>
</tr>
<tr>
<td>D. Assess causality: is a particular kind of adverse event caused by the drug? Can it be distinguished from similar events not caused by it, and if so, how?</td>
<td>Done, but often by people not medically trained nor experienced</td>
<td>Some results, published with delay</td>
</tr>
<tr>
<td>E. Describe the characteristics and natural history of the effect</td>
<td>Rarely done</td>
<td>It seems to be no-one’s responsibility</td>
</tr>
<tr>
<td>F. Investigate and discover the pharmacological/ biological mechanisms involved</td>
<td>Rarely discussed; rarely done?</td>
<td>Regulators not equipped companies not interested?</td>
</tr>
<tr>
<td>G. Investigate the epidemiology of the effect: frequency, seriousness, risk factors</td>
<td>Sometimes done</td>
<td>Selectively published in summary with delay</td>
</tr>
<tr>
<td>H. Work out possible ways of preventing or attenuating the effect, and testing them</td>
<td>Rarely done properly</td>
<td>Mostly attempted by desk/armchair work</td>
</tr>
<tr>
<td>I. Develop treatments for people who have suffered damage</td>
<td>Rarely done systemically</td>
<td>No-one’s official job</td>
</tr>
<tr>
<td>J. Review the balance of benefits and harmful effects of the drug in different clinical situations</td>
<td>Done by regulators</td>
<td>Process and methods secret, results published</td>
</tr>
<tr>
<td>K. Communicate the knowledge gained to health professionals and the public</td>
<td>Poorly done</td>
<td>Not considered a priority by regulators; distortion by marketing efforts</td>
</tr>
<tr>
<td>L. Revise the official Summary of Product Characteristics, leaflet for patients and licensing status</td>
<td>Done by regulators</td>
<td>Usually not linked to the underlying data, nor properly explained</td>
</tr>
<tr>
<td>M. Check that the new knowledge is used in practice</td>
<td>Not done</td>
<td>Seems to be no-one’s job</td>
</tr>
</tbody>
</table>
Witnesses: Mr Richard Brook, Chief Executive, Mind, Professor David Healy, Cardiff University and Professor Andrew Herxheimer, Emeritus Fellow, UK Cochrane Centre, Oxford, examined.

Q152 Chairman: Colleagues, we have one further witness who will be with us in a moment or two. Can I welcome our second group? We are grateful for your cooperation with the inquiry. Can I begin with apologies that I and my colleague, Mr John Austin, will have to leave at 12.30. In my absence Dr Doug Naysmith will be called to take the Chair. We mean no discourtesy; unfortunately we both have other commitments, but I hope we can get through the business by then. Can I ask you to introduce yourselves briefly, starting with you, Mr Brook?

Mr Brook: Yes. My name is Richard Brook. I am Chief Executive of Mind, the mental health charity.

Professor Healy: I am David Healy. I work in what used to be University of Wales College of Medicine, which has just recently changed into Cardiff University.

Q153 Mr Amess: As you know, gentlemen, this inquiry is called “The Influence of the Pharmaceutical Industry”, but what we would like to hear from you about is are there differences between the way the major pharmaceutical industries display their influence and actually operate? Perhaps if you could name a few of the companies and enlarge on the way you perceive their influence to happen in practice?

Mr Brook: I am happy to start, Chairman. My experience is limited to what has obviously been a very high profile issue around anti-depressants, and I have seen, I think, quite clearly through my time sitting on the Expert Working Group which is part of much of the SSRI's investigation of the last two years into this, very clear influences. I think you only have to look at, for instance, the Committee on Safety of Medicine's declaration of interest which has been recently updated to see three-quarters of the committee actually have defined a personal or non-personal interest, not defined by size, and you only have to realise that that raises a whole issue of transparency, and, as you have already heard in evidence today, the relationship between those members and the drug companies and what is going on. I do not want to make any allegations, but you just do not know—the transparency is not there. You ask for two very specific examples. The two that I would give at this point would be GlaxoSmithKline in terms of the issues of Seroxat and Wyeth, which I do not think has been generally mentioned before in relation to venlafaxine and Effexor. Both of those companies had at least two years before the information went to the MRHA, evidence in relation to paediatric trials, and neither of them bothered to place that evidence into the companies you want your drugs marketed most. I would give at this point would be somewhat sharper than perhaps the practices of the pharmaceutical companies based over in the US.

Professor Healy: I have had interactions with many pharmaceutical companies and I cannot recall one that I would wish to praise.

Q154 Mr Amess: Thank you Chairman. Would you tell the Committee who you are?

Professor Herxheimer: I am Andrew Herxheimer, a medical pharmacologist.

Q155 Mr Amess: As you know, this is an inquiry into the influence of the pharmaceutical industry, but there would appear to be differences in the way the major pharmaceutical companies go about influencing general matters. Mr Brook has just decided to be a bit negative about two companies. Would you gentlemen want to praise any of these major pharmaceutical companies or have you got some axes that you would wish to wield publicly?

Professor Herxheimer: I have had interactions with many pharmaceutical companies and I cannot recall one that I would wish to praise.

Q156 Mr Amess: Right. Well, that is that! What about you, Professor Healy?

Professor Healy: Okay, if I can come in on this. One of the things I do is go round and try and work on the history of the field, which means that I interview people who were working in the area during the Sixties, the Seventies, the Eighties, people who worked within the industry, people who worked clinically whatever, and there was a feeling, I think, to about 10 to 15 years ago that the practices of pharmaceutical companies based over in the US were somewhat sharper than perhaps the practices of the pharmaceutical companies based over here. I think that has changed now, and I think, broadly speaking, all of the companies take much the same approach. I would not, like Andrew Herxheimer, say that this is always a bad thing that he would not wish to praise. If you hold shares with pharmaceutical companies you want your drugs marketed most effectively, and I think almost all the companies take the same approach to these issues these days which involve an increasing proportion of the articles on which physicians like me actually depend being ghost-written, which involve those articles not actually reflecting the raw data from clinical trials that people like you, or your wives, families, get involved in, take risks with or are injured by these pills. The hazards that come out in these clinical trials do not get translated through to the articles...
that shape “formularies”. The issue was actually raised earlier: would we not be able to really sort this all out if we just had a decent “formularies”. No; you would not, because the problem is not the ad; the problem is not the free, kind of like . . . Because what you find these days is people like me are brought to the Caribbean. We come out of the meeting halls with our arms stuffed full of bags of free gifts, free rulers, free pens, free mugs, that have the name of the drug on them. We have had our massage done, portrait painted—

Q157 Mr Amess: You have had your massage done? Professor Healy: People have a massage done, their portrait painted, and are ambushed by the media who hold up the mike and say, “Doctor, are you not influenced by this?”, and the answer from people like me and almost all the physicians you would meet is, “No, we are not.” The media say, “What does influence you then?”, and the answer is we are influenced by the articles we read, the articles in the BMJ, the articles in the the Lancet. If you look at the BMJ these days you will see an advert on the left-hand page and an article, or the first page of an article, which appears to be a randomised controlled trial on the opposite page, and we all look at these things and think, “If only the BMJ did not have the adds in it, things would be fine, and if they had more of these articles which are controlled clinical trials, this is the way we need to move forward.” But industry twenty odd years ago or so actually began to realise that, “Yes, if physicians say they are influenced by the evidence, what we are going to use to influence them is the evidence”, and they began to ghost write up the trials, and increasingly the articles that are written in the BMJ and the Lancet will not just be ghost-written but will not represent the raw data from the clinical trials that they purport to represent; and this can lead to the kind of situation where, if you make “formularies”, the drugs that you will put on the “formularies” that appear to be the most evidence-based will actually be less effective than the ones that you are actually removing from the “formularies”.

Q158 Mr Amess: Before moving to my next question, you have got an awful lot off your chest; you want to have a get together with the free lunch chap! Did you enjoy your time in the Caribbean? Professor Healy: Well, yes, I am in a position to speak to all these things, and the issue was raised earlier, having worked very closely with the industry, having been a person who has actually spoken for the industry; so I know just what the practices are. The issue, the interesting issue for me has been just the issue of what is going on here. You hear very clearly from the industry that actually the sales department who want to give the free pens, the free mugs, they know that these do not have quite the influence that you think, and they even play on the fact that physicians like me know that we are not really going to be influenced by this, or at least we think we are actually not going to be influenced by this, but that we are going to be influenced by the articles. So the drug reps when they come round to see me will have the free pen and the free mug and the sheaf of articles, and the article is the advert these days.

Mr Amess: This is all very interesting. Members of Parliament could never be influenced in such a way!

Q159 Mr Naysmith: The pharmaceutical industry is not going to be terribly pleased with what you are saying today. I just want to know what produced the road to Damascus moment for you?

Professor Healy: Nothing in particular. I have actually been writing about these issues for the last fifteen years or so. There has been no particular change in the issues that I have actually been writing about.

Q160 Mr Burns: Have you been in the Caribbean in the last fifteen years?

Professor Healy: To be honest with you, I have not. I have actually only once been in the Caribbean; so in the last fifteen years once—twice actually.

Q161 Mr Burns: Why did you go?

Professor Healy: I went to the Caribbean to try to interview people who were involved in the history of the field.

Q162 Mr Amess: Turning now to Mr Brook, and I believe you did touch on this earlier, you resigned in protest from the Drug Regulatory Committee examining the safety of certain anti-depressant drugs. I wonder if in a moment you could enlarge on that a little! From your experience what can you tell us about the unwelcome or undue industry influence and the regulator’s ability to actually contain it? Do you have any recommendations for this Committee as to how it can all be addressed?

Mr Brook: I will try and answer all those. I just want to say, because I think perhaps it was not clear, we are very concerned. I am personally very concerned, about the drug regulatory system. It does not make us anti-drug, and I think that is very important to understand. If you read Mind’s information leaflets they talk about the positive use of drugs within mental health, but the issue I think that we have, and I think my experience is raised, is have we got a regulator that is robust and trustworthy, because at the end of the day both GPs and patients are relying on the information that comes out of the regulator? I do not think we can expect an industry making huge amounts of profit necessarily to be effective at self-regulation in these areas. For us it is very important that the MHRA is regulated very strongly, and it is very important to recognise that over a decade or more in this area we have had people saying to us that they have concern about the information they have; and, of course, some years ago Mind was involved in the same issue around drugs like Vallium with That’s Life, which most people recall; so there is a long history here. My experience within the MHRA, I think, was quite scary to some extent and quite a painful process: because I joined that committee as a result of a street protest outside the MHRA. I was rung up and they said, “Would you like to join our committee?” On the week I said...
“Yes” it was on the front of the papers about how I would bring the patients’ dimension and the patients’ perspective to it. In the first meeting I had the Director of post-licensing came up to me and said, “We are so grateful that you have not had medicine contributions, we are so grateful that you are here because we are not sure that people like you could actually make a contribution to such a committee”, and I was not quite sure what that actually meant, but it did not seem very affirming or confirming, but I carried on. I think what really worried me was not so much the direct pharmaceutical influence, although it was fair to say that every time we made difficult decisions there was always this issue of: “We have got to be very careful because the pharmaceutical companies will sue us if we get this wrong: they will take us to court and take us through legal processes”; and it was very clear that the MRHA officials were very mindful of the whole time of that dimension, to my view, more than the dimension of public health and public responsibility of the public. For instance, they would talk about Seroxat having 34 generic manufacturers and potentially each one of those generic manufacturers could lead to legal action against them if they got it wrong. So it was hugely big in their thoughts. I think the second thing that actually worried me was when we actually got to things that looked really quite worrying, and I have mentioned Seroxat, and I also mention venlafaxine or exefox, as it is sometimes alternatively known. In both cases the information came late to the MRHA, in my view, two years after the trial had finished, and in both cases it was not seen as hugely important, and I seemed to be the lone voice on this expert committee saying, “This is of concern”, and the response I would get is from the Chairman or the officials, “Yes, this is very worrying, but it is going to have to be formally investigated”, and it seemed to go, in my view, into a black hole and remains there to this day despite questions on the floor of the House and questions elsewhere. It seems to me that even in a criminal investigation situation such as, say, the worst case of murder, we actually get more information than we do about how drugs are regulated. The other problem I have with it, if I am really honest—I know this is a long answer and I will try and bring it to an end—is actually it is a very difficult thing to be confident about the transparency of the regulator when so many people have got long histories, career histories, in the pharmaceutical company. Let me give you some examples without trying to be too personal, but, again, I have data and files which I am happy to provide to you to back up what I am saying. The head of licensing at the MHRA, the current head, had a previous major role in GlaxoSmithKline on the safety of drugs across the whole world; the head of enforcement I had a 20-year career with GlaxoSmithKline before he became head of enforcement; and recently Professor Breckenridge at a fringe meeting, actually the Conservative Party fringe meeting Mind held, said that basically it was a requirement for the head of enforcement to have five years close involvement in the industry as part of their job description. I cannot understand why enforcement needs to actually have that experience. I can understand why an enforcement agency might need that. It also seems to me to be very bizarre that you have got your enforcement inside your licensing, inside your pharmacological division, all speaking to each other, all this work going on in the same committees, all of these people with these interests. So for a number of reasons, and there are others I can give as well, I got very confused and very concerned that actually there was no robustness; and when I looked round I was the only patient representative in this whole group taking up these interests.

Q163 Mr Amess: But what is your solution to all this? We are happy to give therapy and Professor Herxheimer will want to get things off his chest as well, but tell us what you recommend us to do?

Mr Brook: I think, if you look at Mind’s recommendations, it is very, very clear. We want to see a much better way of doing health research and trial data. You have already heard evidence on that. We want to see the licensing and the post-licensing work separated, quite clearly, and we want to see people with a consumer interest and a legal interest coming onto the committees to actually give that moral and ethical dimension.

Q164 Mr Jones: Mr Brook, can I say, firstly, before I ask you any questions, all witnesses to the committee have parliamentary privilege.

Mr Brook: I did know that before I mentioned Wyeth.

Q165 Mr Jones: Just in case you feared?

Mr Brook: I have no fear from you and what I say here. I do certainly remain still somewhat fearful of the MHRA’s approach to me, I must admit.

Q166 Mr Jones: In the answer to the last question you made clear the reasons why you thought the regulation would not work, but in your written evidence to us you say, “The concept of the Department of Health as a regulator is nonsense. It has no power to regulate the vast majority of pharmaceutical activity.” That is not just saying that the way they are brought together means they do not do it; that is saying they have not got any power to do it anyway?

Mr Brook: Absolutely. On the committee time after time after time the experts said, “We need more work done on this work”, and I would say, “How do we get more work done?” and they would say, “That is a real problem. We do not have any funds. We cannot direct the manufacturer to do it. We have said this drug is safe. We are not able to reopen that debate”; in effect, and so they get stuck with that; and the DH does not have that ability. Just a little cameo: after the contra-indicating of Effexor the Department of Health official turns up at the meeting, and says, “We are really worried that you are actually contra-indicating all these drugs for children, because people have not got anything to prescribe to them and we have not got any
alternatives out there; so what are we going to do about this situation?”, and actually I said, “I do not think that is this committee’s problem.”

Q167 Mr Jones: But you are going back into why they do not behave that way?
Mr Brook: Sorry.

Q168 Mr Jones: I am now trying to ask you the question of, you say they do not have the power, well give them the power?
Professor Healy: Chairman, could I enter into this? You perhaps thought that the view that I gave earlier to David Amess was somewhat flip when I said the industry are actually doing things quite well if you hold shares in the various different pharmaceutical companies. I am not sure the industry actually are the problem. I think there are two groups, one is the MHRA, who are not doing their job all that well, and the other is the physicians generally. If I can try and bring out the nature of the problem: as regards suicide on SSRIs, both the FDA in the US—and the MHRA—clearly here thought when this issue blew up first that it was a public relations issue, they took this position without any scientific input at all other than the scientific input they may have had from experts sitting on the CSM who we now know had extraordinarily close links with all of the major pharmaceutical companies. They have held to that position regardless of the scientific evidence that has come through over the course of the last ten to fifteen years, they have held to that point of view even though actually the scientific evidence on which they let the drugs onto the market in the first instance conclusively showed that these drugs could cause a hazard, a hazard that could be greatly reduced if the proper warning had been put on the drugs. The other aspect to the MHRA that I would be keen to bring out quickly is that they say the yellow card system they have got is one of the best in the world in terms of trying to track hazards that may be thrown up by drugs out there in the real world, but in actual fact here in the UK we track the fate of parcels through the post one hundred times more accurately than you track the fate of people who have been killed by SSRIs or other drugs. If you or your wives or children were to go to your GP and be put on one of these drugs and be injured or killed by these drugs, your GP would not file a yellow card with the MHRA. The system as it stands is worthless. But let us move on. There is a third group here that you have not brought into the frame, and that is the Royal College of Physicians, the Royal College of Psychiatrists. Actually we are supposed to be the expert advocates for the consumers, and from us you have heard complete silence. I am not advocating that all drugs should be over the counter, but if you think of the situation where all drugs were over the counter, where it was as easy for you, the consumer, to get these drugs as it was for you to get pints of Guinness or perhaps tobacco, you would go into your physician and he or she, usually, I would say, she, would say to you, “You do not want to believe all the hype, all the adverts you see on TV for instance about Guinness being good for you”, or this, that and the other actually being good for you, “Actually the evidence looks very different to us”, but in the kind of situation which we have, which is drugs are available to you through being prescribed by people like me, what the industry have done has been to try to try to capture the hearts and minds of the Royal College of Physicians here in the UK, the APA over in the USA, and we have been quiet. The canary that should have croaked in the mind has not. So there is a third group of players here.

Q169 Mr Jones: Thank you very much. My next question is to Professor Herxheimer. In your submission, Professor, you state that the close relationship between the industry and the regulatory authority over decades means that the industry’s views are better represented than the interests of the patients and the consumers and the public. Would you elaborate on that and explain why the bias? I am sure you echo some of the views that Professor Healy has just expressed.
Professor Herxheimer: I think that the whole basis of medicine regulation started with Thalidomide, and then there was the Sainsbury Committee and the Medicines Act, and that was very much influenced by the industry, what was to be in the Medicines Act, how strong or weak, etc. The whole confidentiality, the issue of commercial confidentiality, meant that anything submitted by a company to the regulators could not be disclosed under penalty of fines and prison, etc, and that meant that many, many things could be discussed, in the regulatory agency, which were absolutely private; so that was a very privileged position; that led over the years, over the 40 or more years, to a closeness between the regulators and companies that they were often meeting to discuss details of submissions, information to be given on the package insert and the product characteristics, and so on—they became one community—and so, when the agency was hived off from the Department of Health, became independently funded, independent of government funding, was funded by the industry, the culture became confirmed that the industry is the client and the client must be looked after; quick service, good service, easy contact, etc—so it is a closed community in a sense—and outsiders were related to this either by being appointed to one of the committees of the regulators, the Committee on Safety of Medicines and sub-committees, and thereby tied into the culture of secrecy, signing every document as commercially confidential, or whatever; but commercial confidentiality was never defined, so the anxiety, which has been mentioned already, of the regulators, of the civil servants in the agency, that they might be sued by a company for breach of confidentiality—the Department has a horror of being sued by a company for this, and so there have been very few prosecutions by the agency of companies for various misdemeanours. All this has led to this close inbred relationship. I have no idea how social it is. I do not know . . . I am sure they do not go to the Caribbean, but that is at the back of what I wrote.
Q170 Mr Jones: So the laws representing the Government in these committees are sensitive, understandably sensitive, to pressures from the industry for litigation, but they are not subject to other counterweighted pressures in that, I cannot recall, but I am not as knowledgeable in this field as you are, governments being brought to account because they allowed drugs to be distributed inappropriately?

Professor Herxheimer: Quite; yes.

Q171 Mr Jones: Not since possibly Thalidomide, as you have mentioned?

Professor Herxheimer: Yes. I think one very interesting example which typifies the situation is that companies may appeal against licensing decisions. If licences are refused on a drug the company may appeal, and it is then heard at a formal appeal by the Medicines Commission—that is one of its jobs. No-one else may appeal. The evidence may be as ropey as anything, but nobody else has any standing. A licensing decision can only be appealed by the applicant, not anyone else; and that is absurd because everybody else has to swallow the drug willy-nilly.

Q172 Dr Taylor: I was going to ask questions about the MHRA, but we have had such universal condemnation, the only question is: should it be abolished and what should be put in its place?

Professor Healy: There are a few ways you could reform it. I think one of the key issues that you heard during the first hour, and I think you would hear from all three of us, would be the issue of transparency. It is not the case that the data from clinical trials needs to remain concealed. Let us be clear what happens. You and your wives and your families go to see me when you are ill and you are in a very vulnerable kind of position, and I happen to say, “Ah, good news. We are doing a clinical trial on a new drug this week. Would you not like to get involved?”. Partly because you are on your way back to health and because you want to keep me happy, you say, “Yes.” You do not know that I would not get involved in the trial because I know that actually three-quarters of the trials prove that these drugs are too hazardous to market but we go ahead with you. What happens is you take these risks you do it out of a civic sense, you do it as a gift to the community. It is part of the spirit that set up the NHS fifty years ago. You do it for free. The industry takes the data from you, they let you take all the risks, they conceal the data; and this is a thing that has really only happened during the last twenty odd years or so, the capacity of the industry to do this is a fairly recent thing. They take this data, they take out the good bits of the data, the bits that suit them, and market that back to us and call it science, when clearly it is not. In the course of doing this they became the most profitable corporations on the planet with the power even to shape human experience. They can create illnesses out of the blue. We may all have been happily impotent until quite recently, but we will have problems with our impotence these days because Viagra persuades us that actually being impotent is not the kind of thing you should be doing, you should be having Viagra. They can change the nature of what it means to be human. One of the ways round this is access to the raw data. There is no scientific or ethical reason why there could not be access to the raw data.

Q173 Dr Taylor: What about the funding issue?

Mr Brook: I think we do need an equivalent to the MRHA. I think our concern is how it operates. Clearly there is a lot of evidence. You have already heard evidence from us and previous people about the issues around trial data, etc. There are two dimensions that also need to be considered in your thinking: one is funding, because clearly if you look at ABI's submission to you, and no doubt you will be asking about this, there is a whole expectation that we will remain the best in Europe to attract funding and, as a result of that, Part of that reputation is based on the relationship with pharmaceutical companies: so I think you have a whole funding issue that is driven and no independent ability to do much trial data work at all. The second issue I think you have to look at is the European dimension, because, for instance, in Seroxat one of the real dilemmas that people had was that it has got a European licence. It has not got a UK license; it has got a European license. It was often raised. “We cannot do this because we are not going to get support across Europe, and even on the dosage issue that was a real concern in the discussions that were taking place. So a certain number of drugs, an increasing number of drugs, are actually going to be regulated across Europe, and, of course, the work of being a lead rupetevr, as it is called (I am not quite sure why that word is used), actually acquires funds; and so clearly you have got to be in not only with the pharmaceutical companies but actually in terms of how the European regulatory world sees you. So I think you have two issues: one is economic and one is the European dimension, which I think is actually quite pressing.

Q174 Dr Taylor: What about the membership of the MHRA? Should we be making recommendations on that?

Mr Brook: Absolutely. I think we have seen in recent times, if you look across health issues which we have been involved in and others have been involved in, such as the Bristol Inquiry, the Alderhay Inquiry, the Lane/Issacs Inquiry around organ retention, what you have started to see is that when people come in with a moral and ethical dimension to those issues rather than just the medical position, you start to see, I think, policy change, and I think that is perhaps somewhere that I would recommend you might give due thought to about the nature of their composition, and also, of course, I would say, and I would argue strongly, we need to get patient experience in there, because the reality is that, if you look at the experience of the SSRIs, patients have been saying issues that have now been found to be true over the last decade.
**Professor Healy:** Could I add into that one, purely on the issue about who is in there? In terms of the experts, just to point the issues to you, some years ago I wrote a piece. It was known to one of the pharmaceutical companies that I had an article that was due out that was going to be critical of one of their drugs; it was going to lead to the SSRI review on which Richard ultimately ended up, but before the SSRI review that Richard was on there was a previous SSRI review group—and I am trading on the fact that things are privileged here. If you go into the archives of the particular company concerned, I can find there that will be e-mails from the company to journal editors here in the UK and Europe, etc, etc, saying, “Look, there could be this article coming out”, and broadly hinting at, “You know how to handle it. This is not kind of material you would want actually to publish.” If you look at who the e-mails go to, you end up with what in essence was the first SSRI review committee here that the MHRA set up. This is extraordinary. You can also find material which shows that the companies clearly get key figures from within the UK and France and Germany and note these as figures who have links to the regulatory apparatus in each of their countries. They are doing this regardles of the culture in England, Germany and France which has been quite different. The culture in England, there has been some free interchange between experts on groups like the CSM and the industry. In Germany this has not been the case, but the industry has been able to capture the regulatory system there also. It is a fairly systematic process.

Q175 Dr Taylor: Do you think the MHRA can reform themselves in any way: because if you saw the Panorama program I do not think I have ever seen anybody more uncomfortable than the MHRA representative being grilled on that?

**Professor Healy:** Richard, I am sure, is absolutely right that there should be more consumer input into MHRA, and there should not be just one consumer input, but you would have to take care that the consumer is not from a group that has, in effect, been set up by the pharmaceutical companies. Also there is great scope here for experts to be on the MRHA committee who do not have links to the industry. The issues involved of what do clinical trials show, what do the statistics show, which MHRA and their experts have got consistently wrong in the case of the SSRIs, are issues that we have loads of other experts here in the UK who do not have links to the industry who could handle—

Mr Brook: I am sorry. I think it is only my observation, but certainly the committee I was on for people that were most open-minded were the statistician and the academic, and if I had any support it came from that sort of quarter rather than from the medical area. I just wanted to say a little bit about reform. I think it needs a whole new mindset, a major mindset. I was appalled, for instance, because I raised several times the issues around freedom of information and how the Freedom of Information Act will impact on the MHRA sitting on the expert group, and I have read recently that they have actually set up a group that involves the ABPI in themselves to decide what to do about it, and recently, at a fringe meeting again, I made the point, which was not answered, about why are there not patient representatives and why are there not lawyers, why are there not people from Which? sitting on this group? It is just so close, so cosy, you have got to break that mindset.

Q176 Dr Taylor: Can I go back to Professor Healy. How many clinical trials are not funded by the industry?

**Professor Healy:** Very, very few, and this is quite odd in a sense, that within the NHS you would have thought we would be running clinical trials that are not funded by the industry; but one of the colleagues that I worked with looked at this recently, and in the US, which operates a much more privatised system, you have much more state-funded clinical trials than we have here in the UK. There are virtually no state-funded clinical trials here in the UK. This is probably very, very important. It is a point that I mentioned earlier. The MHRA are really a very, very small group of people; they are not the experts on what these drugs do or whether it is good for you to have these drugs, or how this drug compares with other drugs in the field; they are really a very small group of people who probably have been given undue salience here. The expertise lies in the Royal College of Physicians or the Royal College of Psychiatrists, or whoever. You really need experts out there who know what these drugs do and who are able to create the political context in which MHRA will respond. If MHRA know the Royal College of Physicians out there have concerns about a pill, they will be much freer to ignore the worries they may have about being sued by the industry than if there is no standard at all from the Royal College of Physicians.

Q177 Dr Taylor: Going back to the yellow card system, what should we be recommending for reforms of that?

**Professor Healy:** Consumers ought to be filling this up: the work that has been done by Andrew Herxheimer and Charles Medawar on this shows that you get much more information from consumers filling these up. What you might also get if you had that kind of situation, you may also get physicians being more prepared to fill the cards up also and in a more detailed way than they are now.

Q178 Chairman: That is a good question. Professor Healy, a few moments ago you used, in the context of Germany, the term that the regulatory mechanism had been captured there by the industry. You implied, and I want to be sure I understand this, that it had been captured also in this country. Did I understand you correctly?

**Professor Healy:** Yes. I think one of the things that sociologists in this field have been working on recently is what are called “regulatory capture”, and they mean just that.
Q179 Chairman: You say that applies within the UK?
Professor Healy: As regards the area that I work in, the field of both anti-depressant drugs and the drugs that are used to treat people with schizophrenia, I think that has been the case since the late Eighties at least.

Q180 Mr Burns: Professor Healy, I do not know if you were present for the earlier session?
Professor Healy: Yes, I was.

Q181 Mr Burns: So you will know what I am talking about. There was an exchange of questions with Dr Wilmshurst where he in his written evidence has suggested that drug companies would pay eminent cardiologists and others up to £4,000, plus expenses, for an hour long talk on their products. Maybe you will be able to help us, because I see from your CV that your background is in consultancy work with pharmaceutical companies and in recent years you have acted as a consultant, conducted clinical trials, spoken or attended foreign meetings, and then I see about three and a half lines of pharmaceutical companies that presumably you have spoken for or acted as a consultant. Is it your experience that you could earn up to £4,000, plus expenses, for an hour long talk?
Professor Healy: I think, as you might actually expect, general psychiatrists probably come somewhat cheaper than cardiologists, but, yes, if you are asking me in the course of a day, in the course of work for a day or so, could people like me be paid of the order of £4–5,000 per day, the answer is, “Yes”. Do I think that there are people in the field who are at a higher echelon than me who perhaps have closer links to the regulatory apparatus than I have who would be being paid more, the answer is, “Yes”. The industry is also very clever in how they organise these things. For instance, if I get perhaps contacted . . . If I am working in a consultant capacity for one of the pharmaceutical companies, I will have had media training often, and the understanding is if the media were to get hold of you . . . Let’s say some issue blows up about some pill and the media get told, “You can approach Dr Healy” , for instance, I will be able to say, and the media and also the pharmaceutical company will be able to say, “Well, no money passed hands.” When I was asked by the Guardian, for instance, “Is there a hazard with these pills?”, there will not have been any money that has actually passed hands from me doing that piece of work for the pharmaceutical company, but the money comes from elsewhere; it actually comes from the trips to the Caribbean; it comes from being asked to chair meetings which involve no work at all; it comes from having my papers written for me and then I am paid as though I have written the papers. That is where the money comes from.

Q182 Mr Burns: Do you have that done for you?
Professor Healy: I have had papers written for me, sent to me, and I have said, “No. When I actually planned to get involved in this meeting, I had actually planned to write my own paper.” The pharmaceutical company in question was rather surprised at this. When they saw the product that came back to them, they said, “This article that you have actually written is quite good. We think we will hold onto it, but there were certain important commercial points in the one that was done first, so we are going to have that as well”, and they altered just one word, the name of the author, Siegfried Kasper, Professor of Psychiatry in the University of Vienna. There could be not a more symbolic name in all of psychiatry than professors of psychiatry from the University of Vienna. His name ended up on the piece. How much he was paid for it, you will have to ask him.

Q183 Mr Burns: Per se do you think it is always wrong for money to change hands or is there a valid area where it is justified?
Professor Healy: No, I do not. A great proportion of what I have had has gone into research funds. There is a charity that I have also fixed up out of which I am unable to get any funds at all; but the issue is not the funds changing hands, and the issue is not the articles being ghost-written per se. I could live in a world where the editors of journals had links to all of the major companies, where people speaking on company platforms had links to the companies; I could live with their articles being ghost-written. The crucial issue is not all of those. You do not want to tinker with things at the edge: the free pens, the ghost-written articles; the key issue is whether these articles correspond to the raw data that comes from clinical trials that your children may have been involved in for instance: that is the key point that you need to get at.

In the absence of the Chairman, Dr Naysmith was called to the Chair

Q184 Dr Naysmith: The more perceptive of you will have noticed that the Chair has changed. David has now left us and a different figure is in the Chair. David, I think, apologised earlier that for family reasons he had to go. I think we have a number of other areas we need to ask a few questions on yet, if the panel are happy to go on. I was going to ask again Professor Healy, who seems to be rather dominating this panel a little bit—we will have to let the other two have a say in a minute or two—you were talking just then in answer to a previous question about secrecy in drug trials and that there are things that are known that are not published and made public knowledge. When I had a proper job I used to be a scientist and one of the difficulties always was publishing negative results and what you do with things, goodwill designed experiments that come up with the answer that something does not happen which I supposed to happen; and I imagine the same sort of thing happens with drug firms, to a certain extent, that you get your correct information and it does not really tell you much one way or the other. Before I finish the question, there are two aspects to this, efficacy in whether the drug is any better than something that is on the market, and obviously the firms will try to argue that it is, and
then there is the question of danger and possible risk and hazard. What is your answer to what we can do about all this: getting negative results that are many getting out into the public domain; then there is the question of danger and possible risk. Trials need to be registered before they start so you and are in the rest of us the most is the trials that are in the biggest hazard, the thing that influences me and everybody and they are euphemised or disregarded the ones these days that are being published. The the adverse events, by the people who take part in clinical trials that do not show that the drug works not be legal; and I think that requires a change in the picture us. I think there is a real issue about the before people are recruited to it, otherwise it should give a drug to a person like you or your wife or your registration of trials at inception, and ethics changes, which are very welcome but again need to had a specific example, Professor Herxheimer, of happened there was they actually wrote to the then you get more, you get some, but if you ask for adverse experiences, by the people who take part in trials, how you actually collect those and investigate them makes a huge difference to what the data set is about that drug. To give one very simple example, if you do nothing to investigate them and only record those that are mentioned spontaneously by people taking part in a trial, you get a very small number saying, “I had this and this happened.” If you ask them a general question, “Was there any change that actually you just call them failed trials rather than negative trials, and it is, of course, very hard because the trial data is not in the public domain, people do not look at it and those assessments are very hard to be challenged; and so I think we have a real issue about trial data, and I think there is a real issue about our regulator and how robust it is in actually seeking that.

Q186 Dr Naysmith: He is really saying, Professor Herxheimer, that you are the expert?

Professor Herxheimer: I think that there are two aspects to it. Negative trials, I agree with what Richard Brook has said—you would have to have registration of trials at inception, and ethics committees have to demand that a trial be registered before people are recruited to it, otherwise it should not be legal; and I think that requires a change in regulations or law. The other aspects of negative are the adverse effects. These are unwelcome to everybody and they are euphemised or disregarded or just not noticed; so that the resources spent on detecting adverse effects or suspected adverse effects, adverse experiences, by the people who take part in trials, how you actually collect those and investigate them makes a huge difference to what the data set is about that drug. To give one very simple example, if you do nothing to investigate them and only record those that are mentioned spontaneously by people taking part in a trial, you get a very small number saying, “I had this and this happened.” If you ask them a general question, “Was there any change that actually you just call them failed trials rather than negative trials”, i.e. giving a negative result, “we believe they are failed trials”—in other words they are flawed—and actually there is correspondence between Glaxo and the MHRA bringing that out as a very, very clear picture; and I think that happens quite a lot, that people are actually saying, if a trial does not quite work, as there seems to be common acceptance in the work that I was involved in, then actually you just call them failed trials rather than negative trials, and it is, of course, very hard because the data set is not in the public domain, people do not look at it and those assessments are very hard to be challenged; and so I think we have a real issue about trial data, and I think there is a real issue about our regulator and how robust it is in actually seeking that.

Q185 Dr Naysmith: At what stage should such data made available?

Mr Brook: I think we are beginning to see some changes, which are very welcome but again need to be driven by regulation and law, in my view: one is obviously the beginning of having to say that all clinical trial publications are on average as much space as is given to the title and the authors and their affiliations.

Q187 Dr Naysmith: This sort of criticism has been going on quite a long time about the design of clinical trial. Is there any evidence that they are getting better?

Professor Herxheimer: The International Committee of Medical Journal Editors has made recommendations about that and the journals that take part are applying better standards, and there is an international statement, consensus statement, on the reporting of randomised clinical trials which also has raised the standards enormously. The second version of that, which deals with adverse effects, is coming out in a month or two; previously it did not deal very well with adverse effects.
Professor Herxheimer: Well, because their investigations are secret, I have no idea.

Mr Brook: Could I just say that there is actually a role for the regulator here as well, because the regulator in March of this year, when I asked them, had never bothered, for instance, to look at the adverse report data from the FDA, and there is no arrangement, for instance, for adverse reporting data in other regulatory areas to actually exchange data, so we are only looking at the UK data anyway when actually all of these drugs are used worldwide. So there is a real issue about that as well.

Professor Healy: Can I add in on that point. It is clear that in the trials of the SSRIs, people who have gone on to become suicidal have been coded under the heading of “nausea”, they have been coded under the heading of “treatment non-responsiveness”, but in the group of trials Richard has seen, the group of trials in children, children becoming suicidal have been coded as being “emotionally labile”, and this is a thing that very few physicians or people in the street—actually it was a person in the street from the media that picked this up; it was not actually any of the physicians that read the articles that appeared or heard the talks given that actually picked this issue up—children becoming aggressive and even homicidal were coded as “hostile”. This is the kind of thing that slips under the regulator radar awfully well and under the physician’s radar also, and this happens widely.

Q189 Dr Taylor: Can I go on, Professor Herxheimer, with the adverse effects of drugs, because in your paper you gave us you give some recommendations about what should be done. Would you like to spell those out and expand on them? We have already got the message that certainly the consumer is somebody who should be reporting these sort of things. Can you expand on your recommendations?

Professor Herxheimer: Yes. Because the regulators are funded by industry, they have no funds for doing any work of their own, and the work on adverse effects of medicines is absolutely to do with the public health, it is not to do with industry; and that is a public responsibility and it should be possible that the official organisations, including the MHRA, Medical Research Council and so on, should be able to investigate adverse effects independently—academic institutions. I think there is an argument for separating the whole analysis and collection of data on adverse effects from the MHRA, but clearly there are various ways in which that could be done. One way would be to have separate organisations doing it in the way that scientific research is done. There is a scientific community and there is an adverse-effects community and a pharmacovigilance community, but that is all governmental, and I think that is very unhealthy because it has this close relationship with the industry. So, independent collection of analysis and investigation could be funded by a modest levy on sales of pharmaceuticals. This problem is also reflected in the very small staff. There are far more people employed on evaluating applications for licences than there are who are evaluating the whole pharmaceutical market and what happens to the drugs afterwards and the people who take them. There is an enormous disproportion, and these are very hard working people, but it is impossible for them to do a proper job.

Q190 Dr Taylor: You have certainly given us some suggestions of where we should be looking to make recommendations. I am sorry to go back to the yellow card system, but it has suddenly occurred to me that in the West Midlands we had to send yellow cards to the university department. Is that widespread? Did that mean that more reports were sent in from professionals?

Professor Herxheimer: No, I think the reason for that is that you want these reports to be discussed locally and people to learn from them locally and to have an involvement—people should feel involved—not send them off to The Black Hole in London, and I think that has happened to some extent, there has been more discussion and there have been better reports, but it is still quite inadequate; so it has been a bit disappointing.

Professor Healy: If I could just quickly add, this is a point about the reporting of adverse events that should not be seen as industry hostile. Industry to date, as you have heard earlier, has not actually been bringing new drugs on stream all that well. The research, the hypothesis driven research, to get new drugs is not working. Our biggest single source of new drugs still remains adverse events. Viagra was noted because of an adverse event; so it is the kind of thing that should be feasible to have sold to industry as a thing that both they and the consumers and the rest of us can gain from. There is a value in trying to see what these drugs do.

Q191 Dr Taylor: The other effects—

Professor Healy: It is not just trying to penalise the pharmaceutical companies.

Mr Brook: Can I also just say that a large number of patients do not manage to succeed in getting their adverse effects reported. That is a consistently big issue for Mind. We have evidence over several years of people trying to report going to their GP, asking for adverse effects to be reported and the GP saying, “I do not think that is actually what has happened and so I am not doing it.” I know patient reporting is now starting, but it still, I think, raises a real issue, and again you have got a number of case studies of that. The other issue that really worries me is the fact that the adverse reporting is seen as very minor in relation to clinical trials, and time after time I have been told that adverse reporting only can give a signal and it is clinical trials that are definitive. I think that is wrong. Those two must be married up. If we have got a large amount of adverse reporting we must understand what is happening here. I think it is really interesting. Seroxat had the most adverse reporting of any drug world-wide and yet it has taken all this time to sort it out. The last point I would make, which I think is a very relevant point, is it takes 40 days for the MHRA on average, in the last annual report, to license a drug and yet takes it two years to review anti-depressants; and so there is something about the balance that Andrew was
talking about that raises a real issue. If it takes eight weeks to get a drug into the market, why does it take two years sort out its safety afterwards?

Q192 Dr Taylor: So, to come back, there must be a formalised easier route for customers, for patients, to report?

Mr Brook: And they must be alert to what is happening and we must not just dismiss them as a signal; they are actually really big evidence.

Professor Herxheimer: I would also like to add that the reports from patients, the MHRA has no idea how to deal with them. I think it would be far better for some other body to deal with those, obviously in connection or consultation with the MHRA, but I have no confidence in the MHRA being able to analyse and understand them.

Q193 Dr Taylor: Does such a body exist?

Professor Herxheimer: No.

Q194 Dr Naysmith: Does it exist anywhere in the world?

Professor Herxheimer: Yes, in the Netherlands there is an organisation which does that, which deals with all the reports, which is independent of the regulator, which does it for the regulator, but I think that because we do not know how to set up such a body we need to do pilots of various kinds and then work out which is the most effective.

Q195 Mrs Calton: Professor Healy, in your evidence you say that the industry can engineer a clinical consensus that will favour their products and that they will shape assessment. You have already mentioned ghost-writing and some of the other issues, but how does such engineering go on beyond ghost-writing? What examples do you have?

Professor Healy: We could be here for the next hour, but let me just be very brief and focused on one issue that I have grave concerns about. At present the most commonly used anti-psychotic in the UK is a drug called Zyprexa. What will happen is you will I am sure you have had a huge amount of reports from patients, the MHRA has no idea how to deal with them. I think it would be far better for some other body to deal with those, obviously in connection or consultation with the MHRA, but I have no confidence in the MHRA being able to analyse and understand them.

Q196 Mrs Calton: I think you have already indicated, Professor Healy, that the fact that you cannot get at the information is what is causing some
of the problems. How much of a problem is it that official secrecy seems to cover over all of the information that might be there, and do you think that greater transparency would make a difference to the pharmaceutical industry’s contributions to public and personal health?

**Professor Healy:** Yes, I think at this point the pharmaceutical companies regard the data that comes from the clinical trials as theirs, even though I do not think there is a legal basis for that. I have tried to find out what the legal basis might be, but I am not sure it is there. They regard it as theirs to be put into articles that are ghost-written up to be used to promote drugs off label for conditions that are in the process of being created, conditions like sociophobia, what in the US is called premenstrual dysphoric disorder and things like this. What you have is a situation where they are using the data for just the kind of purposes that circumvent the regulatory apparatus, but we cannot get access to the data.

**Q197 Dr Naysmith:** You have mentioned ghost-writing again, or ghost-writing has been mentioned. How does this work? In terms of footballers, famous footballers, journalists write and they stick their names on. Are you suggesting that eminent clinical scientists, academics, add their names to papers that they do not really write?

**Professor Healy:** My estimate is that, even in journals like the BMJ, the Lancet, the New England Journal of Medicine and JAMA, the leading journals in the field, if these articles have to do with therapeutics, with drugs, it may be worse perhaps for psychiatry than elsewhere, but I doubt it. 50% of these articles are ghost-written. It may be higher.

**Q198 Dr Naysmith:** How would that work?

**Professor Healy:** It works in the sense that the industry get the data from the trials, they write the articles up, they approach authors to have their names put on the articles. These authors may not have seen the raw data at all, but they put their name to it, and they may be the most distinguished authors from the most prestigious universities. They are approached precisely because they are the most distinguished authors from the most prestigious universities.

**Q199 Dr Naysmith:** I must say, that is pretty disturbing stuff?

**Mr Brook:** I think what is also very interesting is that it has moved within the regulator, because the regulator actually receives summaries of trial data from the companies; and one of the things that struck me so strongly is that it is extremely rare that they do anything but read the summary as provided by the company and actually do not—they have not got the capacity or the ability to look at the raw data themselves; so it is only when you get an issue such as the Seroxat issue and the Vioxx issue, or whatever, that they start to look at the raw data. So they are totally dependent on the companies whose commercial profits are made by these drugs to produce summaries of what has happened. So it is really quite an amazing situation inside the regulator as well as ghost-writing.

**Q200 Dr Naysmith:** I was just going to ask you another question, Professor Herxheimer, and you can say what you have got to say in reply to this as well. One of the major problems with drug promotion, you say in your written evidence, is to do with volume and intensity rather than the quality of the message. Can you just expand on that a little bit?

**Professor Herxheimer:** Absolutely. I think that the volume is huge. It is not just the mail and the representatives and the meetings, but it penetrates through ghost-written articles and through the consultants who are paid by companies; it creates an enveloping atmosphere that you do not know you are in. There was another point that I was going to add to what Richard Brook was saying, that the timing of the information is, of course, very much in favour of the industry. They have all the data on their new products and on all of their products, and before any independent person can get at the data it takes months or years so that independent information limps a long way behind the commercially driven information and is in a much lower volume. The funding for that is extremely small compared with the industrial funding of promotion; so that creates a very overwhelming imbalance, and I think that an approach to that would be to have, again, some mechanism for ensuring that independent information is properly funded and maybe there should be a levy on promotion to do that.

**Q201 Mr Jones:** It is going to be extremely expensive to do what Professor Herxheimer has just proposed, extremely expensive, and the level of expenditure that is in any likelihood going to be made available to this form of checking and regulating is infinitesimally small in comparison to the level of funding available on the opposite side. Since what the drugs companies wish to do is influence the industry and the Government in order to sell their product, would it not be better if, one way or another, either through the Royal Colleges, or whatever, you regulated the system whereby information was brought into the public arena, into the Royal Colleges’ attention, in such a way that the only way to get that information out properly from the industry would be in order to publish data properly and that there would be an intolerance within the industry for publishing data improperly? Then you would not have to try and find some huge balancing sum of money; you will have changed the rules of the game so that the only way that the industry can play the game is according to your rules?

**Professor Herxheimer:** I think that the Royal Colleges are not really set up in a way that would make that straightforward. I think that by limiting the amount of promotion and taxing it so that it would have financial independent information but there would not be an end cost from that, you would have to limit this flood somehow and balance it with
independent information, and that could be done in terms of money. There is another consideration, which I think is a very important one for your inquiry, which is that if we do not get it right in this country we are also harming many, many other countries which look to the UK as a lead in drug regulation; and that really is a serious mistake.

Q202 Dr Naysmith: I think we need to begin to draw to a close in a couple of minutes. The very final thing is, would each of you like to offer what you think would be an appropriate level of influence for the pharmaceutical industry that they could or should exert in order to sell its products? I will ask Professor Herxheimer first and then Mr Brook and, finally, Professor Healy.

Professor Healy: Very quickly, two points. One is that the problem you face, at least one aspect of it, is that you are trying to force a financial camel through the eye of a scientific needle, and this is always going to cause problems. The best you can do in this area, I think, is to get people to adhere to what are the norms of science, the norms of ethics, and increasingly the norms of business whatever side of the political divide you come from, which involve transparency—this is an issue we put great store on these days—and, the other point, where there is a changing mood so that people are beginning to say "If prescribers actually prescribe these drugs, are forced to prescribe these drugs, given how we look at the corporate world, that we can expect in every situation pharmaceutical companies to behave in a way that I would like. So I think for me the emphasis is around regulation, and particularly around communication to patients and tough ways of looking at how pharmaceutical companies interrelate with that regulator. I think there are a whole lot of issues around communication which we have not had time to talk about today that are desperately important for patients, because they just do not receive that information. I end with a final example of why I think it is so difficult. On a working group recently on the patient information leaflet reforms we were sent some information about how the patient information leaflet should change and they were marked, "Confidential. You will be breaking the law if you release these to people." It was just about how to communicate with patients, and I think that is the strength of the pharmaceutical companies' influence at the moment within the regulator, and until we break that and create a new structure, and you have heard some ideas today, I am sure you will hear other ideas, but until we get post-licensing away from the influence of pre-licensing in particular, I think actually that is the issue, in a sense, that is how you will start to make pharmaceutical companies have the appropriate influence, by better and clear regulation.

Professor Healy: I think that we would all hope for impartial statements, impartial advocacy, if such a thing is possible, whereby companies have to compare their offerings with other things that are being used for the same purpose and make those comparisons objective, clear and open to public discussion.

Mr Brook: I think for me it is quite hard to believe, given how we look at the corporate world, that we can expect in every situation pharmaceutical companies to behave in a way that I would like. So I think for me the emphasis is around regulation, and particularly around communication to patients and tough ways of looking at how pharmaceutical companies interrelate with that regulator. I think there are a whole lot of issues around communication which we have not had time to talk about today that are desperately important for patients, because they just do not receive that information. I end with a final example of why I think it is so difficult. On a working group recently on the patient information leaflet reforms we were sent some information about how the patient information leaflet should change and they were marked, "Confidential. You will be breaking the law if you release these to people." It was just about how to communicate with patients, and I think that is the strength of the pharmaceutical companies' influence at the moment within the regulator, and until we break that and create a new structure, and you have heard some ideas today, I am sure you will hear other ideas, but until we get post-licensing away from the influence of pre-licensing in particular, I think actually that is the issue, in a sense, that is how you will start to make pharmaceutical companies have the appropriate influence, by better and clear regulation.

Dr Naysmith: Can I thank all three of you for the evidence you have given and for the witnesses from the previous session earlier this morning. I think it has been a fascinating morning. Thank you all very much indeed.
Thursday 11 November 2004

Members present:

Mr David Hinchliffe, in the Chair

Mr David Amess Mr Jon Owen Jones
John Austin Siobhain McDonagh
Mrs Patsy Calton Dr Doug Naysmith

Memorandum by Royal College of General Practitioners (PI 19)

1. The College welcomes the opportunity to submit comments on the terms of reference and other issues relevant to the new Inquiry announced by the House of Commons Health Committee.

2. The Royal College of General Practitioners is the largest membership organisation in the United Kingdom solely for GPs. It aims to encourage and maintain the highest standards of general medical practice and to act as the “voice” of GPs on issues concerned with education; training; research; and clinical standards. Founded in 1952, the RCGP has over 21,500 members who are committed to improving patient care, developing their own skills and promoting general practice as a discipline.

3. The College is willing to give oral evidence to the Committee if requested.

4. The issuing of a prescription is, after the consultation itself, the commonest intervention the health service has with the patients it serves. A significant proportion of the population receives at least one prescription on an annual basis and the vast majority of the population receives at least one prescription in any five year period. Therefore the Health Service and the pharmaceutical industry have a valid shared interest. In the year to April 2003, 650 million prescriptions were generated from general practices in England. Although the NHS is a major consumer of pharmaceutical products, we have to recognise that globally, NHS consumption is relatively insignificant.

5. It is vital that the Health Service interacts and communicates constructively and strategically with its major supplier, the pharmaceutical industry. The relationship between the Health Service and the pharmaceutical industry must mature and become more strategic if there is to be greater influence on the future direction of drug research, the methods of drug provision and utilization and the re-establishing of the UK as a premier site for drug innovation and development. There are linked benefits for our population of patients, the academic and clinical sectors and the economy as a whole (the pharmaceutical industry being the third biggest “earner” for UK plc behind tourism and the City). The development and implementation of new drugs is a vital part of the overall public health strategy for the UK.

DRUG INNOVATION AND DRUG RESEARCH

6. There is evidence the pharmaceutical industry is moving its research and development to other health economies outside the UK. The reasons are many and complex and include:

- Tax regimes.
- The high level of opposition to testing in the UK from extremist animal rights groups.
- The complex and often conflicting demands of legislation (particularly the over restrictive interpretation of legislation on data protection and confidentiality of medical data to restrict population based research).
- The poor information and IT infrastructure of the UK health service.
- The fragmented and customer un-friendly nature of academic units and clinical services. Multiple layers of Research Ethics approval may be required and a disparate, and sometimes competing, collection of clinical and academic teams may need to be brought together to achieve sufficient mass for such research. Such broad based collaboration between units is not adequately recognized and rewarded currently by our clinical academic and research bodies and therefore there is a disincentive for individuals to participate in such networks. However, much modern clinical research requires large numbers of subjects and locations, and therefore requires large, well organized and efficient research networks. Other countries are forming networks of clinicians and researchers who then can go out and compete collectively to be commissioned by the pharmaceutical industry for this research business.
- The poorly rewarded academic and insecure career structure for clinical academics results in many dropping out of this career and the best being attracted overseas by more attractive working conditions and remuneration packages.
7. The UK will fall even further behind in competing for this international research business if it does not urgently recognize the issues around genetic research and establish a legislative and organizational framework that recognizes and protects the interests of the patients, the researchers and the pharmaceutical industry.

8. A healthy and robust research environment in the UK retains excellence in the UK and stimulates development and improvement in clinical practice. It directly benefits patients by developing new treatments and making them available earlier (and when in trials often in a subsidized format) for the population of the UK.

9. The development of a strong and vibrant pharmaceutical industry in the UK working in partnership with the Health Service allows two way exchange of ideas. It allows the health service to influence the direction and nature of pharmaceutical research, and encourages the pharmaceutical industry to align its strategies and practices to those of the NHS.

10. While there will, quite rightly, be much to consider about the positive aspects of the pharmaceutical industry, there can be a negative influence where there is no research and development because the industry does not believe there is a good market. This is illustrated by influenza and neuraminidase inhibitors: influenza research, both epidemiology and treatment, was greatly enhanced by the discovery of neuraminidase inhibitor drugs but this was carried out because the industry thought that there was a large market for it. That did not turn out to be the case—and while we have an important new class of drugs (which will be very relevant should a pandemic occur)—had the industry anticipated the lack of market demand it could not have been expected to take on the initiative.

11. We welcome the very real therapeutic advances that have been made in recent years but we regret the large number of expensive “me-too” drugs which offer no genuine improvement and seem to be produced merely to enable different companies to gain financially on each major advance. As an example of this sort of practice, we would refer the Committee to the following point made by Andrew Hersheimer in the most recent edition of the Drug and Therapeutics Bulletin: “A company introducing a new drug aims to achieve high sales rapidly to recoup the research costs quickly. To persuade prescribers to try the drug, they must be offered impressive advantages—typically high effectiveness and simple usage. An early response to treatment reinforces the prescriber’s decision, and is more likely at a higher than a lower therapeutic dose. Low doses that might be effective in fewer patients are not developed. Drug companies are not required to provide data on the lowest effective dose or to produce low-dosage forms. So, often, patients receive higher doses than they need.”

12. It would also be fruitful to look into the increase in “disease-mongering” (see British Medical Journal’s theme issue of April 2002) and the medicalisation of normal human variation into normal and abnormal, with the interest of the pharmaceutical industry in seeing an increase in the “abnormal” population who need drugs for one reason or another. We are concerned about those disease conditions which lie at one end of a biological continuum—examples include hypertension, hyperlipidaemia, osteoporosis, anxiety, depression. It is always very difficult to draw a line and dichotomise a continuous variable into normal and abnormal categories but it is very much in the interest of the pharmaceutical industry to draw a line which includes as large a population as possible within the range of abnormality. However, it is almost certainly not in the interests of patients or citizens. A paper in press at the Scandinavian Journal of Primary Care looks at the 2003 European guidelines on cardiovascular disease in the context of the Norwegian population which is one of the world’s healthiest and longest living populations. Implementation of the current guidelines would lead to identification of one or more “unfavourable” cardiovascular risk factors in a large majority of the population, including more than nine out of 10 individuals aged 50 years and older. We ask in whose interest are such guidelines operating and point out the huge and increasing burden on publicly funded health systems which result from this level of intervention. If current trends continue, publicly funded health care systems will be at risk of financial collapse and the principle of inclusive health care may be lost with huge costs to society as a whole.

13. This can also increase health inequalities both nationally and globally. Nationally, in rich countries like the UK, only a minority of the population is acutely ill at any one time whereas the majority are healthy and can be persuaded of a need to take action to remain so by undergoing screening and taking preventive medication. As the overall health of the population increases, there is more money to be made out of selling health care interventions for the healthy majority than for the sick minority. More money is now invested in research into the prevention of disease than into its treatment—which serves to divert investment away from the sick towards the well, away from the old towards the young and away from the poor towards the rich. Similarly, the excessive consumption of medication, particularly preventive medication, in richer countries is a powerful driver of global health inequalities because there is much more profit to be made from developing and selling medication to the rich and well than to the poor and sick. This is frighteningly well illustrated by the response of the pharmaceutical companies to the AIDS epidemic in Africa. And there are also some dangers for the rich. Excessive prescribing drives iatrogenesis to the extent that 28% of US hospital admissions of older people are estimated to be caused by a drug related problem with significantly more being the result of adverse reactions than of “non-compliance”. Too often a prescribing cascade is set in motion whereby the side effects of one drug produce a new health problem and so a second medication is
prescribed, which in turn produces a new symptom and the need for a third medication. The pathway that leads from osteoarthritis to a NSAID to mild hypertension to a thiazide diuretic and on to diabetes and/or gout is but one example. The over-consumption of pharmaceuticals is a serious and growing health problem.

THE PROVISION OF DRUG INFORMATION AND PROMOTION

14. The health service must influence the nature and extent of pharmaceutical promotion to clinicians and the public. Joint codes of conduct should be developed between the pharmaceutical industry and NHS organizations (Primary Care Trusts and Hospital Trusts) detailing the standards of behaviour of the pharmaceutical industry representatives and health service staff. Examples of such understanding already exist (eg Hillingdon PCT code of conduct for interactions with the pharmaceutical industry) and have been effective in discouraging the worst excesses of practice.

15. The Committee might wish to consider the influence of the pharmaceutical industry on patients’ organisations and on the pressure to implement “Direct to Consumer” advertising in Europe and the balance between genuine information to patients on the one hand and advertising and health promotion on the other. Attached to this memorandum is a paper (“The influence of the pharmaceutical industry on patients’ organisations within Europe”) written by Dr Iona Heath for the British Medical Association’s European Forum in her capacity as the Royal College of General Practitioners’ representative on that group.

16. Patient Information Leaflets (PILs) are often effectively written currently to minimize the legal exposure of the pharmaceutical industry. Therefore their potential role to inform and educate the public is not fully exploited. The whole issue of the provision of unbiased informative and understandable information to clinicians and the public needs to be addressed and this should be considered by joint working groups of the health service, the public, and the pharmaceutical industry. It would be preferable for PILs to be written by sources independent of the pharmaceutical industry and should emphasise the place of the particular drug in the overall scheme of disease management.

PROFESSIONAL AND PATIENT EDUCATION

17. Much postgraduate GP education is funded directly or indirectly by the pharmaceutical industry. Their involvement is heavily regulated and the vast majority of such sponsorship and funding is carried out in a professional and non-promotional way. However, the Committee might like to consider the current over reliance placed on pharmaceutical funded education (eg multi sponsorship of patient groups such as Asthma UK) and what the consequences might be for research and education if the industry did not provide so much funding in the future.

REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY

18. The UK requires a large database of routinely collected clinical information to act as a quick response database for drug safety queries. The population to be covered would need to be at least 2 million; it could be a by-product of the electronic patient record. It would allow regulatory authorities, for instance, to rapidly double check drug safety concerns in weeks or months rather than the years required for a specially designed and constructed prospective study. An example of an occasion on which such a database could have been used rapidly and with great success is the third generation combined oral contraceptive scare.

19. The reporting of adverse drug events and safety data must be extended very significantly and updated to recognize and include the potential of the electronic patient record and the computerization of patient information systems and clinical notes.

20. The potential impact of genetic medicine must be recognized and prepared for by both the health service and researchers.

21. The question of efficacy has traditionally dominated the issue of cost-effectiveness; while NICE is redressing that balance, the next issue must be long term effects on individuals, groups and society as a whole. That will be even more challenging. For example, HRT, if invented now, would be regarded as both efficacious and cost-effective in the short/medium term for individuals and the population; but the longer term effects on individuals and society (given what we know now) might mean that the decision to introduce or recommend HRT would be much more balanced.

22. This argues for Phase 3 and post-marketing research to be independent of the pharmaceutical industry and for evidence to be systematically collected on all major types of drug over sustained periods after introduction.

23. If the UK becomes more directive over such matters, the pharmaceutical companies will threaten (again) to leave the UK. There is therefore a balance between rational dissemination and evaluation of innovation and the interests of the pharmaceutical companies (and of the UK economy), and that balance should be explicit.
24. Increasingly the regulatory and cultural climate in the UK mitigates against big second and third phase drug trials which are increasingly being carried out in Eastern Europe or third world countries. There are significant ethical issues there.

**PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY**

25. Current evaluations are severely limited and biased. They are essentially dominated by papers published in peer reviewed papers, where it is already known that there is a bias to positive results rather than negative results, and towards the specialist secondary and tertiary setting rather than primary care and where there is an under-representation in the research of the elderly, the young, pregnant women, and ethnic and cultural subgroups. The current use of the double blind random controlled trial can see the results being controlled in some way by the company supporting the research and the possibility that negative results are suppressed.

26. The economic evaluations are frequently severely limited and over simplified. They are not sufficiently extensive and long term to recognize adequately the impact of service redesign, opportunity costs and benefits and the impact of secondary disease or concurrent diseases (ie by preventing a fatal myocardial event a patient may then go on to develop vascular dementia, require anti-dementia drugs, need long term residential and nursing care, and a hip replacement for his osteoarthritis, before eventually dying with prostate cancer.

August 2004

Annex

**THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY ON PATIENTS’ ORGANISATIONS WITHIN EUROPE**

**EUROPEAN PATIENTS’ FORUM**

On 31 January 2003, responding to calls by the European Commission and other EU institutions for one pan-European patient body to address and be consulted on issues concerning the interests of patients, 12 pan-European patient organisations came together in Brussels to create a common platform, the European Patients’ Forum1.

The main published objectives of the Forum are:

— To facilitate an open and inclusive Patients’ Forum enabling all pan-European patients’ groups to exchange information and points of view in the area of EU Health Policy and all other EU initiatives of interest or concern to patients.
— To share health experiences and examples of good practice in order to strengthen the role and voice of European patients’ organisations.
— To offer the views of patients, as external stakeholders in the European healthcare debate, by means of a broad, truly representative and independent patient group resource.
— To provide a forum for patients’ organisations to develop common positions on European health policy issues and to lobby on behalf of those organisations, giving them a central position in the provision of healthcare in Europe.
— To become the natural first point of reference for the European Commission and other European institutions when seeking the opinions of patients and/or when seeking to consult patient groups.
— To co-operate in the formation and execution of joint projects aimed at improving health outcomes and the quality of life of European patients.

All members of the forum are required to fulfil the following criteria:

— Legitimacy: EPF member organisations should have statutes registered in one of the member states of the European Union. If the applicant organisation is not registered in an EU Member State, additional information needs to be provided demonstrating EU focus and activities.
— Representation: EPF member organisations should have members of their own in more than half of the member states of the European Union.
— Democracy: EPF member organisations should have governing bodies which are elected by their members, who shall be patients, their carers, or their elected representatives.
— Accountability: Statements and opinions of EPF member organisations should reflect the views and opinions of their memberships and consultation procedures with those memberships should be put in place.

1 [www.europeanpatientsforum.org/](http://www.europeanpatientsforum.org/)
— Transparency: European patients’ organisations should disclose their sources of funding and generally make available their audited financial accounts.

So far, so good.

**ALZHEIMER EUROPE**

Alzheimer Europe is one of the full member organisations of the European Patients’ Forum and complies with the Forum’s requirement for transparency by making available its annual report on its website. The most recent available report for 2002, shows that the organisation has an annual turnover of approximately €300,000. Income from membership fees is static at about €44,000 for both 2002 and 2001. However, income from sponsorship has risen from €91,000 in 2001 to €130,000 in 2002. Donors are listed with Janssen-Cilag, Lundbeck and Pfizer all shown as contributing between €20,000 and €49,999 in 2003. However, precise amounts are not given and the proportion of total donations arising from the pharmaceutical industry is not declared. Alzheimer Scotland is a board member of Alzheimer Europe and, again, its annual report is made available on its website. This shows an annual turnover of approximately £7 million and lists Janssen-Cilag, Lundbeck, Novartis and Pfizer as corporate supporters. Again, precise amounts are not given and the proportion of total donations arising from the pharmaceutical industry is not declared.

**EUROPEAN FEDERATION OF ALLERGY AND AIRWAYS DISEASES PATIENTS’ ASSOCIATIONS**

The European Federation of Allergy and Airways Diseases Patients’ Associations is also a full member of the EPF but neither accounts nor a list of sponsors is currently available on its website. Asthma UK (previously known as the National Asthma Campaign) is a member of the European Federation of Allergy and Airways Diseases Patients’ Associations and its annual report for 2003 is available on its website although not easy to reach from the home page. The group’s annual income was more than £10 million and the report lists Boots the Chemist Ltd as donating more that £100,000, Allen& Hanbury and AstraZeneca as donating more than £50,000 each, IVAX, Novartis and Superdrug as donating more than £20,000 each and Aventis Pharma, Merck, Sharp and Dohme, Schering-Plough Ltd as donating more than £10,000 each.

**Increasing conflict of interest?**

The number and size of health campaigning organisations across Europe is increasing every year. The public, as both citizens and patients, turn increasingly to these organisations to represent their interests and campaigners speak regularly at key meetings and conferences and are consulted routinely by governments. Global economic slowdown has led to a decline in government and public philanthropy and the faltering stock market has reduced the amount of money available from charitable foundations. The result is that a rapidly increasing proportion of the funding for health campaigning groups comes from the pharmaceutical industry. The industry hopes that an ever closer relationship with health-based charities will stimulate public demand for more of their products and put pressure on healthcare systems and governments to respond. Very few of the health campaigning organisations are completely transparent about the sources of their funding and how it is spent which leads to increasing suspicion of the extent of influence of the pharmaceutical industry. Where organisations do publicise the sources of their funding, pharmaceutical companies figure very prominently but the amounts given are not made public and, again, the extent of influence is difficult to estimate.

Health campaigning organisations are subjected to increasing pressure from specialist health PR companies as patient groups are created or wooed to assist with “disease awareness campaigns” or to provide emotionally charged testimony in favour of speedy regulatory approval of new drugs. Such specialist PR companies include the UK’s Shire Health Group. The company’s website includes the following rhetoric:

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2 www.alzheimer-europe.org
3 www.alzscot.org
4 www.efanet.org
5 www.asthma.org.uk/donate/images/annrep03.pdf
8 www.shirehealth.com/index.html (my emphasis)
Public Relations

The core of public relations is media relations—delivering your message to a wide audience, cost-effectively, through an authoritative third party. We have specialists in international PR and specialists in local PR. At an international level, we plan and deliver global media campaigns centrally, but we also know how to excite and engage local markets to implement a core programme.

Local media work is much more about one-to-one relationships with journalists. Building individual journalists as advocates for your product or issue. Our media unit is run by ex-journalists who know what makes a story. They take your data or any other source material and turn it into emotive news and train your spokespeople to deliver the right message. We have media planners that tailor the right media to your audience ensuring you get the best return on investment.

Advocacy

Our belief is that the effective development of opinion leaders, in all your stakeholder groups, is essential for your commercial success. We take a customer-centric approach that identifies a common agenda between you and your stakeholder, be it an individual, an organisation or coalition of groups, policy and funding.

In a growing number of markets around the world, non-prescribing customers are making decisions about your product and issues that are key to your business. Our job is to shape their thinking. Our programmes lobby and build partnerships with mutual benefit.

Consumer

We have long recognised patients, and physicians for that matter, as consumers in their own right. We can show you how and when to communicate with your ultimate customers, the patients, in the very best way to engage them and achieve the desired response.

Herxheimer has argued that if the pharmaceutical industry directly or indirectly provides over 20% of an organisations budget, the organisation necessarily becomes dependent on it and this, if nothing else, will influence policies. He cites the interesting case of the Lymphoma Association, a charity that is linked with Roche. The portal www.lymphoma.org.uk leads to two sites: www.lymphoma.org.uk/healthcare.htm for professionals and www.lymphoma.org.uk/support for the public. The first is password protected, “is made possible by an educational grant from Roche Products,” and links to a Roche site. The second, which is freely accessible, does not mention Roche. Herxheimer states that one consultancy firm manages both sites.

It is not the intention of this paper to undermine the important work of health campaigning organisations or to suggest that such organisations are in any way corrupt, but to draw attention to the degree to which third parties, in pursuit of their own commercial interest, are attempting to manipulate the activities of such organisations.

RESPONSE OF EUROPEAN MEDICAL ORGANISATIONS

In this context, European Medical Organisations need to be very wary of uncritically endorsing recommendations and statements from European and/or national patient and/or health campaigning organisations.

9 June 2004

Memorandum by Head of Policy Development, Royal Pharmaceutical Society of Great Britain (PI 16)

INQUIRY INTO THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY: HEALTH POLICY, RESEARCH, PRESCRIBING PRACTICE AND PATIENT USE

I am writing on behalf of the Royal Pharmaceutical Society of Great Britain (RPSGB), the professional and regulatory body for pharmacists. We welcome the opportunity to submit evidence to this inquiry.

Please find attached six reports on direct-to-consumer advertising (DTCA) of prescription medicines which were commissioned by the RPSGB, and three responses we made to external consultations on the topics of DTCA and information for patients.

2. Meek C (November 2001). Recent developments in DTCA.

7. RPSGB response to Consumers’ Association consultation on Shaping the future of patient information and education, September 2002.
9. RPSGB response to MCA consultation on Disease awareness campaigns: draft guidelines,10 July 2002.
I hope this information will be useful to the Committee.
12 August 2004

Memorandum by The Royal College of Psychiatrists of the Pharmaceutical Companies (PI 103)

THE BENEFITS & SAFETY OF SSRIs IN CHILDREN: THE THREAT TO EVIDENCE-BASED MEDICINE RESULTING FROM SELECTIVE PUBLICATION OF CLINICAL TRIALS AND THE ROLE OF PHARMACEUTICAL COMPANIES

INTRODUCTION

The decision to give/receive treatment should be based upon the balance of risks and benefits. If the benefits outweigh the risks, the treatment is worth considering. If the risks outweigh the benefits, alternative treatments should be sought. To make a decision to give/receive a treatment, the doctor and patient should know about ALL the risks and potential benefits of the treatment. Most of our knowledge about the benefit and harm associated with any drug comes from clinical research undertaken by drug companies. If pharmaceutical companies only publish clinical research that is positive, and hold back on publishing clinical research which is negative (selective reporting), then patients may well be given treatments which, unknown to either the patient or the doctor, are likely to do more harm than good.

We want to present evidence that at the present time, neither doctors nor patients can be confident that they will have access to ALL the evidence needed to make treatment decisions, and that this appears to be the result of selective reporting of clinical trials by drug companies.

SUMMARISING THE EVIDENCE

In December 2003, in an unprecedented move, the Department of Health agency responsible for ensuring that medicines meet appropriate standards of safety and effectiveness (the Medicines and Healthcare products Regulatory Agency—MHRA), released data regarding the risks and benefits of newer antidepressants used to treat depression in children and young people.

The information published on the MHRA’s website included both previously published and never before published data obtained directly from the manufacturers of the SSRIs (“selective serotonin reuptake inhibitors”) and other newer atypical antidepressant drugs. These data were collected after earlier work had raised concerns about the safety of paroxetine (Seroxat) and venlafaxine (Efexor, Efexor XL) in children and young people with depression.

Based on their review of the data, the MHRA concluded that all of the newer antidepressant drugs, other than fluoxetine (Prozac), carried serious risks that outweighed any benefits. The MHRA, therefore gave warning of the potential that these drugs could increase the risk of suicide-related behaviour (rather than decreasing it—as would be expected of an antidepressant) when using these drugs in the treatment of depression in childhood and adolescence.

The MHRA, therefore, informed all doctors that the use of SSRIs (except fluoxetine) was now “contraindicated” in this context. However, this was not the commonly held view in the published literature with recent studies in particular suggesting that these drugs were beneficial and well tolerated with no serious side effects.

10 Not printed.
At this time, we* had been commissioned by the National Institute for Clinical Excellence (NICE) to produce national guidelines for the whole of the NHS on the treatment of depression in children and young people. We produce most of the NICE guidelines in mental health, each one taking about two years to produce and giving advice on the treatments which have the best evidence for their effectiveness.

It is important to note that up until this point in our work for NICE, all our guidelines (and all other NICE guidelines as far as we are aware) have been based upon an in-depth assessment of the PUBLISHED evidence. So, when the MHRA verdict on the SSRIs became public, we became aware that the MHRA had a total of 11 trials, of which we had only seen five, since only five had been published.

We had already written to all relevant drug companies, asking them to furnish us with ALL relevant published and unpublished trials of the treatment of children and young people with depression—no unpublished trials were forthcoming.

Because of the inconsistency between the MHRA’s findings and the published literature, several members of our guideline committee, decided to compare and contrast the published data with the unpublished data. This work was designed as an experiment to test out what the difference might (or might not) be if, in producing a guideline, we had access to the unpublished as well as the published literature. The results of this work** were published in The Lancet, a British-based medical journal.

The authors of the Lancet article concluded that the published evidence was more favourable than the unpublished evidence, and most importantly that it was only when all evidence was examined that it was clear that the risks (particularly the increased risk of suicidal behaviour and thinking) outweighed the benefits.

We also found evidence to suggest that at least one of the drug companies who had undertaken trials of an SSRI in the treatment of childhood and adolescent depression had withheld publication of trial data on the grounds that it contained evidence that the drug was unlikely to be effective in treating depression in this age group.

The arguably profound implications of this study are relevant, not just for the treatment of children and adolescents who are depressed, but for the whole of evidence-based medicine, which depends upon the honesty and transparency of all people who undertake clinical research to publish ALL the findings of research and not just selective and positive findings as a means of encouraging the use of a drug.

SUGGESTED CHANGES TO THE CURRENT “REGULATORY ENVIRONMENT”

1. Mandatory pre-trial public registration of all clinical trials, with estimated completion dates, and rapid release of all relevant safety data.

2. Clinical trials supporting licensing applications should have been undertaken by an independent clinical trials unit.

3. Thorough review of the regulatory framework within which pharmaceutical companies currently operate and the processes involved in licensing drugs.

4. Thorough review of the role and regulation of medical practitioners in pharmaceutical companies by the GMC.

5. Consideration given to incorporating health technology appraisals (NICE) into the regulatory process.

6. Ensuring that all NICE programmes (Health Technology Assessment, Guidelines, Interventional Procedures) have full access to published and unpublished data.

Notes

*The National Collaborating Centre for Mental Health (NCCMH) on behalf of the National Institute for Clinical Excellence (NICE). The NCCMH is an evidence-based guideline development unit jointly run by the Royal College of Psychiatrists and the British Psychological Society and funded by NICE.


The Lancet editors also penned a hard-hitting and extremely critical editorial calling for new regulation of drug companies in the light of an increasing weight of evidence (including our review) suggesting that drug companies were not publishing evidence that showed their own drugs may be ineffective and/or harmful to patients (“Depressing Research” in the same edition of The Lancet).

Memorandum by Dr Richard Nicholson—Bulletin of Medical Ethics (PI 104)

The overall impression given by this section is that research ethics committees (RECs) have been rather difficult, but that the DoH through COREC has made lots of improvements and now has a good system up and running. The reality is rather different. For many years the DoH did nothing to support RECs and the 3,000+ members who volunteer to do the tough and rigorous analysis needed. When DoH finally
recognised that it could no longer get away with doing nothing, it set up the Central Office for Research Ethics Committees and gave its dictatorial director free rein to impose whatever ideas he liked on RECs without any requirement for proper consultation. The result has been hundreds of pages of rules and regulations for RECs to follow, dozens of standard letters to be used in every eventuality, and an attempt to impose so much bureaucracy that RECs have no time left for the ethics review and patient protection that are their proper functions.

3.1 RECs started work in 1967. The 1991 guidance from the DoH was brief and of little consequence because it came with no instructions to health authorities to support RECs and their administrators. DoH did not make any funds available specifically for ethics review until COREC was set up.

3.2 Training for REC members has been available since the late 1980s, well before 1997, but many RECs had no funding from their health authorities to take it up. The DoH commissioned its own report into the training needs of REC members in 1992, but never acted on its recommendations. When COREC presented a training strategy three years ago (without consulting any of the training providers) it was clear that it did not know of the existence of the earlier report. Both the 1992 report and one by Rabbi Julia Neuberger for the King’s Fund recommended that all REC members should receive the Bulletin that I edit: both DoH and COREC have refused even to discuss with me how that might be achieved.

There is no fundamental reason why every REC should come to the same conclusion on a given protocol, and ask for the same protocol amendments. Ethics review is not a mechanistic process that must always produce the same answer. Inconsistency between REC opinions often arises because the average protocol consists under the various “national systems” introduced without adequate consultation by COREC. They have added to administrative burden and reduced morale. Although five possible, commercially-available, software systems were already in use by comparable committees in North America that could have greatly eased the administrative burden, COREC did not look at any of them, choosing instead to have a system created de novo with all the inevitable delays and teething problems.

3.4 There may have been discussion of ethical review in the PICTF clinical research working group, but little evidence that it has made any difference. Given that a constant moan of the pharmaceutical industry is that any delay to their clinical trials may cost them millions of pounds per month, it is extraordinary that most companies remain incapable of writing adequate patient information sheets for clinical trials. My REC still requires over 90% of the information sheets it sees to be rewritten, resulting inevitably in at least one month’s delay in starting the clinical trial. I helped to produce guidelines on writing information sheets six years ago, but my analyses show that there has been no significant improvement since then. Only one company, Novartis, has made a serious attempt to produce better information sheets.

3.5 One should remember that there was no consultation of RECs during development of the EU clinical trials directive. In the UK the negotiations were left to the then Medicines Control Agency: even though it had no knowledge of RECs or any routine involvement with them, it did not find it necessary to involve anyone with such knowledge in formulating its approach. There is nothing in the directive to suggest that we have to have an UKECA that is made up of ministers. It would still make much more sense if it were to be reconstituted as a committee of experts.

3.6 This paragraph implies that the appeal mechanism is required by the directive: it is not. It also says that the Regulations reflect international standards. In one important respect they do not. The current most widely accepted ethical guidance on medical research is the version of the Declaration of Helsinki agreed unanimously by the World Medical Association in 2000. The Regulations require that UK clinical trials be carried out according to an out-of-date version, almost all of which was written in 1975. Were RECs allowed to work to the 2000 version, they could for instance insist on publication of trial results as a condition of ethics approval. But they cannot, because that was not a requirement of the old version to which we have to work.

3.7 UKECA may, in practice, choose not to appoint or dismiss REC members. But the Regulations give it the power to set up or abolish any committee and to appoint or dismiss the members, the chairman or the vice-chairman of any NHS REC. If that power is not to be used, why was it created earlier this year? There is nothing in the Regulations to indicate that UKECA is only the appointing authority for NHS RECs as a transitional measure, as claimed here.

3.8/9 I doubt that COREC is anywhere near being competent enough to qualify as an “expert unit”.

The training provided by COREC is of very doubtful quality. It has not engaged constructively with the eight or nine providers of training to RECs, and has sought to limit their activities by maintaining central control of the training budget.
While Ministers may wish to avoid excessive bureaucracy and micromanagement, COREC certainly does not. COREC’s micromanagement extends to specifying how many spaces to leave after a full stop in letters written by RECs. COREC has also been responsible for many arbitrary decisions.

November 2004

Memorandum by Royal College of Nursing (PI 42)

1. Introduction

1.1 The Royal College of Nursing (RCN) is the UK’s largest professional association and trade union for nurses, with over 370,000 members. The RCN works locally, nationally and internationally to promote high standards of care and the interests of patients and nurses, and of nursing as a profession.

1.2 The RCN agrees that the pharmaceutical industry contributes substantially to the nation’s health and therefore brings important benefits to the national economy. The RCN is working increasingly closely with the pharmaceutical industry as nurse prescribing powers expand, and greatly values the support the pharmaceutical industry offers in terms of the sponsorship of professional events and the provision of education programmes.

1.3 The following offers the RCN’s views on the pharmaceutical industry and its influence as laid out in the terms of reference.

2. Conduct of Medical Research

2.1 The RCN believes that the conduct of medical research should be the responsibility of the research team. Funding from the pharmaceutical industry for such work must be transparent and not bias the study in any way.

3. Provision of Drug Information and Promotion

3.1 Many pharmaceutical companies provide high quality drug information materials which in the interests of transparency should be acknowledged. However the RCN does not condone the use of this literature for promotional purposes. The distinction between product information and promotional material should not be blurred.

3.2 The RCN believes that in general the names of drugs on literature should be generic and not branded, and that any claims or facts included on literature must be evidence based.

4. Professional and Patient Information

4.1 The pharmaceutical industry has an important role and a corporate responsibility in the provision and support of education and professional development. Validation of this educational material by an appropriate body such as the Royal Colleges or universities etc, ensures that this material is unbiased and of a high standard.

4.2 However the RCN does have concerns that the use of advertising inappropriately promotes the consumption of medicines, particularly when vulnerable patients are not always able to exercise critical judgement.

5. Nurse Prescribers

5.1 The increasing number of qualified nurse prescribers and the expanding list of medicines and conditions for which nurses are able to prescribe, has meant increasing contact between the nursing profession and the pharmaceutical industry. Preparation for this relationship is included in the extended/supplementary prescribing educational programme. The influence of the pharmaceutical industry on prescribing decisions is also addressed during this training.

5.2 Students on the extended/supplementary prescribing programme are provided with the knowledge and skills enabling the critique of research evidence. These skills ensure prescribing decisions are based on the available evidence, in line with the Nursing and Midwifery Councils code of conduct. The RCN agrees that nurses should not use their professional status to promote a particular product. Any prescribing decision is made within the context of the available evidence and the individual needs of the patient.

November 2004
Chairman: Can we make a start? I will begin by welcoming our witnesses and thanking you for your co-operation with our inquiry. Could I now ask each of the witnesses briefly to introduce themselves to the Committee, starting with you, Mr Darracott?

Mr Darracott: Good Morning. My name is Robert Darracott. I am the director of corporate and strategic development at the Royal Pharmaceutical Society and my responsibilities include support for policy developments across the organisation and the Society’s research and development programme.

Chairman: Was there any particular reason why you did not submit any evidence to the Committee other than some old papers? Was a particular decision taken not to submit evidence? All the other witnesses have actually submitted fairly detailed evidence upon which we can ask questions this morning. Was there a reason for that?

Mr Darracott: No, there was no particular reason.

Mr Griffiths: I am Mike Griffiths and I am the joint prescribing and medicines management adviser at the Royal College of Nursing. We support our members; we have 370,000 members and support industry. Would that accord with your own views?

Dr Heath: I am Iona Heath. I have been a GP in Kentish Town since 1975 and I am a member of the Council of the Royal College of GPs. Currently, until tomorrow, I chair their ethics committee; my six-year term finishes tomorrow.

Mr D’Arcy: I am John D’Arcy. I am chief executive of the National Pharmaceutical Association. We represent community pharmacy owners and we have a membership of about 4,300 owners who collectively own 11,000 pharmacies in the UK. To put it into perspective, that is just about everybody except Boots. We provide a range of services to support members, act as a voice for members, provide services and also provide professional indemnity.

Dr Kendall: I am Dr Tim Kendall, I am a consultant psychiatrist and medical director at Sheffield Care Trust, but I am also deputy director of the Royal College of Psychiatry’s research unit and co-director of the National Collaborating Centre for Mental Health, within which we do most of NICE’s mental health guidelines.

Dr Nicholson: I am Dr Richard Nicholson. I trained as a physician, but for the last 20 years I have been working in medical ethics, editing the Bulletin of Medical Ethics and specialising in research ethics. I also set up the Association of Research Ethics Committees seven years ago.

Chairman: May I begin by asking a general point about the mechanisms the organisation you represent have to deal with what might be regarded by some as undesirable influence from the pharmaceutical industry on the work that your members do and any conflicts of interest that there may be? How are these declared, how do you actually take account of the possible difficulties which might arise where such a conflict could occur? Obviously all of you represent different areas of work and I should be interested, briefly, in how you fully address some of the concerns that you will be aware we have picked up as a Committee so far in this inquiry. Who wants to begin?

Dr Heath: We face a problem in that every major national and international conference for general practice is financially dependent upon pharmaceutical company sponsorship, which is a deeply regrettable situation and it is one in which a lot of people have colluded really to create unrealistic expectations of how much post-graduate education will cost. That is a whole area.

Chairman: One of the questions I asked at our last session was on continuing education and the answer I received, I cannot remember which witness it was, was that 90% of the sourcing of continuing education for people such as you is funded by the industry. Would that accord with your own views?

Dr Heath: No, that would not accord with my idea.

Chairman: What would your view be?

Dr Heath: I think it is very individually variable. A minute proportion of my own post-graduate education is pharmaceutically sponsored and the whole range is there. The only time in which I personally am in that situation is when I attend major national/international conferences. I cannot not do that.

Chairman: Yes, but are you unusual?

Dr Heath: No, I am not unusual.

Chairman: I am trying to get a picture overall of your members.

Dr Heath: There is still a lot of sponsorship of small educational meetings, but the changes in the way general practice post-graduate education is organised, now much more based on the appraisal system and on personal development plans, means that you can structure your own learning and you can do study from the internet, you can do study from books and it counts in a way that it did not before. You used to have to collect a whole load of events, the vast majority of which were sponsored, but I do think that the situation has changed with this new way of looking at post-graduate education. I do think that it has improved at the level of day-to-day continuing education. There is still a real, big problem about major meetings and about a minority of the profession whose entire education comes from attending meetings that are pharmaceutically sponsored.
Q210 Chairman: You would challenge the evidence of 90% that was given to the Committee but another witness.

Dr Heath: That would certainly not accord with my experience.

Q211 Chairman: You would also perhaps challenge the suggestion that new GPs are dining out every lunchtime with the drug reps, which was one point that came over from one witness. What is the extent to which GPs, your members, might accept hospitality with a drug rep? Is it common practice when they are marketing at a local level?

Dr Heath: It is very difficult for me to have a grasp of exactly how much my colleagues . . . I should be amazed if my colleagues had the time to dine out every lunchtime. It is very hard to find the time to grab a sandwich, let alone accept extensive hospitality. Again, there is undoubtedly a minority which makes the most of the offers available. For that sort of caricature picture, it is a very small minority. It is like the GPs spending all their time on the golf course; that was the previous caricature. I think that caricature is in that league. Just to go back to answer the question, the College has created a series of ethical guidelines about the sponsorship of their own meetings, so that we try to make sure that there is no direct linkage between the educational content and the sponsorship. You have to try to do that and I think to an extent, we succeed. We also have a register of interest for all our council members and try to make things explicit in that way and expect people to declare conflicts of interests, if they have them, when we are debating issues.

Q212 Chairman: So you feel that system works reasonably well.

Dr Heath: Up to a point. I still think, and the College’s view is that it is regrettable that we are dependent on this financial support for the highest status meetings. It is regrettable.

Q213 Mr Jones: You say that the College tries to ensure there is not a conflict of interest in the sponsor and the type of event. What is the point for the sponsor then, if there is no influence?

Dr Heath: Precisely. It has to be said that since we have been taking a firmer ethical stance and trying very hard to make sure that there is no linkage and making very clear, if there are sessions within, that those are directly sponsored sessions, it has been more difficult for us to get sponsorship. It is also extremely difficult to get sponsorship for topics such as learning disabilities, just to grab one out of the air, for obvious reasons. That is just one of a whole range.

Mr Griffiths: There is sponsorship in major conferences that the RCN are involved with from pharmaceutical companies, particularly as far as exhibitions go, and that does obviously help generate income to make educational conferences accessible. There are 370,000 members of the RCN and about half million nurses in the UK and a lot of nurses, including myself, pay for continuing professional development (CPD) out of their money and do it in their own time. Now, obviously an awful lot of commitment comes with nursing and making sure that you get the best education, so that you can deliver the best care to your patients, but there is a need for continuing professional development to be helped out. Now as far as continuing professional development and the split of what is paid for is concerned, I do not know, but higher education institutions do develop some continuing professional development which is paid for the workforce development confederations and the strategic health authorities. We do work in conjunction with some pharmaceutical companies and the reason that we work in conjunction with them is to ensure that when they are putting education out to our members it is validated, it is non-promotional, there is a certain quality element to the education and to make sure obviously that our members are getting decent information across at the same time.

Q214 Chairman: Obviously nurse prescribing is a relatively recent development. Has the relationship between your organisation and the industry changed as a consequence in recent times and if so, how?

Mr Griffiths: We have probably had more interest in the nursing profession since we have become prescribers and since the formulary has been opened up. Nurses can now prescribe as supplementary prescribers from virtually the entire British national formulary. There has been an increase in interest. There has also been an increase in the debates within the nursing press and within several publications which I edit we have had several articles written on the influence of the pharmaceutical industry to make sure that we are not going down the line of influencing our clinical practice. There is some evidence that yes, we may be influenced as well by marketing, by a whole host of different tactics, but we try to ensure that our patient care is not compromised and we are discussing and debating the issues with the profession.

Q215 Chairman: Do any other witnesses want to come in on this general point?

Dr Kendall: The Royal College of Psychiatrists has taken an increasingly tough stance about the influence of drug companies and less than 5% of the income of the College is from drug companies now, so it is not dependent on them. The membership, on the other hand, is rather divided. There are people who are very adamantly opposed to the use of drug company money because of the influence that it inevitably brings, but there are others who seem to exploit it quite openly.

Q216 Chairman: And the resolution of conflict of interest within your Royal College? You have a register along the lines of Dr Heath’s organisation.

Dr Kendall: I think there is a registry, but I am not that familiar with it.
Q217 Mrs Calton: What is the influence of personal contact, repeated personal contact, the development of relationships as opposed to individual pieces of information? Is there some tendency for strong personal relationships to develop which, over a period of months or years, might well lead to some influencing of prescribing?

Dr Heath: I am sure there is and for that reason our practice has not seen a drug rep in 40 years and will never see them, for just that reason. I think more and more GPs take that sort of stand, but not all by any means.

Dr Kendall: I personally, as a psychiatrist, have never seen, maybe once or twice in my youth, a drug rep, but I am very aware that there are psychiatrists whose prescribing is obviously influenced by those relationships.

Q218 Mrs Calton: I do not mean anything untoward in those relationships.

Dr Kendall: No, the problem in an area like psychiatry is that it is full of me-too drugs, so that when prescribing an anti-depressant you have a choice of a whole range of them, but all doing much the same type of thing. I believe whichever drug rep becomes your closest friend does have an influence on you.

Dr Nicholson: Just to come back to your original general point, members of research ethics committees have to declare their interests in a register of members’ interests before they join the committee. At every meeting, we have a declaration of interests at the beginning of the meeting, so that anybody who has any link with any of the proposals we are reviewing withdraws from the discussion. The association of research ethics committees has never taken any drug company money and would not, as a matter of policy, and the bulletin I edit has never had any advertising from drug companies.

Q219 Chairman: You and I have talked before about your work. In terms of local level, the ethics committees that would operate within our NHS trusts, is that the same procedure that you described there that if there are any conflicts of interests, they are recorded and there are clear principles at work.

Dr Nicholson: Yes, it is a general principle.

Mr Darracott: In response to your general question, Chairman, I would make a number of points in respect of pharmacists. First of all, just to clear up the point, we have a register of interests for council members and a register of interests for staff working at the Society and I would expect people to declare interests in discussions.

Q220 Chairman: What might those interests be, just out of interest, from your point of view? Where could there be conflicts potentially?

Mr Darracott: It would not be unusual, but it is not common, for pharmacists to act as consultants to pharmaceutical companies from time to time. We do not see a lot of it, but it does happen. The other thing, which again relates back to a point that you raised earlier with respect to nursing, is that we are seeing increasing numbers of pharmacists involved in prescribing activities and we have certainly acknowledged that, like nurses I guess, pharmacists can be expected to be approached in greater numbers by representative of the industry.

Q221 Chairman: Is that already happening?

Mr Darracott: Pharmacists have always been approached by representatives of the industry.

Q222 Chairman: Has the change in terms of prescribing arrangements meant, as it has with the RCN, that you have more contact with the industry than previously?

Mr Darracott: I think it is beginning. The nurses are a few more years down the tracks than we are and we are only now really getting a few hundred pharmacists through the accreditation process for being in a position to begin to prescribe and then local arrangements will need to be made for that actually to begin to happen in reality. I am sure it is starting, but these are early days with respect to that in particular. As an organisation we have produced some guidance for pharmacists on working with the pharmaceutical industry and that covers everything and reminds pharmacists of the sorts of skills that they might have to do in their preparation for initial practice, things like critical appraisal and evaluation; it covers things like hospitality. We are very much mirrors, sorts of industry codes, in terms of what is acceptable and what is not acceptable. It also covers commercial sponsorship and, again, I guess like a number of other organisations, we do have protocols for sponsorship of things like the British Pharmaceutical Conference where we will have industry involvement in an exhibition at the time. The other thing I should perhaps also mention is that, as an organisation, we publish both Martindale which is an enormous reference book to help professionals and, jointly with the BMA, we publish the British National Formulary which is purchased by health departments for all doctors and pharmacists. It is generally regarded as independent advice for all prescribers.

Q223 Chairman: In relation to the way your role in prescribing is changing, where a pharmacist will have a particular relationship with a GP and a local practice, how aware would you be, where the initial prescription was from the GP in that practice, of any influences that there might be on that GP on the initial prescription that you probably would follow on?

Mr Darracott: I am not sure that we would be aware that a prescription was particularly influenced.

Q224 Chairman: In terms of how a practice relates to the drug reps who will visit GPs, would you be aware of those influences which might have a bearing on the prescribing practices of a particular doctor, who would link in with your practice?

Mr Darracott: That very much depends on the relationship, as you said at the beginning, between the pharmacist and the local practice and obviously
we have encouraged pharmacists as part of a wider health care team to have good relationships with local prescribers. If that relationship develops and they then fundamentally become part of the team, then I guess the pharmacist would be more likely to know whether the doctor is seeing representatives or not, because they may well be invited along to the team meeting in which that sort of thing takes place. That is the level at which a pharmacist would be aware of the influence, particularly of a representative of the industry, on a particular practice.

Q225 Chairman: Have any of your members given examples of where perhaps they have raised a concern about prescribing which has maybe been influenced in a way that they were concerned about? This is anecdotal stuff which has come to one or two of us on the Committee, but is that anything that has come up through your members?
Mr Darracott: Not to my knowledge, no.
Mr D’Arcy: To add on that from a pharmacy committee perspective, taking your original point where you said other mechanisms were dealing with undesirable activity, pharmacists are slightly at arm’s length from that prescription pharmaceutical industry in that, although prescribing is coming on stream, traditionally the main prescribers have been GPs. Where we do have a problem with industry, where an issue occurs, and to be honest it occurs very rarely, then what we would do would be to take it up directly with the company, or to take it up with the ABPI, or, if it was a very extreme example, perhaps refer a matter to the code of practice committee. In my time at the MPA, I am aware of us doing that once on a leaflet some time ago, something said in a leaflet, but issues like that are very, very rare. Just to give a little bit of background about changing pharmacy, because I think prescribing fits into that, a pharmacist’s role, and it is an important role in modern health care, is to ensure that patients get the right medicine at the right time and with the information necessary to ensure that they take that medicine safely and appropriately. Whilst this is the principal role of pharmacists and in delivering that role, medicines are clearly a principal tool of the trade, the role is changing and pharmacists are taking on a much wider public health role. This is on the back of government policy which is aimed at making better use of the skills of pharmacists and increasing access to pharmacy services. Indeed we have just negotiated a new contract between the negotiating body for pharmacy, the Department of Health and the NHS Confederation. The other thing is that as the role of pharmacists is changing we are looking more at the pharmacy team these days: there is the pharmacist but there will also be behind the pharmacist a range of qualified staff, medicine counter assistants, who have to do accredited training, dispensary assistants who will have to do a Level 2 NVQ or equivalent, dispensing technicians who do a Level 3. As far as pharmacists are concerned, they are bound by a code of ethics as health care professionals and one of the key responsibilities of a pharmacist, and this is enshrined in the code of ethics, is to act at all times in the best interests of patients. Pharmacists do need to ensure that patients receive sufficient information and advice to enable them to use their medicine safely and appropriately. The point was made about CPD and, similar I think to my colleague from the nursing profession, pharmacists do their own CPD and are responsible for their own CPD and will undertake CPD, support their CPD with a range of materials. As part of that they will from time to time use materials produced by the industry and I think that is a reasonable thing to do because a manufacturer who researches and produces the drugs will be a natural source of that material. However, they are not influenced in terms of CPD in that it is up to pharmacists individually to decide how to do that CPD. As far as hospitality is concerned, there is not a great deal of it in pharmacy, but we do get sponsorship for meetings. I spoke, for example, at a meeting last night in Southampton that had industry sponsorship to extent of providing money to put on a buffet supper. They will have a display and will tell people about what they are doing, but from a pharmacy perspective, it is more, I would say, general marketing, to create awareness about the company and what it is doing, rather than what you could refer to as straightforward promotion. Finally, just to say a little bit about pharmacists prescribing, it is still early days with pharmacy prescribing. No doubt that will alter and affect the relationship between pharmacy and industry, but, given that pharmacists are bound by a code of ethics, we would expect pharmacists to adhere to their code of ethics and to realise that in any relationship they have with industry, they do have to keep an arm’s-length relationship, professional relationship and at all times think about what is in the best interests of patients.

Q226 Mr Jones: I want to come in on prescribed medicines first and Mr Darracott. You described in answer to the Chairman the safeguards that your organisation tries to use to ensure that patients get balanced advice and so on. Have there ever been any occasions where you, as an organisation, had to warn one of your members, or perhaps even withdraw the licence from one of your members where you believed that medicines were being inappropriately prescribed or a pharmacist had been inappropriately influenced?

Mr Darracott: Inappropriately influenced? Not to my knowledge. In a sense the supply of prescription medicines through a pharmacist is also dependent on one having receipt of a prescription by another practitioner, so the pharmacist is acting on the instructions of another health professional. What we do have instances of, and indeed there are a few cases which have come before our statutory committee, are pharmacists who have inappropriately supplied quantities of over-the-counter medicines. We would see one or two cases of those per year. Now whether that is as a result of an undue influence from the pharmaceutical industry or the pharmacist getting
into a position where they are faced with the pressure to supply the sort of products which might be misused, is a moot point. The instances of supplies of large quantities tend to be around narcotic medicines, rather than other types.

Q229 Mr Jones: May I take you back to the code of ethics? You quoted some of the code of ethics to me. What I can remember is that you would wish to ensure that you do no harm to your patient. Does the code of ethics cover whether you do any good? Mr D’Arcy: By implication it does. It might not specifically say you must do the public good.

Q227 Mr Jones: But in prescription medicines, is it just because it is early days, or is it because the ethical system and code are perfect and there is never any need for any regulatory mechanism or sanction? Mr Darracott: We would never say it was perfect, but I think it is early days and it is something that we will certainly be looking out for as we go on.

Q230 Mr Jones: You exist in order to sell medicines and it should be the priority to ensure that the medicines you sell do not do any harm, I can understand that. But if the medicines you sell do not do any good, you still exist in order to sell the medicines. Mr D’Arcy: It is a bit more than that you just exist to sell medicines. If we look at the way the regulatory process works, and this applies to prescription medicines and over-the-counter medicines, medicines are assessed, and there are regulatory controls for this, against quality, safety and efficacy. It does not just stop at that point: it is not just that once you have a product licence that is it, that is the end of the game. Pharmacists are an important part of the supply chain and in fact the last link in the supply chain before patients. So pharmacists are critical evaluators of medicines and their skill base is about evaluating the safety and efficacy of medicines. I would expect pharmacists as professionals, and this would be underpinned by the code of ethics, to assess, as part of the supply of a medicine, whether it is on a prescription or whether it is over the counter, whether or not that medicine was appropriate and actually not put themselves in such a position. In fact the code of ethics does say you should not supply a medicine where you doubt its efficacy—I cannot think of the exact wording, but I am paraphrasing—and we would not expect pharmacists to do that. In fact in something like 25% of cases pharmacists do not recommend any product at all. My view would be that we can rely upon pharmacists and indeed it would be part of their professional duty, if they do provide a medicine, to provide only those medicines that work.

Q228 Mr Jones: It is early days, but Mr D’Arcy in his evidence was saying that of course if there are no examples of anyone ever having anything withdrawn, then the conclusions are either that the system is perfect, or that the regulatory system is inadequate. In terms of the over-the-counter medicines, Mr D’Arcy, increasing numbers of medicines are available over the counter. Where do the pharmacists get information about the new products? Do you think that information is fair and balanced? The Committee suspended for a two-minute silence Mr D’Arcy: Pharmacists will get the information they need from a variety of sources and the first thing to say is that by the time the medicine goes over the counter, it has been used on prescription for quite a while before so pharmacists will already be familiar with that product. So there will be information from a variety of sources. We may produce information, the Pharmaceutical Society may produce information, there will be other information from other academic, I suppose you could say, sources, the industry will produce information, the manufacturer of that product will produce information and it varies. It varies from being credible robust objective information about the product and its use at one extreme, to in some cases something which may be no more than company propaganda. What will happen is that pharmacists will make their own judgment on materials. The experience we have is that because they are clinicians with expertise in the actual use of medicines pharmacists can very readily see what is credible, objective information and differentiate that from what you might call company propaganda. The message we give to industry is that if they are producing training materials, and indeed we would expect them to produce training materials, if they are not objective, if they are not balanced and they are not meeting the needs of pharmacists in their capacity as a clinician with an expertise in medicine, they will go in the bin. Pharmacists will do that. In fact one of the areas in which we work with manufacturers is to help them with their materials, to try to produce what we believe to be objective materials.

Q231 Mr Jones: Since you do not represent Boots, I can use them as an example. Next time I walk round Boots, I can be assured that all the medicines I see are efficacious, can I? Mr D’Arcy: If it is a medicine, then yes, I think you can. If it is a medicine, it will have a product licence and in order to get that product licence it has passed a regulatory test which satisfies the regulators, in this case the MHRA, that that product is of sufficient quality, is sufficiently safe and is efficacious. Yes, you can in the case of a medicine. Dr Kendall: Pharmacists like doctors are absolutely dependent upon a regulatory body which actually does not look at efficacy in the way that has been described. They are primarily concerned with safety and the same is true in the United States with the FDA. You only have to have two trials that show efficacy for a drug to be regulated. I also wanted to say that all of us are dependent on what is published and drug companies do not always publish their
Chairman: We might get onto that point a bit later on.

Q232 Dr Naysmith: I want to ask Mr D’Arcy a question really. If, as has just been pointed out by Dr Kendall, what the regulatory bodies look at is safety rather than efficacy, and that is almost certainly true, do you have any mechanism for feeding back problems you might observe or your members might observe in terms of safety? There is the yellow card scheme for GPs. What is there for pharmacists?

Mr D’Arcy: Pharmacists now are included in the adverse drug reporting scheme, that is the yellow card scheme and pharmacists can and indeed do report instances where they experience problems with drugs; they report that back on the mechanism. There is proportionately less reporting from pharmacists than GPs, and I think that is probably in part due to the fact that pharmacists do not carry out the diagnosis, but where they do see a problem with medicines—and indeed identifying problems with medicines is part of their core role—then they can and do report through the yellow card scheme.

Q233 Dr Naysmith: Is it working? As you say, it did not always apply to pharmacists but it does now.

Mr D’Arcy: As far as I am aware it is working and it is working well.

Mr Darracott: The latest figures I saw about the yellow card scheme, and yes of course, there could always be more reports, was that around a quarter of all reports are now submitted by pharmacists, in particular by hospital pharmacists. I think 24% of reports are submitted by hospital pharmacists and there is a small proportion submitted by community pharmacists. I would agree with John that one of the issues around that is about access to the information required to provide a full report within the yellow card scheme. What we would certainly argue very strongly for as we go forward is that pharmacists have access to more information, the sort of information that is going to be put on the national care record, and allowing us to see that information means that we are going to have more of the information that is needed for a yellow card report.

It is working reasonably well, but I am sure we could always have more reports.

Q234 John Austin: We put this to other witnesses before. The yellow card scheme is voluntary rather than mandatory. Do you think it is right that it should be?

Mr D’Arcy: I have no problem with it being voluntary. Perhaps the question to be asked in terms of a mandatory scheme is: how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that, how would you mandate that? In the case of pharmacy, and I can only speak for pharmacy, it is relatively early days and we are still seeing it bed down. Certainly our view initially would be that we would like to see a voluntary scheme to see how it works and learn lessons. I do not have a particularly strong view one way or the other on that.

Dr Heath: The people with the most interest in reporting are of course patients themselves and I do not know why we do not have a system of allowing patients to feed back their experience directly. I think that would be much more effective than trying to mandate people around something which is actually a continuum, from the most minor side effect to a very serious side effect and the way you draw the line in that range. I would really like to see a system that invited feedback from patients about their own experience of using medicines.

Q235 Chairman: May I turn to a slightly different area? In one of our earlier sessions we had a GP who came to the Committee and was arguing very strongly on the issue of so-called disease-mongering about some of the concerns he had, and I quote. He said “One of the issues that I feel very strongly about as a day-to-day general practitioner is the amount of health anxiety and health neurosis that has been generated, often through things like disease awareness campaigns. We certainly feel that is undermining people’s sense of health and wellbeing. To put it bluntly, the reasons for that is because it is in the commercial interests of the pharmaceutical industry to promote new conditions and different conditions”. I notice in your organisation’s evidence Dr Heath, you refer to certain disease conditions and say it is very much in the interests of the industry to draw a line which includes as large a proportion as possible within the range of abnormality. Could you expand on that and your comments about the over-consumption of pharmaceuticals being a serious and growing health problem? Are we taking too many drugs and if we are, are you people not in a prime position to do something about it? I do not often go to the doctors, I do not know how many years it has been since I saw a doctor, but certainly going back to my experience, and the experience of most people as patients, it is interesting that when you go in front of the doctor you will see that the prescription pad has your name and address written on it before you have even said what is wrong with you. So there is an assumption that there is going to be something on that prescription pad before you even sit down.

Dr Heath: There is not. There certainly is not a system like that.

Q236 Chairman: Perhaps there are different procedures, but I have certainly seen many doctors and talked to people who have made the same point, that you go in front of a GP and the receptionist will make sure you go and have a certain condition diagnosed and start a certain treatment. That is the point I am really trying to get across that automatically we are straight into me coming out with a piece of paper, which may not necessarily be the best thing from my point of view.
Dr Heath: Oh, absolutely not. That is not my experience. Obviously computers are changing all that; the vast majority of prescriptions are now computer generated and there would be no point putting your name on it beforehand. I do not have the data about how many consultations end with a prescription, but it is nowhere near 100% General practitioners regard part of their role as defending patients against the healthcare system in general and the pharmaceutical industry in particular, because medicines are as dangerous as they are beneficial. According to the government's own medicines partnership—what is it called?—the one working on concordance and compliance, 70% of the UK population are taking medications regularly every day, either over-the-counter ones or other. We are healthier than we have ever been before in history and it is appropriate that 70% of the population are taking medications? I think the data from Norway, which is an even healthier population, which we put in our report, is about the new guidance putting 90% of over-50-year olds in a sort of disease category. The problem I really wanted to emphasise today is the difference between treatment and preventive technologies. When you are treating someone with a condition, you have some chance to assess whether the treatment you are giving is having an impact, is efficacious, is more beneficial than harmful, you have a framework within which to work. However, the pharmaceutical industry is now investing much more in developing preventive technologies than treatment technologies because humanity seems to have this constant illusion that you can prevent all ill health. It has been a very costly struggle to realise the limits of that approach.

Q237 Chairman: Can you get up to the point which was the key point in my question in a sense that? Are people presenting to you and your colleagues assuming there is something wrong with them as a result of what has been termed disease-mongering by certain people in the industry which is the argument which has been put to us by other witnesses? Dr Heath: Absolutely. I see women worrying about osteoporosis every day of my working life. I see people inappropriately worried about cholesterol every day of my working life. We are including an ever greater proportion of the population within a group who considers themselves to have some sort of health problem and that has huge psychological and social implications for them and it has huge financial implications for society.

Q238 Chairman: What can we do about the issue you have just described? Dr Heath: We need a huge public debate. We have to have a really adult conversation within society about the limits of medicine about the limits of pharmaceuticals, about how much gain. I am sure you have been informed about numbers needed to treat. Some of these preventive technologies have huge numbers needed to treat. There are people who will take drugs for years with no tangible benefit whatsoever and others who gain a very, very small amount. The cost per gain is becoming increasingly huge and it is a sort of collision of different strands: the fact that we now have preventive technologies, but we now also have this kind of computer surveillance of the population where we know where everybody is and we can target everybody. Those two working together seem to me to be increasingly malign. I am supposed to be able to make people feel better and I spend my life working in a situation which seems hell-bent on making everybody feel worse.

Q239 Chairman: Do you find yourself as a GP in a situation where patients come with a particular expectation of an outcome from a consultation with you and go away disappointed if the outcome is not a prescription of some sort which can offer them some sort of instant cure, when you might say that there are other means of dealing with their condition, or you might say that they do not have a condition? Is that increasingly a problem? Dr Heath: It is certainly a problem. I hope people do not go away disappointed. I have to work very hard to make sure they do not go away disappointed. I think what has happened about antibiotic prescribing over recent years shows that GPs have been successful in having that sort of conversation about treatment therapeutics. It is much more difficult in preventive therapeutics because of the global fear about early death. It is very hard.

Q240 Chairman: You obviously think very deeply about these issues. With the greatest respect, and it is human nature, not all your colleagues who are GPs will think as deeply. Is it not the easiest thing for a GP, who has a patient with certain expectations of the outcome of that consultation, to write a piece of paper and send them on their way? In view of the pressure that you and your colleagues are under, is that not probably the easiest way out for many of them? Does that not happen in many instances? Dr Heath: Not necessarily, because, particularly in older people, we are in a situation with older people where we now have guidance for every single condition. Most older people have got a minimum of four and with the number of different medications that people are on you add another one at your peril. It just gets more and more of a mess, but you are not meeting the sort of audit guideline for the single condition. I am not sure I should say this in this setting, but I sometimes say to my patients that they can have 10 medications, they must choose, but they cannot have 20 because of the risks to them of these things compounding with each other. Of course there are no studies about the sort of combinations of drugs that we are now using every single day; there are only studies around single or at most double prescriptions. All general practitioners have a large number of people taking at least 10, pharmacologically active products, let alone what they are buying over the counter as well. This is going nowhere good.
Dr Naysmith: I just wanted to pick up on what you said about people who are inappropriately worried about cholesterol levels. One of the ways of dealing with it now is to prescribe statins and there is evidence of course that statins do reduce, on a population level; we do not know yet how to prescribe the ones at an individual level who are going to benefit from them. However, it is becoming so costly, that the answer seems to be that we are going to allow people to buy them over the counter. What do you think about that? That ties in exactly with what you have just been talking about, but it is a specific example that faces us with the costs and not really knowing whether it works for individuals or not, so we are prescribing on a population level.

Why did you say inappropriately worried about the cholesterol level?

Dr Heath: Because, as always, it is the old inverse care law: it is the fittest, wealthiest people who seem to spend most time worrying about cholesterol. The people from poorer situations who are facing much greater surviving-from-day-to-day sorts of problems actually do not have time, or the energy, to concern themselves about their cholesterol. Of course, because they are on poorer diets, that group is the one which could benefit much more statistically.

Q242 Dr Naysmith: From other measures.

Dr Heath: If you put it onto over-the-counter, all you are going to do is exacerbate that health inequality, because poorer people cannot afford to buy Paracetamol for their children, let alone to buy a statin over the counter. It is a question of how we target these interventions and really to have a realistic estimate of the amount of input and how little, I think this government is doing more, but how little we put into non-therapeutic, non-pharmaceutical interventions, into exercise, into giving people opportunity. Things like hope keep you alive. There is definite data that having a positive view that your life is worth living makes you live longer. When patients ask me about their cholesterol, be happy, be rich, it is not always easy but those are by far the best determinants, far above your cholesterol level.

Q243 Dr Naysmith: I just wanted to pick up one other thing you said directly on this. You were saying look at antibiotics and GPs. Actually, although they have been some successes in educating patients not to ask and demand antibiotics, it has not been hugely successful. There are still a lot of patients who do still pop in and say right, I have a sniffle, I have a cold, give me an antibiotic and the easiest way to get them out of the surgery is to give them what they ask for. There have been some successes but it has not been hugely successful.

Dr Heath: I think there is a definite downward trend and I think it does show the benefit of having a campaign aimed at the prescribers, but also having a campaign aimed at citizens themselves. That same sort of thing needs to happen around these preventive technologies because statins are only just the beginning. The pharmaceutical industry will come up with any number. I would say we are going to have 10 over-the-counter preventive technologies by 2050; I should be amazed if we do not.

Dr Nicholson: I just want to make the point that it is important to remember that the supposed efficacy of all these new drugs that have come on-line is shown in very tightly controlled clinical trials, where the circumstances of the individual subjects of the trials are rigidly controlled. They do not relate to real life at all, they do not relate to the way that people actually take drugs in real life and I think we vastly overestimate the value of most of these drugs. If one just looks at an overall picture of life expectancy in this country, it went up by 32 years in the twentieth century. Now only the most optimistic commentator suggests that maybe three and a half years of that is down to having a health service and a year and a half of that is down to having childhood immunisation, so the rest of the 99.9% of what we spent on the NHS gives us perhaps two years added life expectancy. OK, we say it produces vast improvements in quality of life, but actually when you start measuring morbidity, you find that the main activity of the NHS is to keep chronically ill elderly people alive at a bit longer, so actually we are probably adding to the burden of morbidity as well in society.

Chairman: Thank you for cheering us up.

Q244 John Austin: I want to go back to Dr Heath, because whilst I would accept that we should be concerned about inappropriate prescribing and we should be concerned about unnecessary self-medication, I was somewhat concerned that when the Chairman used the term disease-mongering he mentioned osteoporosis, since this is a condition which is easily preventable and treatable, affects far more women than it does men, affects far more women than does breast cancer or cardiac disease and if we are going to live longer, it is going increasingly to affect more and more people.

Dr Heath: You speak like someone how has been speaking to a drug rep. Osteoporosis, thinning of the bones, happens naturally with ageing. Everybody at my age has thinner bones than somebody at 20. When I am in my eighties I will have even thinner bones. Some people’s bones get thinner earlier than others. It is absolutely a continuum. There is no cut-off where people have good bones and people have bad osteoporotic bones. I would not dispute that at one end of that continuum, there are people whose thinness of their bones causes them very serious problems.

Q245 John Austin: And serious problems for the NHS.

Dr Heath: Yes and that those people would benefit from being identified and treated. But the whole drift of the osteoporosis public discussion has been to widen that, to make people worried about their bones. It is very interesting that the measurement for osteoporosis is to compare the current bone density with a young woman’s bone density, so there is a whole thing about it. The other important thing, and
we do not understand why, it is that actually fracture rates do not correlate with your bone density measurement. You would expect, and the whole drift of the publicity is, is that the thinner your bones, the more likely you are to sustain a fracture. It is not actually true when you look and it remains an idiosyncratic thing. There are all sorts of non-pharmacological things that you can do to improve your bone density.

Q246 John Austin: I was not suggesting that one should instantly put everybody on HRT.

Dr Heath: Least of all HRT.

Q247 John Austin: That is what I would have been saying to if I had been listening to the drug companies. However, there are things people can do in terms of dietary supplement, in terms of exercise.

Dr Heath: Stamping. I recommend stamping for all women in their fifties, it is extremely good. Impact exercise. You should stamp regularly.

Q248 John Austin: That is not to suggest it is disease-mongering, but that people should be concerned.

Dr Heath: No, but it is disease-mongering to look to extend that range across the continuum. That is disease-mongering and exactly the same process is happening in blood pressure. Of course if you treat across a wider range, you will get an incremental benefit, you will, but it is an exponentially declining benefit. The more you treat, the less benefit you will get. So the pharmaceutical industry clearly wants the cut-off point at the broadest point. I suspect society would benefit very considerably from having it drawn somewhere else. The last point I want to make it that we are only just beginning to understand the health effects of making people worried about their health. We are only beginning to see that and I predict that is also going to be a huge health problem for the future where people more and more feel that their body is in some way sabotaging them. We know that once you diagnose somebody as having raised blood pressure, they think about their blood pressure a minimum of seven times a day. That is not a definition of health and if they are not only worrying about their blood pressure but their cholesterol and their bone density, there becomes a sort of introspective health surveillance attitude that is the very antithesis of health.

Q249 Chairman: Do you have any appointments available? Can I actually ask our pharmacy colleagues about the general point about disease-mongering and whether you concur with Dr Heath’s organisation’s views on this and if so, what is your role in countering this kind of situation?

Mr D’Arcy: From a political standpoint, we do not really have a view on the disease-mongering, so there is not a NPA position on it, but I would accept what Dr Heath said, that there does need to be a debate about this and I think it is debate that requires all stakeholders to take part. So in responding to that it is probably more personal comments, partly as a pharmacist and partly as a patient I suppose, but I will feed them in. The debate is whether we tell patients, whether we do not tell patients, whether we disease-monger, or not disease-monger. We need to recognise that we live in an information world and people will get information from a variety of sources. They will get it from the internet, they will get it from friends, they will get it from healthcare professionals, they will get it from the media and health sells. If you put a health column in your magazine or whatever, people want to know about it, people are interested in it. The question is whether patients have a right to know. In other words, if we tell patients more then they get alarmed. I think that is for patients to decide and as an individual it should be my decision. I was interested in the comment on the blood pressure. Speaking as me, as a male, I had my blood pressure measured the other day and I was pleased and surprised and I have to say mightily surprised, relieved as well, to find that it was normal. But had it not been normal, there is no doubt my mindset would be adjusted by that. I would think differently, I would feel differently and I would start worrying about it an awful lot and it would leak into other area. So do you want to know, do you not want to know? On the other hand, if I had high blood pressure and it was indicative of an underlying condition, I would probably on the one hand not want to know that because I should just like to live in ignorant bliss, but on the other hand, I might need to know as a father with children and do what I can to prevent that. It is down to me to decide on that and I think the debate needs to centre around whether patients do have a right to know about this and to make their own decisions. The big issue then is, if patients do have a right to know and as time goes on we know more and more about conditions and we have a debate about whether or not it is disease-mongering or whether it is a real level of concern, what is affordable. Of course that is the ultimate policy decision that has to be taken. We talked earlier about quality safety and efficacy; the so-called fourth hurdle, of course, was and is NICE which was to look at cost-effectiveness of medicines. So there can be a range of opinions on what is right or what is wrong; from a pharmacy perspective, we have not got involved in the debate and listening to it I think we must and I think we must need a wider debate. Ultimately, I do think it is going to come down to a political decision about what is affordable. Statins have been talked about and actually statins are an example of that. NICE guidelines say that below a certain level, you do not treat and that is where the gap comes for statins. It is down to individuals to decide whether or not they want to take a statin, whether or not they are sufficiently worried about cholesterol and to get back to the decision about whether to be sufficiently worried they need sources of advice and they will choose a source of advice themselves, but what they need to be assured about in the whole healthcare system is getting access to objective advice somewhere down the line, and they need to be able to rely upon honest brokers in the healthcare system.

Q250 Chairman: No disrespect to you personally, but are your people honest brokers in the context of
where some of us are, to pick up Dr Heath’s concerns, convinced that we have all sorts of things wrong with us that might be absolute nonsense and I come along to you as a middle-aged man with all sorts of fears about my health, convinced, because of marketing techniques, that if I acquire a certain product, that will help me. I do not go through Dr Heath for that product; I can probably buy it over the counter. Ethically, would you say frankly I do not need it, or is it a waste of time, or really this has built up to an issue it is not and I am just wasting my money by buying it? Or would you members think well, sell it and off you go and make the money on the product?

**Mr D’Arcy:** You are going to get a variety, but I would say in the main pharmacists would do that: they would look at it, they would look at you, they would talk to you and they would consider whether it is in your best interests. If they believed that it was not in your best interests, or they believed, taking the earlier point, that it actually was not a therapeutically effective product, whatever it was, that is the advice they would give you and that is actually what pharmacists do on a day-to-day basis. In terms of a pharmacist taking commercial decisions, thinking they will just sell it to you, actually pharmacists do not operate particularly commercially in that respect. They tend to favour more giving impartial advice to patients, because they believe in giving objective advice, and they believe in providing a service to patients which is based around that objective advice because that is the way they operate and, going back to it, the code of ethics underpins that. You will, however, get some patients who will come into a pharmacy, sticking with statins again, who will say—and it may be another medicine—“I am aware there is a product to deal with X, Y and Z, give it to me”. Sometimes a pharmacist will have difficulty saying “Well, actually hang on a minute, is this right for you? Is this appropriate for you? Are you taking any other medicines?” asking a variety of questions. Sometimes that discussion is difficult because a patient has such a mindset that they want a particular product or a customer has a mindset that they want a product and they will try to get it. Where pharmacists are given an opportunity to engage in giving advice, they are duty bound to and will give objective advice about that and will act for what they perceive to be in the best interest of the patient.

**Mr Darracott:** I should like to add a couple of things to that. We have expressed particular concern about disease awareness campaigns where they relate to a new product, approaching a new area where there is effectively no direct competition. So the disease awareness campaign is really a straight link to a single product, not just because there are no direct competitors, but also with a new product on the market, there is only a provisional risk benefit profile and one of the approaches that the BNF takes in dealing with new medicines is that it will note the launch of a new product and the product will only really be considered in terms of its place within the armamentarium after two or three years of use. So the new product will appear and say such and such a product has been launched in a column under the drug class and after a couple of years there will be some more information as the product gets used. We also have a particular concern, looking at the American experience, that disease awareness campaigns really were the precursors to direct-to-consumer advertising and we have great concerns about direct-to-consumer advertising. I just observe that the five products advertised across the Super Bowl weekend in the USA tend to be three prescription drugs and two alcohol products, which is an interesting combination. We have some serious concerns about that. One thing we have taken the opportunity to do, and it relates back to an earlier point, is that with prescription switches to pharmacy from prescription-only controlled pharmacy medicine status the Society does have a policy of producing our own guidance to pharmacists on the major products. We did include in the guidance on the switch of the statin product recently, that questions from customers on a statin was an opportunity to discuss other things like smoking and weight reduction. The other I would say, anecdotally is that I think there is a healthy debate within pharmacy about some of the new products which are available for sale over the counter and I recently had an opportunity talk to a pharmacist from Liverpool who said that this had cropped up at a local meeting that he was at with colleagues and they had managed to find two pharmacists in Liverpool who were stocking statins on the grounds that actually they really could not imagine anybody coming in and asking for them. On the other hand, I also spoke to a pharmacist recently who said that he had been approached about a product which had been read about, saying could they have statins, and when the pharmacist began to ask some questions about what they wanted it for they said “Well if you’re going to ask me all these questions, I’ll go to somebody who will sell it to me”. We do have to face the fact that where consumers want a particular product, they want a product.

**Q251 John Austin:** Could I come on to the issue of drug research and drug use, especially to Dr Heath. In your evidence, you said the relationship between the health service and the pharmaceutical industry must mature. In what way is the relationship immature at the present time? How would you see it in the future?

**Dr Heath:** One would not want to understate the very real therapeutic advances there have been. Just during my career as a doctor, for example, the complete disappearance of surgery for peptic ulceration, except on the rare occasions now where people still perforate, is an astonishing turnaround. So the challenge is to find some sort of regulatory framework which encourages genuine innovation, which actively discourages the whole me-too culture and somehow discourages this whole area of disease-mongering and risk factor creep, as we could perhaps call it. I think that is in an immensely difficult task and the regulatory framework at the
moment certainly does not seem to distinguish adequately between genuine innovation and me-toos and does not seem to have any grasp on risk factor creep. I am not speaking for my organisation now. Personally I am always much better at seeing what is wrong with the situation, than what can be done to right it.

**Q252 John Austin:** I was going to ask you about the me-too culture as well. Certainly it was suggested in one of our visits as well that where a specific drug was reaching the end of its patent period, then it was likely that the pharmaceutical company would develop a new improved drug with a new patent.

**Dr Heath:** Absolutely and the whole research base of me-toos, where you read the research and you are just amazed why they are not using the commonest drug to compare it with. They are comparing it with something that you are not using anyway, so how the hell are you supposed to make a decision; so the range of comparisons. The other thing, particularly again with preventive technologies, there was the issue that has already been made about the multiple morbidity of real people as opposed to research subjects, but also the length of follow-up and the way that people are allowed to extrapolate over a relatively short follow up into a huge follow-up. Do you see what I mean? That is what happened with HRT, the rapid reversal of the HRT situation, and as a doctor the HRT chaos, even though it has been very distressing for patients, has been enormously beneficial because here we have a whole group of women who have been confronted with the uncertainty and the mobility of the evidence base and have begun to understand, as a very useful group of citizens, the lack of absolutes in this game. It is an opportunity to build on that understanding which a whole group of women now has and actually there is a real sort of issue that we could be a better control of what sort of uses are made of drugs and a degree of very healthy scepticism about initial reporting.

**Q253 John Austin:** I know that Dr Nicholson wanted to come in and perhaps I could widen it as well and bring in the suggestion we have had from the King’s Fund that the areas of research and the development of research do not go into priority areas as far as the health service is concerned and go into a very narrow base and whether there is a possibility that the health service could, by some mechanism, influence the direction and development of drug research.

**Dr Nicholson:** May I just carry on from what Dr Heath was saying, that she was not certain why she was presented with some comparisons between a new drug and an old drug. I am sure that is usually for marketing purposes. Take as an example, Vioxx, which has been removed from the market recently. A clinical trial was proposed to my ethics committee some years ago of Vioxx versus Naproxen and we wondered to ourselves why on earth Merck want to compare this with Naproxen. They did not give us the details initially and then when we asked and asked, we finally found out that they had already carried out major trials against the two major anti-inflammatory drugs, Ibuprofen and Indomethacin and found absolutely no advantage of their drug. They were hoping that by comparing it to Naproxen, which had just 5% of the market, they would be able to show an advantage. Now that presents us, as an ethics committee, with a real problem. It might be that a few patients, one in a thousand patients, eventually might benefit from having this drug. We would be really delighted to be empowered to say, “Look, this is just a straight marketing exercise. This is not a proper clinical trial” we would like to be able to reject that. But, sure enough, we do not have the power, so it seemed like a moderately safe clinical trial and we allowed it to go ahead and all the advertising in this country for Vioxx was that it was better than Naproxen with no mention of the fact that it was no better than Indomethacin and Ibuprofen which are the market leaders. There is a sense in which ethics committees, if they were to be somewhat empowered, would have some function in trying to prevent the disease-mongering element. Of course these drugs, if you are going to extend their use to new conditions, have to be tested, they have to be tried out. If we are presented with a clinical trial to approve one of the SSRI anti-depressants because people think it might be useful in social phobia or for people who are a bit shy when they go into a party and maybe if they take their Seroxat, they will do better, we would love to be able to say no, this is a ridiculous use of a drug.

**Q254 John Austin:** Do you not have the power to say you are not comparing like with like and you should be comparing with something else?

**Dr Nicholson:** If it is unscientific, if the design of the trial is bad, then obviously we can reject it. However, it is an opportunity to build on that understanding which a whole group of women now has and actually a degree of very healthy scepticism about initial reporting.

**Q255 John Austin:** Do you think it is possible for the NHS to develop a national drug policy which might influence the direction of research?

**Dr Nicholson:** It would require research itself to be less dominated by drug company money and the proportion of medical research that is funded by drug company money at the moment is really much too high. Curiously, I suspect one would be in a better position to do that if one were in the United States where well over half of all medical research funds come from the federal government. In this country it is well under a quarter.
Q256 Chairman: Why is that? I find that the point you have just made very interesting about the distinction between the two countries. What is the background to that being the case in the States?
Dr Nicholson: I think there is a very long history of the national institutes of health being extremely well funded by the federal government, setting up a whole series of major research institutes which have always run to a very high quality, attracted very good scientists, produced good results and successive governments continue to fund it well.
Chairman: We have a socialised healthcare system in the UK but do not have the kind of regime you are describing in the States. I find that interesting.

Q257 John Austin: One of the suggestions the King’s Fund put forward is “New forms of public/private partnership are required in which the public interest would be given greater weight . . . the Department of Health should aim to create a level playing field, by appropriate research commissioning policies, between drugs and other forms of treatment”. Is that a view that you would share?
Dr Nicholson: I suspect I would be sceptical, knowing our failures in other public/private arrangements, to think that this was going to be a good way of dealing with research.

Q258 Dr Naysmith: Just picking up on what Dr Nicholson was saying about drug trials, one question related specifically to what you were saying. In testing a drug, whether you have an ethics committee looking at it or any kind of research committee looking at it, do you have any control of what the drug is tested against? You mentioned that the one you were talking about was tested against a not very effective, probably slightly old-fashioned drug. Can you insist that the placebo is not enough nowadays? If you have an effective treatment, or semi-effective treatment, can you say that it is no good just showing that it is better than a placebo, it has to be better than that?
Dr Nicholson: We cannot positively require researchers to use a different comparator from the one they have chosen, but in cases where a placebo is being used and there is already effective treatment, then we can just decline to approve that study. Another example from one of the major drug companies a couple of years ago to my committee was that they wished to try out a new drug for Type 2 diabetes, a glitazone-type drug and they wished to compare it against placebo but the inclusion criterion for that trial was that the person with diabetes had failed to achieve control using diet and exercise and their physician believed that they needed pharmaceutical treatment. That trial would have, if we had allowed it to go ahead, consigned half the people in the trial to receive the new drug, half of them to receive a placebo for nine months, during which period the side effects to their diabetes could have got a great deal worse in terms of visual deterioration, deterioration of kidney function and so forth. So we rejected that one but now the problem we have is that is the sort of trial that the FDA in the States still wishes to do and we would have had a good argument against it had the Department of Health, in the clinical trials regulations which came into force on 1 May, said that we were allowed to insist on clinical trials being done according to the most up-to-date ethical guidelines. However, in the clinical trials guidelines, it says that all clinical trials in this country must be conducted according to an out-of-date version of the declaration of Helsinki which is the internationally accepted agreement. The version according to which they have to be done was effectively written in 1975, with one or two minor changes since then, because the Department of Health believes that this makes it easier to make placebo control trials, where we would, as ethics committees, insist that there will not be placebo control trials. If we were allowed to use the 2000 version of the declaration of Helsinki, there would also be other advantages as well.

Q259 Dr Naysmith: Is that something that you reckon we should look at and possibly make recommendations about?
Dr Nicholson: I think you have to. The 2000 version of the declaration of Helsinki requires that any clinical trials results be made publicly available or published. We could, if we were allowed to work to that version of the declaration of Helsinki, insist that unless you made the results of your trial public at the end of it, you had never had effective ethical approval, but the Department of Health has removed that power from us.

Q260 Mr Jones: Another way of potentially addressing this issue of the effectiveness of me-too drugs might be, rather than specifying what sort of trial should be required, that the Department of Health should agree prices for drugs, dependent upon the evidence of its therapeutic value. Where a drug has not been able to demonstrate its effective therapeutic value, as compared to a well-known market leader, the Department of Health would agree only to pay a much more modest price for this drug.
Dr Nicholson: Whether the drug companies would be willing to sell at a much lower price is something the Department of Health could explore.

Q261 Mr Jones: I ask the question, because something similar apparently applies in Australia.
Dr Nicholson: I do not know the Australian scene, but it is certainly something that would be worth exploring and if countries around the world could adopt such a policy, then the emphasis on pharmaceutical companies trying to produce me-too drugs rather than looking for really innovative drugs would be much reduced. It is worth remembering that the proportion of new drugs which have been licensed over the last two or three years which really are a new principle rather than just a me-too drug is well under 10%
Q262 Dr Naysmith: Moving to the question of the protection of patients who are involved in clinical trials and we actually just touched on it a moment ago, are you satisfied that the ethics committee system is working well in terms of protecting patients? I know you have had a look at the evidence that we got from the Department of Health about ethical audit a couple of weeks ago.

Dr Nicholson: I think the Department of Health was extremely optimistic in the picture that it painted in the evidence it sent to you. The ethics committees have had two overriding needs for well over 20 years: firstly, support for their administration; secondly, support for training of the members. The need for support for administration is shown in that even in the last three years I have come across committees where there is a lay chairman and the only support that he has is 10 hours of a temp per month. That is absolutely no way to run a serious committee. These committees are made up volunteers who put in on average 150 hours of completely unpaid time and unsupported time and they are not even sent a publication on a regular basis. They do need some support. Likewise, if they are to work together effectively and come to reasonably common decisions—there is no reason why they should always come to the same conclusion because very often protocols are so riddled with ethical problems that one committee will pick up one set of ethical problems, another committee will pick up a different set, so there is no absolute reason why they should all come to the same decision—were they to have much more training, then you probably would get better uniformity.

Q263 Dr Naysmith: So you are suggesting more training, more resources. Any other recommendations?

Dr Nicholson: The resources have gone into the Central Office for Research Ethics Committees (COREC), but they have not come out the other side. It has decided to build itself an empire and COREC is now made up of nearly 40 staff. In 1997 the Department of Health thought that 250 ethics committees could be supervised by half the time of a higher executive officer. Now, when there are only about 180 committees, we have an office of about 40 staff. Interestingly, the American equivalent, the Office for Human Research Protections in Washington, also has about 40 staff, but it has oversight of 10,000 research ethics committees and is a great deal more effective. So the real problem is that there is a variety of ways in which the work of COREC completely lacks coherence. For instance, at the moment, we have the clinical trials regulations which were approved in April this year, and came into force on 1 May, which have one approach to getting consent to the involvement of an adult who lacks capacity who is to be in a clinical trial in that sort of research. The latest version of the Human Tissue Bill which has come out of the House of Lords has another version of how consent is to be obtained from adults who lack capacity, if their tissue is to be involved in research. The mental capacity bill which is going to be before parliament next session has a third set of regulations proposed for how to obtain consent when you are dealing with an adult who lacks capacity.

Q264 Dr Naysmith: We are struggling with that at the moment.

Dr Nicholson: Already we are likely, with the Human Tissue Bill—it is likely to go through, is it not?—to have some proposals and what it has to say about consent is contrary to what the clinical trials regulations say. Many clinical trials involve human tissue nowadays because people take blood samples to do DNA analysis at a later stage and so that research comes under the Human Tissue Bill. We are having real problems with coherence and the other problem with coherence is that, unlike America where one has institutions trying to develop a proper system throughout the institution for protecting the subjects of research which involves the researchers having to have training in research ethics, it involves those who assess the science as well as those who assess the science working together, we do not have that here. The R&D departments have to approve research before it goes ahead and they are working totally differently to the ethics committees and sometimes on totally different timescales. Recently, a clinical trial was proposed in East Anglia to be done at four centres. All four research ethics committees approved it within a month, three out of the four R&D departments approved it within the month, the fourth R&D department took five months to approve it, by which time the trial had been up and running in Poland for three months because this is a competitive field and if you do not get on and do things quickly, the research will go elsewhere.

Q265 Dr Naysmith: What you have just said brings me on to the second major question I wanted to ask. What evidence do you have that patients are well enough informed before consenting to take part in drug trials? I am going to bring in Dr Kendall in a moment as he has been sitting there very quietly for the last half an hour not saying very much but I am sure this is an area that you will have views on also.

Dr Nicholson: Essentially very little evidence because the empirical studies on informed consent show that, as with any form of education, patients are best informed if you give them the information in a variety of different ways on a variety of different occasions. The problem is that we are stuck in a routine of giving an information sheet and having one conversation with a researcher and that is really inadequate.

Q266 Dr Naysmith: Bearing in mind that we are looking at the pharmaceutical industry and its effect on the National Health Service.

Dr Nicholson: The pharmaceutical industry is as bad as any because the patient information sheets which they submit have on average a reading age of about 19 years, when they should be aiming at a reading age of about 11 years. They do not include on
average about 20 of the items which the various international regulations say should be in a patient information sheet. Normally they are called Version 1 and they have been written a few days before the application to the ethics committee. Absolutely no effort has been put into providing information in a way that patients are likely to understand. That means that every time their research proposal is delayed for a month because the ethics committee rejects it and says “Go away and rewrite this patient information sheet” they have wasted a month. Yet this happens on 90% of the information sheets sent to us.

Q267 Dr Naysmith: What about the relationship with the pharmaceutical industry? Do they have influences on patients and patient selection and that sort of thing?

Dr Nicholson: Not directly, because of course it is going to be the researcher who should be approaching the patient and we would regard it as highly unethical for there to be any direct approach from the pharmaceutical company sponsoring the trial to the patients. Normally it is the researcher who makes the approaches. In some situations, if the researcher has written one of these patient information sheets, one has to wonder what language he would use when he talks to the patient and whether he is capable of communicating.

Q268 Dr Naysmith: Dr Kendall, what do you think about all this area of conducting clinical trials and making sure that the patients understand what they are doing it for and that kind of thing?

Dr Kendall: Unfortunately an awful lot of the clinical trials done by drug companies are done probably not to find out whether or not the drug is efficacious or safe or whatever, although those are concerns. They are largely done to support advertising campaigns so that the results which come out of trials are very selectively used for that. There are also problems with things like recruitment. For a lot of the trials which drug companies recruit to, they recruit from populations which are completely inappropriate. For example, in some of the work on treatment of depressed children, some of the trials have recruited depressed children by advert. They are not people who in this country would have been treated with any anti-depressant, but it is on the basis of those studies.

Q269 Dr Naysmith: We will be talking about that a little later on, but at the moment we are just talking about clinical trials. You are saying that the real reason for some of the clinical trials being carried out is to back up advertising.

Dr Kendall: Yes, it does seem to be and certainly that is reflected in the publication bias I suppose. What appear in print are generally only things which are favourable to the drug.

Q270 Mrs Calton: Dr Heath, can we turn to post-marketing research? You say in your submission that post-marketing research should be independent of the pharmaceutical industry. Who do you think should conduct such research? Should this independent body, if there is one, have legal rights of access to all company data in order to compare post-market data with pre-market results?

Dr Heath: I am absolutely certain that any data should be publicly available for any product which is going to be used by the National Health Service. Selective publication is dreadful, because half the information is missing and everybody at every level is making decisions on the basis of half the data and therefore is being misled. The huge problem of unravelling post-marketing research from marketing is something which is crying out to be solved in some way; the fact that a large number of campaigns which involve financial inducements seem really designed just to get the product prescribed and somebody into the habit of prescribing it rather than to do a serious evaluation. It has to be some sort of arm’s-length . . . On the problem of who should fund it, it is not for us to say, but if it continues to be funded by the pharmaceutical industry it has to be in some way at arm’s-length so that the actual regulation of the research and the publication of the research is not in any way controlled by the industry. I also think that patients need to be very much more fully informed about what exactly they are involved in. Our College definitely has debated this issue and made a statement about full information being available to patients involved and this thing about inducements offered to the prescribing doctor, for example.

Q271 Mrs Calton: We have heard in previous evidence that actually not that much post-marketing research goes on, but most of the research is pre-marketing. The very little which goes on is not in the hands of independent people. Do you believe that it is possible for an independent body to be set up which could look at post-marketing research?

Dr Heath: I am wondering whether the same organisation that looks at the adverse drug reactions in that first crucial interval with a new drug, when adverse drug reaction surveillance is so much more important than in any other stage in the life of the drug, could in some way be tied into post-marketing research.

Q272 Mrs Calton: In some senses the fact that people are being prescribed a drug is a whole new, big trial, is it not?

Dr Heath: Exactly and there is an opportunity there to put a research framework round it and to get real prospective data which is lost at the moment.

Q273 Mrs Calton: Do you think it could be linked to the yellow card system?

Dr Heath: I do and also systematically getting feedback from patients who take new drugs, rather than waiting for the patient to come to tell their doctor or their pharmacist who then may or may not do a yellow card depending on what sort of morning they have had.
Q274 Mrs Calton: How much do you think it would cost to do that?

Mr Griffiths: I do not have the first idea.

Q275 Mrs Calton: May I turn now to Dr Nicholson? In our last evidence session, Dr Andrew Hersheimer suggested that ethics committees might have a key role to play in relation to disclosure of clinical trial results by insisting that trials be registered at inception on an appropriate registry before people are recruited to it. Do you see merit in this proposal?

Dr Nicholson: Certainly I see merit in that proposal. However, as I explained earlier, we are stymied by the Department of Health saying that clinical trials are to be conducted according to out-of-date ethical guidelines, so we do not have any way of enforcing such a requirement. Personally I have been arguing that all research should be registered for over 20 years now. I am absolutely in favour of giving ethics committees the power to insist on registration of any trial they approve.

Q276 Mrs Calton: And the parts of the trial, so that all the different parts of the research are all fully reported at a later date.

Dr Nicholson: Yes; not necessarily published, because one cannot insist on journals taking material, but they must be publicly available and put on the website. Indeed the most recent version of the Declaration of Helsinki says that the design of all the studies should be publicly available. I see absolutely no reason why the protocols of these trials should not be required to be put on the internet or made publicly available in some way before you even start the trial. The drug companies will shout and scream about commercial confidentiality, but if their competitors have not already done their industrial espionage at least five years earlier I would be amazed. Their competitors will know very well what is going on by the time something gets to clinical trials. The idea of commercial confidentiality is meaningless in that situation.

Q277 Mrs Calton: Thank you; that is helpful. You think the main way of doing this would be to insist on publication on the website rather than depending on the journals such as The Lancet requiring that sort of publication.

Dr Nicholson: Obviously you have to leave the journals to choose what they are going to publish; they are independent bodies in that sense. I do think that there are ways in which one could ensure that the material is publicly available via the internet. May I just make one point about the post-marketing studies? It should be remembered that every study of evidence—because obviously the material which has gone into the regulators is confidential—that in trying to find any evidence at all about the use of the drug available in the published literature we are getting down to the stage of finding abstracts of proceedings, which are papers about some of these being presented somewhere at a conference. He is saying that happens far too often in his view. I am sure he would agree that registration of trials would...
be very beneficial, because they would certainly want to follow those things through. If there were a register, that would be one way for them to bring this information together much faster.

Q281 Mrs Calton: May we turn now to information for patients? It may be appropriate for Mr Darracott and Mr D’Arcy to answer my question, although I think Dr Nicholson has already talked about information for patients in trials. I was interested, as an ex teacher, to hear that the reading age is about 19 and that would certainly go with what I have seen so far of the material which is put in front of people. In its evidence the Royal College of General Practitioners suggests that “... it would be preferable for Patient Information Leaflets to be written by sources independent of the pharmaceutical industry and should emphasise the place of the particular drug in the overall scheme of disease management”. How could this be done?

Mr D’Arcy: There is probably some merit in it. I agree with the age of 19. We see patient information leaflets as being a legal defence document rather than actually being a patient information leaflet. I have an example here. I shall not talk about the actual product, because that is probably unfair, but just give you an idea of it. This is the patient information leaflet and it says “Are you suffering from untreated widespread systemic infection? Are you suffering from herpes infection of the eye? Have you taken this product before? Do you suffer any heart condition or high blood pressure? Do you suffer from kidney problems? Do you suffer from liver problems? Do you suffer from stomach ulcers? Do you suffer from glaucoma or does glaucoma run in your family? Do you suffer from diabetes or does diabetes run in your family? Do you suffer from thyroid problems?” I am going on. “Do you suffer from epilepsy? Are you suffering from or have you had tuberculosis? Are you past the menopause—the change of life? Are you past the menopause and suffering from osteoporosis—thinning of the bones?” It goes on. “Do you have Cushing’s disease? Are you pregnant or trying to become pregnant?” To be honest, anybody reading this would want their bolts tightening if they then took the medicine. That is the legal defence point: you have to put this stuff down otherwise you are not giving everybody full information.

Q282 Chairman: It would be very helpful if you could leave that with the Committee to have a look at.

Mr D’Arcy: Yes, I can send that through. The point is that that is what it is. It is not particularly helpful. At one level what that will do is prompt a load of other questions and you will then clog up the GP service or clog up a pharmacy asking all these questions. The first thing to say is that whilst that information has to be out there, because you have to put it there, how do you grade that and what does it actually mean to you in terms of taking that? There does need to be some kind of additional information just to explain in layman’s terms what this medicine is. I would agree with the objectivity then, because then you can say this has been looked at separately. It is right for the patient information leaflet to come from the industry because they have researched the product and they should be the people who put the information in. Getting the patient information leaflet approved is part of the regulatory process. The other thing about it is that whatever information you put out, it will raise more questions. Somebody will say either “What does this mean? Actually I don’t understand a word or don’t understand the way it is put” or “What does it mean to me as an individual?” They need help with that and whatever leaflets you put with products, one of the things about information leaflets is that they request more information. Certainly from our members’ perspectives, one of the things they are doing increasingly is helping patients try to understand that information and put a perspective on it. One of the roles of pharmacists is to take an objective view on it in providing that information.

Dr Nicholson: May I just mention that there is one company in this country which has made a serious effort to produce patient information sheets for their clinical trials which are understandable. Novartis realised that they were wasting an awful lot of time by having their projects rejected just because they could not write patient information sheets. They got together various writers, worked with focus groups of potential participants in their trials and ended up with extremely long information sheets, but ones which people were happy to read. They had narrow columns of text like a newspaper, they did not have enormously long lines which were totally unreadable and they had plenty of white space, short words, short sentences, short paragraphs, diagrams, flow charts wherever possible. The commonest response of people in focus groups after reading 15 pages of this was “That’s fine. I think I understand that. What else do I need to know about the trial?” They were obviously having the right effect. They were taking people forward and not just turning them off.

Mr D’Arcy: Something I meant to say as well was that pharmacists are obliged to give a patient a patient information leaflet. However, one problem we have in pharmacies is an inability to do that in all cases because in dispensing a medicine we are required in many cases to give the exact quantity written on the prescription and if that does not coincide with the patient pack which has the leaflet in it, you are left without a leaflet. This is still an unresolved issue. Some pharmacists try to photocopy leaflets if they can, but that is difficult and it is a breach of copyright. Trying to download them from the internet has also been put forward as a solution. Some of the patient information leaflets are booklets. The contraceptive pill leaflet tends to come as a booklet and it is impossible to download that in any kind of sensible format. I shall send you a copy of that as well. That is an example of how difficult it can be. It means that in some cases pharmacies are forced to dispense a prescription and have the inability to provide the leaflet. Notwithstanding the limitations of the leaflet in terms of its content, in
some cases patients do not actually get it because they cannot get it. That is actually a breach of a European obligation.

Mr Darracott: One thing I want to bring to the Committee's attention is that one of the elements of the work which is funded through the task force on medicines partnership is called the medicines' information project. I cannot give you any reassurance that it is not a wide stakeholder group, so it does have the industry as one of the stakeholders in this project, but what this particular group is attempting to do is to develop information for patients of the sort we should all like to see. It is early days yet, it is in its second year, but it is linked to NHS Direct Online. The material about individual products, whether by brand or by generic name, can be accessed through and is linked to the section of NHS Direct Online which is related to the condition that somebody might be suffering from. The areas they have explored so far are epilepsy, influenza and during Ask About Medicines Week, last week, they released a new area looking at hypercholesterolemia. It is a developing area, but it is small scale, though the work is funded through the medicines partnership by the Department of Health. If you have not had anything on that, it is perhaps something you would like to look at as well.

Q283 Mrs Calton: It would be useful, but it is dependent obviously for individual patients on being able to access the internet which not everybody can.

Mr Darracott: Indeed.

Dr Heath: A definite problem is that people are frightened by these things and the fact is that huge list of potential side effects is written to defend the company legally with no indication of prevalence. I had one particular patient who came back the day sort of thing you need so that we can see the material and educational material, it would be useful, but it is not of value. Obviously there are experts in this and we could utilise those experts—not everybody is good at critiques—as part of the validation process, to break down what the good information is here, the dubious information here and what can be utilised in that.

Q285 Mrs Calton: If you could send us some examples, that would be very useful. Mr Griffiths, in your submission you state that the distinction between product information provided by industry, which may be useful to healthcare professionals, and promotional material should not be blurred. How should this distinction be sharpened?

Mr Griffiths: Particularly when it comes to educational material we recommend that it should be validated to make sure that the quality is there, but also that there is a distinction between what is promotional and what is educational; generic names used wherever possible. Nurses are being taught to research critique, to look at research, rip it to bits and try to take out what is of value and what is not of value. Obviously there are experts in this and we could utilise those experts—not everybody is good at critiques—as part of the validation process, to break down what the good information is here, the dubious information here and what can be utilised in that.

Q286 Mrs Calton: Could we ask for examples of that to be sent? If you have examples that you could send us, not masses and masses but one or two examples that you could send us, to give us an indication of the sort of thing you need so that we can see the difference between straightforward promotional material and educational material, it would be helpful. Thank you.

Mr Griffiths: Okay.

Chairman: I am conscious that we have been going for two hours. We ought to conclude before one o'clock as we have a health debate and I know that some colleagues will want to participate. I know we are going to get some snappy questions from Doug. Can we have some snappy answers as well, so we can get through what we have to cover?

Q287 Dr Naysmith: This is one of the areas where there was a bit of blurring I am sure. I gave an indication earlier on that I was going to talk about the selective serotonin reuptake inhibitors (SSRIs) and anti-depression. I just want to ask in a very snappy way whether the Royal College now regrets accepting pharmaceutical company sponsorship for its Defeat Depression campaign which was largely supported by the College.

Dr Kendall: I am not convinced that they did actually receive support from the pharmaceutical industry. I can certainly find out and let the Committee know.

Chairman: We understood you did.
Health Committee: Evidence

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Q288 Dr Naysmith: Our information is that you did. Dr Kendall: I did notice that in looking at a previous select committee hearing. It struck me when I saw it that I was not aware that they did receive pharmaceutical company money.

Q289 Chairman: Would you get back in touch with us? Dr Kendall: Yes.

Q290 Dr Naysmith: Would you think it a bad thing if you had? Dr Kendall: Yes, because money usually brings with it some sort of influence and in having a campaign to raise awareness about depression, we need to be really careful that is not to try to increase the use of anti-depressants just to increase profits.

Q291 Dr Naysmith: That maps into the whole question of disease awareness campaigns and the disease-mongering and the distinction between the two. It certainly happens with depression.

Dr Kendall: It is very difficult with mental health, because you do want people to see mental health problems in a less stigmatising way. That does mean we need to talk about the fact that people get depressed quite often and people have schizophrenia, manic depressive illnesses and so on, rather than hide it away, but there is an inherent danger, as soon as you try to raise awareness, that drug companies will capitalise on it.

Q292 Dr Naysmith: That is possibly also related to the fact that it is quite difficult clinically sometimes to distinguish between clinical depression and ordinary fed-up-with-life in a serious way.

Dr Kendall: Yes.

Q293 Dr Naysmith: That is really a professional job for you to do, to make it very clear, if you can, what qualifies and what does not. Most mental problems are dealt with by GPs anyway these days and it must be at your level, Dr Heath, that these things are dealt with and you have to make this distinction. We have your views from earlier on, but if there is anything else you want to add here, it would be useful.

Dr Heath: Depression is a classic example. GPs are always being told that they fail to diagnose depression adequately, but if you actually follow up patients with so-called depression whom GPs missed, they are actually a group who do very well. Maybe it was appropriate not to label people with that sort of a diagnosis. It is definitely an area of disease creep, if not risk factor creep. The other one I was talking about, treating depression in children, is the nightmare of hyperactivity disorder and the increasing prescription of amphetamines for children when the problems they face are not pharmacological in the vast majority of cases. There is always going to be a small core where there is benefit, but in the hinterland of negative prescribing which just labels a child as having an illness, there are real, real issues around these sorts of huge diagnostic baskets. Depression is a huge diagnostic basket, as is behaviour disorder in children.

Q294 Dr Naysmith: I am sorry to embarrass Dr Kendall, but I have here a copy of a letter from the President of the Royal College of Psychiatrists to the Social Audit, published Volume 28, which says that the campaign’s total income amounted to £449,800, of which only £129,530, that is 28.8%, came from pharmaceutical companies.

Dr Kendall: That is terrible; I did not know that.

Q295 Dr Naysmith: I am sure you did not, or you would not have said what you said.

Dr Kendall: Which I have to say is embarrassing. I do know that our current president is very unhappy about this type of relationship.

Q296 Dr Naysmith: That brings us into another area where there is a lot of pharmaceutical industry involvement with patients’ organisations nowadays and we touched on that earlier too. This also brings pressures and I just wondered what you think about that. I am sure it operates in psychiatric illness. It is often a single disease and pharmaceutical companies provide funds to help them lobby.

Dr Kendall: Increasingly so. It presents a real difficulty. Say, for example, I was an observer to the health technology appraisal for atypicals at the National Institute for Clinical Excellence and in that process they bring in representatives from patient organisations as well as experts as witnesses. The professionals declare their interests and the patient organisations declare their individual interests but I am not aware that they declare the funding they get from pharmaceuticals. They do lobby for an increased accessibility to drugs which the drug companies are selling to these patient organisations. They are persuading them that these are the drugs they must have, with very little evidence to support it.

Q297 Mr Jones: Dr Kendall, in your submission you call for “...a review of the role and regulation of medical practitioners in pharmaceutical companies by the General Medical Council”. Could you explain why you feel such a review is needed?

Dr Kendall: Because you cannot conduct clinical trials without having doctors and since we know that there are trials which go unpublished because they are negative, we have to look at the role doctors have in that process. For us to recruit patients into a trial, that is patients with real illnesses whom we are taking into a trial and are putting them through treatments or placebos or whatever and then not publishing those results, strikes me as unethical from a doctor’s point of view. I do think that the medical profession has to look at their part in this.
Q298 Mr Jones: Mr Griffiths, you state that nurses should not use their professional status to promote individual products. What are your views on the use of nurses to conduct prescribing audits in general practice, with the presumed intent of increasing prescribing of a particular product?

Mr Griffiths: At the end of the day we have members who are both working in the NHS and in the independent sector, whether that is in industry or in the independent health sector. At the end of the day we do expect that they will enhance patient care. We have to stick within the Nursing and Midwifery Council’s (NMC) code of conduct and nurses treat their NMC code of conduct as the ultimate.

Q299 Mr Jones: I noticed that answer from all professional organisations I have ever dealt with, that they have a professional code of conduct.

Mr Griffiths: At the end of the day, if you go disciplined, if you go against the NMC code of conduct and you get disciplined, you get struck off and you lose your livelihood.

Q300 Mr Jones: Are there any examples of nurses being struck off for inappropriately advising the use of a particular pharmaceutical?

Mr Griffiths: I could not tell you whether any have been struck off recently; that is for the Nursing and Midwifery Council. Nurses do get struck off.

Q301 Mr Jones: I know that. I have asked a similar question of several professional bodies in this inquiry so far and so far nobody has come up with a single example of any of their professional organisations being deregulated, unlicensed, struck off or whatever for inappropriate prescription or advice on prescriptions. Either it does not happen and there is no problem with a big chunk of what this inquiry is about, or the regulatory system organised by the professionals is inadequate.

Mr Griffiths: I do not think it is inadequate. I think nurses are going up in front of disciplinary councils and they are being called to answer for what they are actually doing. A recent case was a nurse who gave a prescription-only medicine without it being prescribed and I believe they were struck off by the Nursing and Midwifery Council.

Q302 Mr Jones: That is a different sort of thing. Since the nurses are employed by the pharmaceutical company, there is an inherent conflict of interest if they are conducting an audit within the practice.

Mr Griffiths: I do not believe so. I believe that at the end of the day you need to have people there with some clinical skills.

Q303 Mr Jones: You do not think that he who pays the piper calls the tune.

Mr Griffiths: At the end of the day if you are auditing, you are auditing. If you are changing a prescription, that is a different, but even then under supplementary prescribing by nurses, for example, the supplementary prescribing takes place in a partnership. It has to be backed up with an evidence base which is basically supporting your prescribing decision. It is not as though people are just going in and changing people’s scripts, it has to be evidence based. If it is not evidence based, they would have to answer why it was not evidence based.

Mr Jones: You are satisfied. Thank you.

Q304 Siobhain McDonagh: GSK told us that it funded the diplomas in respiratory disease management of 235 nurses and 199 nurses in diabetic management in 2003. How did the deal come about? Could funding mean that training in some areas is done at the expense of training in others and thereby distort the overall output of specially trained nurses?

Mr Griffiths: I do not know how the deal came about, because I have never had any dealings with GSK to tell you the honest truth. As far as the amount of training which has gone on is concerned, it is actually worthwhile and thank you very much to GSK for actually providing that sponsorship. If they had not provided the sponsorship, then the nurses probably would not have got the actual training. As long as there is some sort of quality indicator in there and somebody actually making sure it was independent and not biased only towards their drugs, but giving them education around the disease process, I do not see a problem with that as long as it is the case. I am sorry, what was your last question?

Q305 Siobhain McDonagh: Could funding mean that training in some areas is done at the expense of training in others and thereby distort the overall output of specially trained nurses?

Mr Griffiths: Not necessarily. Obviously they were picking up diabetes and asthma and there are national service frameworks around diabetes and asthma. The new GMC contract which pays GPs on quality has diabetes and asthma in it as quality indicators. So they are not only targeting areas which are of interest to them as a company commercially, but also areas which are important to clinicians in ensuring that quality care is delivered and making sure that national service frameworks are also delivered.

Dr Heath: May I come in because I am astonished by that figure and it makes a lot of sense of my local experience. We now all have local respiratory nurses and local diabetic nurses and it is very interesting how much of their recommendation is proprietary rather than generic and how often they suggest changing to a different glucose measurer, how often they suggest a different pen system. I think it is having more of an influence and it is very worrying for a practice like ours which tries very hard not to have a direct . . . We were all rather uncomfortable after one of our sessions with the respiratory nurse which was all around different gadgets. That just throws light on that experience, which is interesting.

Mr Griffiths: Most diabetic nurses I have come across have actually not come through with any pharmaceutical company qualification, they have come through with a higher education institute qualification; they are coming through with the Warwick diabetic diploma or the Warwick asthma
Siobhain McDonagh: This is not picking on nurses in any sense but the next question is about the whole area which we have dealt with in other inquiries, not just in the pharmaceutical industry but in terms of work done on obesity and the relationship of sponsorship from good companies and stuff. Has the RCN any real concerns about safeguarding its own independence as its relationship with the pharmaceutical industry develops? Has the RCN developed any formal policy, defining how that relationship should and should not be pursued?

Mr Griffiths: We do and any sponsorship which comes in, anything commercial which comes into the Royal College of Nursing—and there are things which do come in, we do work in partnership where possible—goes through a sponsorship manager, it goes through committees within the Royal College of Nursing which is a member-led organisation and at the end of the day we will represent our members, but our members are involved in the running of the organisation. We are looking out for them and obviously to make sure that patient care is kept to a high quality. Our independence is important to us and I know we cannot be truly independent if they are validating something on behalf of a pharmaceutical company, but we do have to look at working partnerships to make sure that we can get the education out of our nurses.

Chairman: Do you know overall how much you are receiving directly from the industry?

Mr Griffiths: I could not tell you.

Chairman: Is there any way of getting back to us?

Mr Griffiths: We could get back to you.

Chairman: Could I put that question to the other organisations here today who have some relationship? Is it possible for you to give us some feedback on the full financial support which is received and the various ways in which it is received? That would be very, very helpful.

Dr Kendall: The drug industry’s relationship throughout all of medical education is a constant presence, even down to the Wednesday morning case conference. You will have a pharmaceutical company stand there and it is all around you.

Dr Nicholson: The drug industry’s relationship with the pharmaceutical industry and the importance of choosing your ghost writer handles the academics whose names are going to go onto the paper in a proper manner to keep them on side.

Chairman: Did you say this was a published article?

Dr Nicholson: Yes.

Chairman: It would be nice to have a look at that.

Dr Nicholson: Yes.

Chairman: May I conclude with one question? All of you have made some critical comments about the industry in a variety of ways. I think we are all conscious that the industry plays a very important role in our economy and we are also conscious of concerns about increasing movement of the industry out of the UK, for a variety of reasons which I do not want to go into, but you will be aware of some of them. Do you have any fears that if we cannot act or recommend action on some of the issues you have pinpointed as concerns from your organisations, we may add to that process even further of losing the industry within the UK? Could a balance be struck without us losing the industry, addressing some of the areas you have raised?
Dr Kendall: I suspect that you would need to have at least a Europe-wide approach to it. At the moment the different regulatory agencies are not properly synchronised, but they do all talk and they do share some regulations. Unless you did it Europe-wide there might be a risk. If a new regulatory framework could be agreed throughout Europe, it is an industry which is in need of pressures on what amount to massive profits. I am sure they could sustain better regulation and still make profit.

Mr D’Arcy: We are at the end of the supply chain and I made the point earlier that a key part of the tools of our trade are medicines which come from the industry. So a relationship with the industry is very, very important to us and critical to us. You are quite right that the industry on the one hand does do a lot of good. It provides medicines and Dr Heath gave the example of a peptic ulcer, which is a good example of how medicine has contributed to healthcare, made patients’ lives better and reduced healthcare expenditure in secondary care. There are issues which face industry: no doubt tax regimes, animal rights issues are a big one which is a growing concern, the regulatory burden is there. The regulatory burden has to be there and we have to work within that. It is a difficult job balancing the commercial role and a healthcare contribution role and a balance does have to be struck. It is possible to draft this and make recommendations where the two can co-exist, to say that we do need the industry and we do need to recognise the good that the industry brings and certainly from a pharmacy perspective we need to work with industry, but we need to work with industry in a way which is credible, in a way which is objective. I think therefore that within the regulatory burden, or within ethical codes or code of practice, controls over there, we need to make sure that they are there to deal with these issues of probity. It would be a great shame if we took all of these issues. It is easy to go through a session like this and be very, very negative about everything and ignore the positive. It is about getting a balance and it would be a great shame indeed if we came to a conclusion and said that because there are loads of problems we need to diss the industry or rubbish the industry. What we need to do is to find a balance and one that works and deals with that effectively through controls.

Dr Heath: The relative proportions that companies spend on PR and promotion and that they spend on original research seem to have got out of kilter. That must be something to do with the incentives which we are offering the industry and that seems to me where there is room for shift.

Dr Nicholson: Two quick points. One is that the Department of Health has failed to help the pharmaceutical industry in terms of running clinical trials in this country. In particular the Central Office for Research Ethics Committees and what it has been doing and its failure to get hold of the R&D departments has meant that a lot of research is now going to other parts of Europe, which is why the Europe-wide approach may not work well because it is much cheaper to do the research in Poland or Hungary or even Croatia, countries like that, than it is in this country. The second point is that I wonder whether there is any way that one can produce some sort of moral pressure on the pharmaceutical industry to spend some of its time looking towards long-term interests rather than short-term profits. I suspect the pharmaceutical industry would look a great deal more pleasant in many people’s eyes if they started making serious efforts to address that 90% of the global disease burden which they do not address at the moment.

Mr Darracott: You have had the King’s Fund paper which I think is called Getting the Right Medicines. This is a personal view but there is a positive contribution in there for what might be done. It seemed to me that what the King’s Fund was suggesting was that there was an opportunity for a grouping within the Department of Health or within government to look systematically at the whole disease burden. We recognise that at the moment there is investment in specific areas and that there are some neglected areas which are not being looked at which from society’s point of view might be more appropriate to be looked at and we might want to look at them. The other thing the King’s Fund did point out in that paper was that that sort of group could be a place where the public voice could be a serious part of what needs to be done as well. That paper does have some merits and could certainly be looked at.

Chairman: On behalf of the Committee may I thank you for what has been an excellent session. We have learned a great deal and a number of you indicated that you would come back to us with further information on certain issues. I should like to thank you all for your co-operation with this inquiry. Thank you very much.
Thursday 25 November 2004

Members present:

Mr David Hinchliffe, in the Chair

John Austin          Dr Doug Naysmith
Siobhain McDonagh   Dr Richard Taylor

Memorandum by Mr Paul Flynn, MP (PI 38)

This Memorandum is relevant to the following terms of reference:
— Provision of drug information and promotion.
— Professional and patient education.

The Committee's decision to undertake this inquiry is warmly welcomed. This brief report is intended to add to and to support fully the submissions to the Committee by MIND and Charles Medawar.

The focus of this memorandum is the relationship between pharmaceutical companies and patients’ organisations and lack of regulation of this relationship. These relationships have developed partly as a consequence of legislation preventing “direct-to-consumer” advertising and need of pharmaceutical companies to find other means of marketing medicines. They are driven by the demand for profits in an increasingly competitive sector. The ban on “direct-to-consumer” advertising should remain in place.

While on the surface this relationship appears to be “win-win” for both parties, the power undoubtedly lies with the pharmaceutical companies, who according to the Association of the British Pharmaceutical Industry (ABPI), are worth almost as much as North Sea oil to the UK economy.1

There are very serious concerns that pharmaceutical companies are using patient’s organisations as conduits to promote their products in a subtle form of marketing. There is a complete lack of transparency in the regulation of these relationships and few formal legal requirements. Instead of representing the interests of patients, groups in some cases have become marketing tools for the pharmaceutical companies and this raises serious concerns about their credibility.

Patients Organisations

The Consumers' Association estimates that there are more than 200 national patient organisations and support groups in the UK.2 Medical research charities and groups representing particular medical conditions receive around 25% of total donations made each year from all donors.3 A substantial amount of this money comes from pharmaceutical companies and is used for a number of purposes including the funding of leaflets and sponsorship of campaigns. Patients’ organisations perform many roles including providing information to the general public and representing those who suffer from a particular medical condition. Increasingly they are campaigning bodies, fighting for access to a particular drug. Naturally this coincides with the interests of the producers of drugs.

A survey4 carried out to illustrate this memorandum gives a snapshot of the extent of this relationship and how the money is used. Many of the groups contacted provide support for All-Party Groups within the House of Commons, which is another area of concern within this broader topic. The groups supporting APPGs do not have to declare their interests and given that many of them have links with pharmaceutical companies, there is a danger that it is an indirect form of lobbying for those companies.

The survey revealed a number of concerns about this financial relationship and the way it is regulated or rather the way it is not regulated. Each organisation was asked for details of the funds it received.

1 “Pharmaceutical Industry trade surplus higher than expected” ABPI press release 19 May 2004.
2 “Who’s injecting the cash?” Consumers’ Association April 2003.
4 Survey carried out through my office by writing to a selection of patient groups chosen at random.
<table>
<thead>
<tr>
<th>Organisation</th>
<th>Receipt of funding from pharmaceutical companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Association</td>
<td>Yes</td>
</tr>
<tr>
<td>National Osteoporosis Society</td>
<td>Yes</td>
</tr>
<tr>
<td>Arthritis Care</td>
<td>Yes</td>
</tr>
<tr>
<td>Alzheimer’s Society</td>
<td>Yes</td>
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<tr>
<td>Sane</td>
<td>Yes</td>
</tr>
<tr>
<td>Backcare</td>
<td>Yes</td>
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<tr>
<td>MS Society</td>
<td>Yes</td>
</tr>
<tr>
<td>Migraine Action</td>
<td>Yes</td>
</tr>
<tr>
<td>Alcohol Concern</td>
<td>No</td>
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<tr>
<td>Cancer BACUP</td>
<td>Yes</td>
</tr>
<tr>
<td>British Lung Foundation</td>
<td>Yes</td>
</tr>
<tr>
<td>Breakthrough Breast Cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>Motor Neurone Disease Association</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemophilia Society</td>
<td>Yes</td>
</tr>
<tr>
<td>Action for ME</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes UK</td>
<td>Yes</td>
</tr>
<tr>
<td>National Kidney Federation</td>
<td>Yes</td>
</tr>
<tr>
<td>Crusaid</td>
<td>Yes</td>
</tr>
<tr>
<td>Muscular Dystrophy Campaign</td>
<td>No</td>
</tr>
<tr>
<td>Young Minds</td>
<td>No</td>
</tr>
<tr>
<td>MIND</td>
<td>No</td>
</tr>
<tr>
<td>Depression Alliance</td>
<td>Yes</td>
</tr>
<tr>
<td>National Autistic Society</td>
<td>No</td>
</tr>
<tr>
<td>British Heart Foundation</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The vast majority of organisations do receive donations of varying amounts, although a handful did not accept donations from pharmaceutical companies. In its response, Young Minds, a charity supporting young people with mental problems stated, “It is YoungMinds policy not to enter into financial partnerships with Pharmaceutical companies. This enables the organisation to maintain its independence and avoid any possible instances of compromise.”

A similar survey carried out by Patient View for HSC News found that 76% of EU-based patient groups received funding from pharmaceutical companies to pay for occasional projects.

Many organisations who declare funding from pharmaceutical companies do so alongside a policy document governing the relationship.

The extent to which these organisations revealed the identity of the donors varied a great deal. Some merely printed their names and donations were recorded as a total. There was only one case where the individual donations of each company were recorded. One organisation, SANE, was “reluctant to provide company names due to the Data Protection Act,” and another explained why it did not publish detailed accounts by saying, “this would embarrass the smaller supporting companies by way of comparison.”

Interestingly, the HSC News survey recorded that 14% of EU-based groups declared using revenue from pharmaceutical companies for core costs, which suggests the survival of groups is not dependent on the support of these companies. There would therefore be no disadvantage in fully declaring funding or perhaps being more circumspect in accepting it in the first place.

While the mere act of receiving money from a company does not necessarily lead to a group being used by a pharmaceutical company or having questionable independence, there are examples of groups who have not been critical of their sponsors when products have been found to be ineffective. A major part of the problem is that many of the links are not clear.

— The Alzheimer’s Society, which campaigned strongly for access a drug called Aricept and cost the NHS £39 million a year. A study paid for by the NHS found the drugs to be ineffective. In response to this, a statement was released by the drugs’ companies which went out in the name of the Society. The Society does receive funding from these companies.

5 These included the Muscular Dystrophy Campaign, Young Minds, Action for ME, Alcohol Concern, MIND.
6 “Fundraising and the growth of industry involvement.” HSC News Issue 6 April 2004 Published by Patient View p 29.
7 Alzheimer’s Society.
8 Letter from Chief Executive of SANE April 2004.
9 E-mail from Chief Executive of National Kidney Federation June 2004.
The Impotence Association, which campaigns for wider availability of impotence treatments. It receives funding from Pfizer, the makers of Viagra, for its website, which makes no statement of editorial independence.  

A public relations agency called Phase IV contacted me via e-mail in July 2004 asking for my views on a campaign they were putting together to increase funding for anti-TNF drugs used for the treatment of arthritis. The campaign proposal included plans to contact patient groups to demonstrate the worth of anti-TNF drugs. It later transpired that the agency would be seeking support for this from pharmaceutical companies and had already approached the National Rheumatoid Arthritis Society. Regardless of the fact that doubts surround the effectiveness of anti-TNF drugs, this highlights the role of PR agencies in acting as a third party for pharmaceutical companies, adding a further shade of grey to an already unclear situation.

There is world wide alarm because of the effects of the Selective Serotonin Uptake Inhibitors and allegations that information from clinical trials has been suppressed. A courageous leading campaign has been pursued by MIND who receives no contributions from any pharmaceutical company. There has been silence from SANE and Depression Alliance who accept donations. I have been in contact with all three organisations. There are grounds for suspicion that, at best, donations may have an inhibiting effect on the two latter groups. This may explain why they have failed to add to the concerns eloquently expressed by MIND.

Following the suicide of a constituent who was using the drug Roaccutane for persistent acne, I investigated the alleged link with the use of the drug and other suicides. While no causal links have been established there is widespread international concern. A newspaper alleged that an Acne patients group failed to act on behalf on their clients to investigate any possible link. They also alleged that the group received a substantial annual grant from the company that produces Roaccutane.

Some groups have been critical of their sponsors, although examples are few and far between. The National Kidney Federation, in response to the survey detailed on page, reported that it had been critical of some of its sponsors and supported the introduction of generic drugs, which would have a serious effect on the market share of those sponsors.

Problems with Existing Regulation

The regulation of charities with regards their relationship with pharmaceutical companies lacks transparency and is fundamentally flawed.

While the Charities Act 1992 charges trustees with the responsibility of deciding whether donations are in the charities' interests, this specifically relates to the financial position of the charity. Patient's organisations share the same interests of pharmaceutical companies, so in general refusing funding would be difficult.

Although charities with an income of over £10,000 per annum are required to submit accounts to the Charity Commission in a defined format, a representative of the Commission confirmed that “the requirements to provide information on the source of donations are less stringent than those relating to the expenditure of the charity.”

There is no requirement to publish the names of all donors and how much they have contributed as was noted on page 3. “Under the charity accounting regulations (SORP) there is no general requirement for charities to disclose the sources of their donations.” Transparency is lacking because there is no legal requirement for it. The Charity Commission and other similar bodies can only really contribute in an advisory role to how this relationship is regulated.

The Long Term Medical Alliance (LMCA) is an umbrella body of patient organisations. It publishes guidelines for groups to consider in their dealings with the pharmaceutical industry. The LMCA has no way of enforcing or monitoring this. “To make them work, however, would need monitoring, enforcement, and sanctions, with compliance as a condition of membership of the alliance—a distant hope.” This lack of transparency is confirmed by the findings of the HSC News survey, which found that only 26% of UK based groups surveyed had drawn up a “conflict-of-interest” statement.

Equally, the Institute of Fundraising publishes a code for its members, which it expects them to adhere to. It recommends as best practice to establish a policy of working with companies and recognises that “In this competitive age the reasons for a company wishing to work with a charity are seldom purely philanthropic.”

12 “Who’s injecting the cash?” Consumers’ Association April 2003.
13 E-mail from Chief Executive of National Kidney Federation June 2004.
14 “Funding of charities/patient groups” Dr Kate Haire Science and Environment Section House of Commons’ library.
15 Letter from Director of Policy and Strategy at the Charity Commission.
16 “Relationships between the pharmaceutical industry and patients’ organisations” Andrew Herxheimer BMJ 2003;326:1208–1210 (31 May).
17 “Fundraising and the growth of industry involvement.” HSC News Issue 6 April 2004 Published by Patient View p 59.
18 Institute of Fundraising Codes of Fundraising Practice 2004 p 16.
PHARMACEUTICAL COMPANIES

As mentioned in the opening paragraphs, pharmaceutical companies face limits on advertising and patients’ groups offer a platform to reach members of the public. Patient groups campaigning for disease awareness or the availability of latest drug inevitably attract such interest. Consequently it pays to support these groups and in some cases companies have gone as far as creating a group. “In 1999 Biogen set up Action for Access in their effort to get the NHS to provide interferon beta for multiple sclerosis.”19 This promotion was stopped as it breached guidelines.

PROBLEMS WITH EXISTING REGULATION

Pharmaceutical companies in UK are governed by, among other things, the Medical and Healthcare Regulatory Agency. One of its roles is to regulate the promotion of drugs, but its approach to breaches is to seek a negotiated resolution in the majority of cases. The emphasis is very much on self-regulation and it is well-documented that the MHRA is populated by people with links to pharmaceutical companies20 and is funded 100% by the industry. Little mention appears to be made of patients’ organisations specifically and this leads to the suspicion that there is a gap between two different types of bodies governed by their own codes.

The ABPI publishes a code of practice, but again the emphasis is on self-regulation. Complaints are dealt with by a separate body, The Prescriptions Medicines Code of Practice Authority (PMCPA). The code governs advertising and sponsorship, but again it is self-regulatory and has very little to say about relationships with patients’ organisations and individual donations. Out of a board of 12, six members belong to the pharmaceutical industry. In 1994, the Health Select Committee reported that, “We are not convinced that the present voluntary code is being rigorously applied.”21

The ABPI itself recognised the value of relationships with patients’ organisations. During a campaign in 2000 to relax direct-to-consumer advertising within the EU, it described its battle plan as “to employ ground troops in the form of patient support groups, sympathetic medical opinion and healthcare professionals. This will have the effect of weakening political, ideological and professional defences.”22

The PMCPA publishes notes of each case it considers and sent a selection of those mentioning patient groups. They highlighted that PMCPA only really considers advertising and sponsorship, and does not extend to individual donations or the regulation of relationships. A few examples can illustrate both the influence of pharmaceutical companies and the limited role of the PMCPA.

— Case AUTH 498/2/97 Consultant Psychiatrist v Bristol-Myers Squibb

Allegation that a booklet for Depression Alliance supported by Bristol-Myers Squibb was a subtle advert for a drug called Dultonin. The drug was not mentioned by name and the complaint was dismissed. Even so, this is illustrative of the relationship and the concern of a lack of transparency,

— Case AUTH 1455/4/03 General Practitioner v Pharmacia

Complaint that a campaign called the Public Health Education Campaign sponsored by Pharmacia constituted direct advertising. The campaign had the appearance of a public health campaign and involved two patient organisations, The Continence Foundation and Incontact. A specific drug was not mentioned, but patients were encouraged to consult their doctor. While the complaint was dismissed, it was noted that a phone line established as part of the campaign failed to declare the involvement of Pharmacia and was misleading. Again, this illustrates the problematic nature of this relationship.

— Case AUTH 1316/5/02 Novartis v Fujisawa

Novartis complained that Fujisawa had been involved in a promotional article in the magazine of the National Kidney Foundation. The article was drafted by Fujisawa’s public relations agency and no declaration of Fujisawa’s involvement was made. This was found to be a breach of the code, but the complaint itself was dismissed.

RECOMMENDATIONS

Self-regulation of a one-sided, unbalanced relationship is flawed. While it might be argued that philanthropy is a private affair, the increasing role of patient organisations in providing services and campaigning and the power of pharmaceutical companies’ demands reform. Measures should be considered to increase transparency and accountability and guarantee a greater measure of independence of patients’

19 “Relationships between the pharmaceutical industry and patients’ organisations” Andrew Herxheimer BMJ 2003;326: 1208–1210 (31 May).
20 A survey of the Annual Report 2002 of the MHRA found that of the 34 members of the main committee, 17 declare personal interests, which include having received travel expenses, fees, employment as consultants and the ownership of shares. 14 of the 34 declare non-personal interests such as the receipt of research grants. All the main pharmaceutical companies are represented, from Astra Zeneca to Roche and the trend continues through the various sub-committees of the CSM.
21 House of Commons Health Select Committee.
organisations. The Draft Charities Bill offers an opportunity to clarify the regulation relating to funding relationships where it states, “The Home Secretary would be given power to introduce statutory regulation of fundraising if he deems self-regulation to have failed.”

- Mandatory requirement for patients groups to publish a policy (conflict-of-interest) document detailing their approach to relationships with corporate donors.
- Mandatory requirement for patient groups to publish all donors and their donations.
- Codes of practice should be amalgamated and made a compulsory requirement of registered charities. Monitoring of this code should be carried out by an independent body, possibly the Charity Commission.
- Require all groups who support APPGs in the House of Commons to declare their interests.
- Mandatory requirement for pharmaceutical companies to publish a policy document detailing their approach to relationships with patient organisations.
- Mandatory requirement for pharmaceutical companies to publish all donations made and recipients of those donations.
- Reform of the regulatory bodies of pharmaceutical companies to establish them as completely independent of vested interests and strengthen their powers and scope of responsibility to enforce mandatory requirements set out above.
- Increase public funding for independent sources of health information.

Memorandum by Rethink Severe Mental Illness (P1 02)

SUMMARY

Rethink works with people who rely on medicines to help them recover a full and meaningful life from severe mental illness.

Rethink regularly surveys the views of its members and the people who use its services. This submission is based on those views.

Rethink works in partnership with a wide range of organisations, including the pharmaceutical industry. The pharmaceutical industry is not the only potential source of influence on a charity’s work. All forms of fundraising contain inherent potential for influence.

Financial support from the pharmaceutical industry amounts to 0.47% of Rethink’s turnover.

Medicines are part of a holistic approach to treating severe mental illness but do not offer a cure.

Increased efforts are needed to develop new medicines with still fewer and less severe side effects, although the hopes of a medicinal “cure” are very remote.

Public information is essential to encourage and support informed choice.

Rethink’s policy on accepting sponsorship is publicly available.

We believe that a well publicised public route for patients to contact regulators should be created.

It is our recommendation that the regulatory process is opened up to include all the stakeholders affected by its decisions.

Existing methods of evaluating new and existing drug treatments for schizophrenia are generally poor. Improved economic health models offering sophisticated measures of quality of life are needed.

INTRODUCTION

Rethink severe mental illness is a membership-based charity managing nearly 400 services across England and Northern Ireland. We also operate 135 local voluntary support groups. Most of the people who are our members or who use our services are directly affected by severe mental illnesses such as schizophrenia and bi-polar disorder (manic depression) or severe personality disorders. Increasing numbers of people have a “dual-diagnosis” in which a severe mental illness and abuse of street drugs or alcohol present themselves. The majority of the people using our services rely on long-term use of medicines to assist their efforts to recover a full and meaningful life. Rethink severe mental illness was formally known as the National Schizophrenia Fellowship.

We regularly survey the views of our 7,000 members and the 5,000 people who use our services each day. The findings from these surveys are published as short reports. Relevant titles covering areas of interest to the committee are: A Question of Choice, That’s Just Typical, Doesn’t it make you sick?, Right from the Start, Just One Per Cent, Who Cares? and Under Pressure. These publications are available at: www.rethink.org/research or in hard-copy form.
Rethink works in partnership with a wide range of individuals, statutory, voluntary and corporate organisations to provide services, information, advice and support, and to campaign for improvements in the lives of everyone affected by severe mental illness. These partnerships include working with individual pharmaceutical companies and with industry organisations such as the Pharmaceutical Schizophrenia Initiative and the ABPI. We are a member of the Health Coalition Initiative of pharmaceutical companies and voluntary sector organisations that is developing “A Framework Document for Developing Model Agreements or Compacts on Partnerships between Patient Groups and the Pharmaceutical Industry.”

It is important to recognise that, as a voluntary sector organisation, we are reliant on a number of funding sources, including non-pharmaceutical corporate bodies. These non-pharmaceutical corporate bodies also have agendas and reasons for wishing to work with charities that require careful internal scrutiny and external scrutiny.

Other sources of funding include face-to-face street fundraising, which relies on a charity having a high public profile for success, and funds from grant making bodies which may wish to steer a charity’s work in a particular direction.

The scale and scope of our partnership work with the pharmaceutical industry can be measured in financial terms. Rethink’s turnover for 2003–04 was £41.85 million. Rethink’s financial support from the pharmaceutical industry in unrestricted income, restricted income and benefits in kind amounted to £196,950 or 0.47% of turnover. Rethink’s voluntary income (excluding income from contracts to run services) amounted to £2.77 million. Against this measure, total support from the pharmaceutical industry amounted to 7.11% of voluntary income.

The views contained in this submission reflect those contained in our survey reports and are based on the views and experiences of our members, the 5,000 people using our services each day and our 1,400 staff.

**Drug Innovation**

There is no “cure” for severe mental illness. A simplistic biological approach to severe mental illness concentrates on chemical imbalances in the brain, which might lead to an equally simplistic view that a drug or combination of drugs could now or may in the future be used to “rebalance” the brain’s chemistry and “cure” the illness. Rethink, along with the overwhelming majority of the mental health world, rejects this simplistic view.

Severe mental illness is the result of a complex interaction between individual genetic make-up, brain structure and chemistry, individual life experiences and the wider environment, including shifting views throughout history of what constitutes “illness.” As such, medicines can only ever hope to be one part of a holistic approach that assists people to deal with the symptoms of severe mental illness and one part of a generalised approach to recovering a life that is full and meaningful to the individual.

There is a perception amongst the public and many professionals that there are essentially two types of medicine—ones that are safe, clean and effective and ones that have severe side-effects and are ineffective. In fact, all medicines have the potential to cause side effects, often severe, on particular individuals and all are less than 100% effective. We all need a more critical and sceptical approach to medicines.

In broad terms, over the last 50 years, there have only been two “generations” of medicines to deal with schizophrenia and two to deal with the depression and anxiety that are often associated with it. The first generation medicines, while effective in reducing the symptoms of severe mental illness in around 70% of the people using them, are associated with severe and disabling side effects. Second-generation treatments, while being at least as effective, and possibly more effective, in dealing with the symptoms, are associated with fewer and less severe side effects—but they still have a range of side-effects that can, for individuals using them, prove disabling in themselves.

There is no one single medicine or generation of medicines that is universally effective or that has no side effects. The effectiveness of the medicines routinely used in the treatment of severe mental illness is, like the experience of severe mental illness itself, individual. We believe that informed choice is central to maximising the benefits people can expect from medicines—see Information and Promotion below.

Rethink believes that new generations of medicines that are more generally effective, more individually tailored and carry still fewer and less severe side effects are urgently required.

We are encouraged that the pharmaceutical industry is engaged with developing a new generation of medicines and that there is evidence that research into the genome, some of it government supported, may offer novel approaches in the future. However, the investment being made into medicines for the treatment of severe mental illness is wholly inadequate when measured against need and is disproportionately small compared to the investment being made by industry, the government and the voluntary sector into advances into the understanding and treatment of physical illness and disease, such as cancer and cardiac care.
THE CONDUCT OF MEDICAL RESEARCH

Rethink does not conduct or participate in medical research. We do not routinely encourage our members or the people who use our services to participate in medical research. We have, infrequently, carried articles in our membership magazine, Your Voice, about medical research being carried out in institutions such as the Institute of Psychiatry, particularly in relation to the use of brain imaging techniques.

We are in the process of developing our own five-year research strategy. This will establish a research governance structure and a process for involving service users and carers in the development and operation of social research. We do not envisage conducting medical research over the next three years, but intend to be in a position to consider this option at the end of that period.

We have worked with, and will continue to do so in the future, research organisations whose focus is on the life experiences of people with severe mental illness and their carers—social research.

Many of the points we raise in Product Evaluation (below) are relevant here too.

THE PROVISION OF DRUG INFORMATION AND PROMOTION

Rethink has a publicly available sponsorship policy (Appendix A) that is also available at: www.rethink.org/news+campaigns/policies. The sponsorship policy begins: “The acceptance and continuation of any sponsorship by Rethink is conditional upon Rethink being satisfied that its name will not be used to promote the efficacy of a particular product, service or event.”

Rethink does not promote any single medicine or class of medicine. We do not believe that medicines by themselves are sufficient for an individual to recover a full and meaningful life. Medicines, as part of a holistic package that address an individual’s full set of needs, including accommodation, occupation, finances, family and social inclusion, plays an important role for most people with severe mental illness. We believe in the promotion of informed choice.

To this end, we produce information for service users, carers and professionals about the range of medicines available. We retain full editorial control of that information. The information is available in a range of formats, including specific medicine information leaflets, pamphlets, packs and books. Some of these are provided free and some require payment. Most are available free on our website—www.rethink.org.

In addition, we run a range of seminars, briefings, members’ days and conferences each year in which we promote the concept of informed choice. We also speak at conferences and events organised by others, including academic institutions, commercial organisations and the pharmaceutical industry, for which payment to us is sometimes, but not always, made.

Our most widely distributed publication in this field is Only the Best. The first edition, in a loose-leaf folder format, sold out of its 40,000 print run. A second updated edition in a book format has just been published.

We accept clearly acknowledged financial support for some of these publications when such support is in line with our Sponsorship policy (Appendix A).

It is our view that the publication of unbiased information for service users and carers is essential if the concept of informed choice is to become a reality. It is our view that an open and transparent approach in which Rethink retains editorial control and all financial support is clearly acknowledged allows us to produce unbiased information that can be trusted by our members, service users, carers and professionals.

It is our view that these principles of openness, transparency and editorial independence should underpin the relationship between the pharmaceutical industry and those parts of the voluntary sector that choose to engage with it.

PROFESSIONAL AND PATIENT EDUCATION

Mental health is blighted by stigma and discrimination. Professional and patient education plays an important part in combating this, promoting informed choice and enabling service users and carers to become more assertive. Our developing research strategy includes programmes part funded by the pharmaceutical industry to raise awareness of mental health issues and to combat stigma and discrimination amongst specific groups—schoolchildren, police officers and trainee psychiatrists, to date. Again, financial support is acknowledged and Rethink retains full control over the research including its findings and dissemination of those findings.

We also believe that it is important to raise public awareness and counter existing stereotypes that falsely link severe mental illness and violence. Through our media and campaigns volunteer programme, we offer training and support to service users, carers and staff who wish to speak to the media about their experiences or who want to participate in broader Rethink campaigns. The media and campaigns volunteer programme is part-funded by the pharmaceutical industry. Decisions on whether to take part in media interviews or campaign activities are taken by individual members of the scheme, with the support of specialist Rethink
staff. Financial support for the scheme does not give the sponsor any right to call on staff, service users or carers to participate in a sponsor’s activities. Decisions on whether to take part in this type of activity are taken by individual members of the scheme and with the support of specialist Rethink staff.

Rethink has been experimenting for the last three years with a national “awareness week” which aims to challenge misconceptions about severe mental illness, raise awareness of the organisation and create fundraising opportunities among members of the public. To date, these “awareness weeks” have been funded from general fundraising activity, but we would consider sponsorship of the week where it was in line with our Sponsorship policy.

**REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY**

It is our view that much of the media furore surrounding the activities of the pharmaceutical industry stems from a failure in the regulatory process.

We are concerned that regulators do not, as a matter of course, involve service users and carers and the voluntary sector. Medicines regulation is, perhaps, the last corner of the health world in which the voluntary sector, “patients” and carers fail to find a welcome and a recognition of their value as “experts by experience.”

We believe that regulatory bodies have failed to create open and accessible channels to receive information from “experts by experience.” In particular, the “yellow card” warning scheme has been wholly reliant on professional interpretations of patient experience before concerns are even allowed to reach regulators. We believe that a well publicised public route to regulators should be created.

Commercial confidentiality is too widely used to prevent regulators accessing all the data—published and unpublished—needed to come to reliable decisions on the efficacy and safety of medicines. Academic journals also appear reluctant to publish the results of trials which show that a particular medicine does not work.

Regulatory reliance on industry bodies and their own experts has created a closed system in which the necessary checks and balances that could be provided by the full involvement of service users (“patients”), carers and others is absent.

Although we have separate concerns about some aspects of the work of the National Institute for Clinical Excellence, particularly in relation to the implementation of its guidance and guidelines, it does have a comprehensive and inclusive process that allows stakeholders to participate fully in its deliberations.

It is our recommendation that the regulatory process is opened up to include all the stakeholders affected by its decisions.

**PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY**

When participating in the National Institute for Clinical Excellence’s review of atypical treatments for schizophrenia, it became clear that existing methods of evaluating new and existing drug treatments for schizophrenia are generally poor. Our general criticisms of large numbers of trials revolve around:

- Small numbers of participants.
- Short length of trials.
- High drop out rates.
- Unrepresentative choice of comparator drugs.
- Funding arrangements.
- Lack of transparency of data produced and published.
- Lack of rigorous and critical reading of the data by regulators.

We are aware that the National Institute for Clinical Excellence and other agencies rely heavily on so-called “gold star” randomised control trials (RCTs). It is our experience that RCTs can remove the human experience from the evaluation process. Qualitative evidence, even large amounts of it, can be disregarded. RCTs do not by themselves answer our general criticisms of drug trials above. Indeed, some RCTs score highly on each point of our general criticisms. Our evidence to the NICE review concentrated on the qualitative human experience of using the new (atypical) and old (typical) medicines for the treatment of schizophrenia. It is these human experiences that led us to recommend to NICE not only the ending of postcode prescribing of the new treatments but informed choice for service users in the medicines taken.

The issue of “value for money” is badly drawn in mental health, where individual life expectancy for people with severe mental illness is 10 years below average, unemployment rates exceed 80% and 12% of the NHS budget is spent in this area. Whether an individual medicine or class of medicines can be said to provide “value for money” should depend less on the concept of an individual reducing demand on NHS services or becoming a tax-payer than on incremental improvements in that individual’s quality of life, their degree of social inclusion and their acceptance by and participation in their community.
Economic models within health that allow for sophisticated value for money measures of improved quality of life are poorly developed. The model of chronic disease management enables some measure of reduced costs to services while the model chosen by NICE in its appraisal of atypical treatments for schizophrenia found overall cost savings, despite higher prescription costs of the new drugs.

Rethink believes that more sophisticated economic models need to be developed to measure incremental quality of life improvements amongst people with long-term medical conditions.

**APPENDIX A**

**RETHINK POLICY STATEMENT 21**

_Sponsorship_

The acceptance and continuation of any sponsorship by Rethink is conditional upon Rethink being satisfied that its name will not be used to promote the efficacy of a particular product, service or event.

**CONDITIONS FOR ACCEPTING SPONSORSHIP**

1. The source of sponsorship of any Rethink project, group or event must be clearly identified and described, eg “this booklet has been produced with the support of [name of organisation], this event has been subsidised through funding received from [name of organisation].”

2. The terms of sponsorship must not influence any Rethink policy or service or the content or distribution of any Rethink publication, including any audio-visual material; Rethink has total editorial control. Also, the terms of sponsorship must not unduly influence any Rethink event.

3. A product or service associated with a sponsor must not be promoted by Rethink staff or members, though they may publicise the relationship between the sponsor and Rethink.

4. Rethink projects, groups, events, publications or audio visual material must not be sponsored by a person or organisation whose business consists wholly or mainly in the manufacture or supply, or in the provision of a service, which does not meet with the approval of the Board of Trustees.

5. Opinions must not be given on the efficacy of a particular drug in medication fact sheets sponsored by a pharmaceutical company.

6. The person or organisation providing information must always be stated in medication fact sheets.

7. All requests for sponsorship should first be considered by the Rethink Fundraising Department to check the suitability of the company as a sponsor.

8. Care must be taken to identify whether proposed sponsorship income is taxable.

**ACTION**

Rethink will continue to seek sponsorship, subject to the conditions above. It will not accept sponsorship if those conditions are not met. Rethink will withdraw from sponsorship if those conditions are not met by sponsors at any stage in a partnership with them.

**QUESTIONS AND ANSWERS**

_Q. Doesn’t the acceptance of sponsorship from a pharmaceutical company imply the endorsement of the company’s products by Rethink?_

_A. No. The aim of many pharmaceutical companies is to support activities associated with mental illness rather than to narrowly promote their products. Rethink welcomes this as a valuable source of funding for its work, including:_

- making available detailed fact-sheets explaining aspects of mental health care and treatment and particular medications;
- subsidising the cost of conferences and training events of value to both Rethink members and staff;
- supporting local services provided by Rethink.
Q. How important is it for Rethink to have a good working relationship with pharmaceutical companies?

A. It is important both to attract sponsorship money and because it is in our best interests to work well with pharmaceutical companies for the benefit of everyone concerned.

**BACKGROUND**

1. A Rethink publication, project or service is deemed to be sponsored if any of its costs are met by an organisation or person other than Rethink, with a view to promoting its own commercial interests or activities. The term “publication” includes audio-visual items as well as written material.

2. Rethink has accepted sponsorship of publications, events, and local projects for many years, including sponsorship by pharmaceutical companies on the understanding that:
   - Rethink does not promote particular products of any company;
   - the company accepts Rethink’s sponsorship policy;
   - the total amount of funds received for sponsorship is less than 1% of Rethink’s annual turnover.

3. Sponsorship income received without any services being provided in return will normally be treated as a donation and outside the scope of both Corporation Tax and VAT. The following services provided by a charity to a sponsor would, however, be considered in determining whether sponsorship income is taxable:
   - the use of its mailing list;
   - the use of its logo;
   - the exclusive rights of the sponsor to sell their goods or services on its premises.

Acknowledgement of a sponsor’s support in a charity publication would not be regarded as trading income.

**Witnesses:** Ms Melinda Letts, Chair, Committee on Safety of Medicines Working Group on Patient Information and Past Chair, Long-Term Medical Conditions Alliance, **Paul Flynn**, a Member of the House, Chairman, Commons All-Party Group on Rheumatoid Arthritis, **Mr Phil Woolas** a Member of the House, Trustee, Beat the Benzos Campaign, and **Mr Cliff Prior**, Chief Executive Rethink Severe Mental Illness, examined.

Q316 Chairman: Can I welcome our witnesses to this morning’s first session and thank you all for your helpful written evidence; we are most grateful to you. Could I ask each of the witnesses briefly to introduce themselves to the committee, starting with Ms Letts?

Ms Letts: My name is Melinda Letts. I am an independent consultant working with charities and other health organisations. Until May of this year I chaired the Long-Term Medical Conditions Alliance and among a number of other things I am now a Director of Ask About Medicines Week and Chair of the Committee on Safety of Medicines Patient Information Working Group.

Mr Woolas: I am Mr Phil Woolas. I am Member of Parliament for the Oldham East and Saddleworth constituency and a representative as a trustee of the Beat the Benzos Campaign, which is a support group for involuntary addicts on benzodiazepine drugs.

Paul Flynn: I am Paul Flynn, Member of Parliament for Newport West, a long term critic of the pharmaceutical industry, especially their disease-mongering and over-prescription and the medicalisation of society.

Mr Prior: I am Cliff Prior. I am Chief Executive of Rethink, which is a charity for people affected by severe mental illness. I am also Vice Chair of the Long-Term Medical Conditions Alliance and a member of the Medicines Commission.

Chairman: Thank you. We have one declaration of interest from Mr Austin.

John Austin: I just wish to declare that I chair the All-Party Parliamentary Osteoporosis Group which receives administrative and secretarial support from the National Osteoporosis Society, which is mentioned in Mr Flynn’s evidence as receiving some financial assistance from the pharmaceutical industry.

Q317 Chairman: We are splitting this morning’s session into two, as you well know, and it will be roughly an hour for each group, so could I ask for the questions and answers to be brief and sharp. Mr Flynn, could I start with you? How did you get into this whole area? Am I right in thinking that it was through constituency concerns?

Paul Flynn: Yes, it was; it was entirely through constituency concerns. The first one was when a constituent committed suicide using the drug Roaccutane and I was shocked to discover that there was no organisation for the defence of people in this circumstance and the patient organisation that one would have thought would have represented people was one that had a very large donation from the manufacturers of Roaccutane because there was a widespread belief that those on this drug were more prone to commit suicide. Over the years I have come across in my constituency work a whole range of instances where those that one would have thought would have had a very large donation from the manufacturers of Roaccutane because there was a widespread belief that those on this drug were more prone to commit suicide. Over the years I have learned over the years that it is impossible to over-estimate the greed, the guile and the resourcefulness of the pharmaceutical industry.
products, I am afraid, is very much out of self-interest in order to maximise their profits and I believe that these organisations that we look towards to defend the patients are ones that have been influenced—not corrupted; many of them are magnificent organisations—and we do notice that those that have the largest donations are often the ones that have the quietest voices when it comes to exposing the side effects of pharmaceutical drugs.

Q318 Chairman: You specifically say in your submission that some patient organisations may refrain from criticism of pharmaceutical companies because those companies fund the organisations. You give an example of a concern on page 4 of your evidence where you talk about a particular product, where you suggest that information from clinical trials is being suppressed and, “A courageous leading campaign has been pursued by MIND who receives no contributions from any pharmaceutical company. There has been silence from SANE and Depression Alliance who accept donations”. This is fairly strong criticism. Can you expand on this?

Paul Flynn: I was present at the formation of an All-Party Group on Depression of which the Depression Alliance were the main sponsors. Again, they are an organisation that certainly do very good work but it has been significant during the past year, and I have had two debates on Seroxat in that period, where this international scandal on the damage that is done by Seroxat, involving the suppression of files, an immense scandal involving millions of people, was not exposed by the Depression Alliance or the other patient organisations. Depression Alliance did confess to taking, in meetings we had with them, 80% of their funding from the pharmaceutical industry. They were silent when this matter was being exposed by organisations like MIND who take not a penny and a very courageous stand was made by Richard Brook of MIND. The heroes of the exposure of this scandal were not the MHRA or those bodies that should be defending the patients. It was very much the campaigning patient organisations and I think very recently, when Viox was exposed as being a very dangerous drug, I went on to the Arthritis Care website, again, an organisation that is doing a magnificent job, and it was significant that they were advising people to continue taking Viox even though it has been exposed as a drug that has probably killed by a minimum estimate 7,000 people and caused 25,000 heart attacks. Arthritis Care was suggesting that people continue to take the drug and then see their doctors and probably go on to another drug. It is not insignificant that the website is financed by Merck Sharp and Dohme, manufacturers of Viox itself. The charities and the patient organisations will say they are not influenced unduly by this but why on earth then are they taking the drawings because we certainly know that the ABPI have said that they regard the patients’ associations as the ground troops. They had a battle plan in which they wanted to employ ground troops in the form of patient support groups in order to weaken the political, ideological and professional defences. That is a declared policy of the pharmaceutical industry, to use patient organisations to subvert us. I will make one final point. In Paris last week the WHO were challenged on their view that depression will become the third greatest cause of ill health in the world by 2020 and they were challenged on whether they were being unusually influenced by the pharmaceutical industry. The defence of the World Health Organisation was, “Yes, we are suspicious of the pharmaceutical industry but we do listen to charities and patient organisations”. I believe that for all of us, politicians, the public, our defences go up when we have advertisements and persuasion from the drug companies but we are open to persuasion by organisations like the patient organisations we trust. I believe we see it within this House when some of our All-Party Groups have been used as Trojan horses to bring the voice of the pharmaceutical industry into this House and to use it generally throughout the whole of the medical establishment.

Q319 Chairman: One of the questions I asked at the start of this inquiry internal to our committee was to look at the number of All-Party Groups that do have a connection with the industry. Do you have any specific examples of policies being influenced by All-Party Groups in the interests of the industry?

Paul Flynn: I sit on many of these All-Party Groups in order to watch the activities that go on. I was rather alarmed to receive a document from an organisation called Phase IV recently which tried to recruit me in order to subvert, in my view, the All-Party Group on Rheumatoid Arthritis in order to find what they described as success stories and tragedy stories in order to promote the use of the anti-TNF drugs. These are drugs that have been approved by NICE but have certain side effects that NICE warned of. This was an attempt by a body, which is a PR agency, to use the group in that way. I believe that every time we have invitations to All-Party Groups the invitations are littered, rather like the clothes that are worn by racing drivers, with advertisements for the companies. They are not doing this out of some charitable reason or for the benefit of the patients. They are doing it to advance their position in this way. The damaging effect is not that we can say in this case or that case that they have actually worked in a way that was obviously promoting the drug, but their main effect is to silence the organisations when they should be critical. I believe the evidence is that the regulatory authorities are ones of self-regulation that are not working, that are weak and we are seeing, in the case of many of these organisations that exist, a lack of the alertness and the desire to defend the patient interest against a whole host of examples we have had of drugs over the years from Thalidomide, Destobel, Arafoline, now to Viox and a whole stream of others. My lifetime experience of the pharmaceutical industry is that about 50% of all medicinal drugs have harmful side effects and the other 50% have side effects that we have yet to discover. It has been a history of experimentation on a large scale between patients and drugs and, sadly, the results on the harm of the drugs were only revealed in many cases when they...
had been used by millions of people. We do not have bodies that defend patients’ interests in the way that they should.

**Q320 Chairman:** Mr Prior, a lot of the pharmaceutical companies make donations to charities. Would it not be a more appropriate way of patient organisations receiving income to get it from those charities rather than directly from the companies?

**Mr Prior:** I think a balanced range of funding would be highly desirable. At Rethink we are in a much stronger position in that we have over £40 million a year in alternative sources of income, which makes us very robust against any influence from pharmaceutical companies who provide less than 1% of our income. Many patient organisations struggle to survive. They do not have alternative sources of income.

**Q321 Chairman:** If it is less than 1%, in view of the suggestions from Mr Flynn that you are possibly compromised as a consequence of receiving that money, why, with it being only such a small amount, do you continue to receive it?

**Mr Prior:** I think all sources of funding bring strengths. I know it has been suggested in previous sessions before this committee that government funding, for example, should replace pharmaceutical funding of patient organisations, but I am afraid that anybody who thinks that government funding comes without strings or without influence is being exceedingly naïve. All sources of funding bring their biases. Even raising funds direct from the public brings a bias. It is much easier to raise funds for attractive conditions, if you like, cuddly conditions, rather than for difficult and edgy causes, like severe mental illness, our own area, and in addition, to raise funds from the public you have to stay in the public eye. If you stay in the public eye you are more tempted to make controversial statements. All sources of funding bring bias. What is important here is to know that patient organisations are, as in our own case, genuinely controlled by the people they are there to represent. We have a shareholding membership made up of people living with the conditions we are about and their passion and energy would not allow us to tell anything other than their experience in our campaigns. Secondly, patient organisations should have a balanced range of funding which is fully declared, not just a declaration of money that comes from the pharmaceutical industry; that is important, but also a declaration of what other sources of funding they have, government funding and so on. It would be wonderful if charitable trusts were prepared to put more funds specifically into allowing patient organisations to survey the experiences of the people they represent and campaign on that basis. However, even then most charitable trusts have their own agenda. They set their own criteria. Again, that can distort the message that is heard from patient organisations. Balance and transparency and accountability are what are important here.

**Q322 Chairman:** Ms Letts, do you have any comments on Mr Flynn’s opening remarks?

**Ms Letts:** I would not disagree with anything that Cliff Prior has just said. What I would like to add is that I think that all patient organisations should have guidelines for all the funding that they accept and particularly guidelines that they have with pharmaceutical companies. These should include an absolute insistence on independent governance, on editorial control, on independent decision-making and so on, and an absolute ban on promoting any company’s products, whatever those products are. I have written these policies myself for a National Asthma Campaign in the past and LMCA and most recently for Ask About Medicines Week. I would like to supplement what Cliff Prior said about patient organisations struggling to survive. It is one thing if you are running an organisation such as I did with asthma where you are running a national charity dealing with an emotive issue where it is easy to make your case and get your funding, even though public fundraising, as Cliff has suggested, does drive you sometimes into doing things or emphasising things that perhaps you would not want to emphasise. However, if you run a small support group for a rare condition affecting a small number of people, none of whom is particularly cute or cuddly then it is difficult, or, as in my most recent experience, if you are leading an umbrella body whose interaction is at policy level, not directly at patient level, it is very difficult, and finding core funding for organisations like these is a constant and exhausting struggle. Government does stubbornly refuse to understand this. Government funding tends to come either with explicit or implicit strings attached, or it tends to be in the form of project funding which is no use at all if you have not got an infrastructure to support the projects. I think that what we need to see is much clearer standards to establish the bona fides of a patient organisation. The patient organisation that I chaired until recently, the Long-Term Medical Conditions Alliance, discussed this quite frequently but, ironically, we never had the core funding available to get the infrastructure that we needed built up in order to introduce such a system. We need to introduce these standards to establish the bona fides of patient organisations. What I would add to what Cliff has said about the need for balance in funding is that indeed you are influenced from all sides when you accept funding and what is absolutely essential—and this is very difficult again for a lot of small organisations who have not got the staff or the infrastructure—is to be very clear about your objectives, your policies, your strategies and the things on which you will not compromise. One of the things on which you have to be absolutely clear is that you will declare all sources of funding. I have been on the receiving end on one occasion of an attempt by a company to persuade me not to declare in an annual report some funding that we had received. I think you have to have the courage to stand up to that kind of pressure.

**Q323 Chairman:** The company did not want you to declare money that they had given?
Ms Letts: They had not given it. They had paid for something that we had carried out so, because they had not given it directly to us, it had not gone through our books, the suggestion was that it should not be declared and I insisted that it must be declared.

Q324 Chairman: Do you want to mention the company?
Ms Letts: Yes. It was Glaxo Wellcome.

Q325 John Austin: If I could stay with Ms Letts, nothing in my questioning should be taken as implying any criticism of your integrity. We know that you have always argued for a relationship with the pharmaceutical industry and that it should be restrained by a code of practice. During your period with the Long-Term Medical Conditions Alliance and, as you say, you have always been open in your declarations, you were working for or did undertake some consultancy work for a number of organisations, including one of the companies which was involved in the drug launches of Viagra and Celebrex. We now understand that Celebrex is one of those—
Ms Letts: Sorry—which company was that?

Q326 John Austin: With the Chandler Chicco agency.
Ms Letts: Ah, Chandler Chicco, yes.

Q327 Chairman: Who were working for the pharmaceutical industry and involved in the drug launch of Celebrex, about which I think there are considerable safety concerns and questions at the moment. In that capacity did possible conflicts of interest ever occur and, if so, how did you handle them?
Ms Letts: I had no idea that Chandler Chicco was even involved with that drug. In fact, I have ever heard of that drug, Celebrex, that you mentioned. They commissioned me to write a report on something which I was happy to write a report on for them. They are a communications consultancy and I had absolutely no involvement in any of their direct work with any of those drugs that you mentioned. I simply wrote a report for them. It was a research report that I put together for them on the current European situation and current European campaigning about direct-to-consumer communications, and I put both sides of the story very clearly in that report. No, I do not think there is any possible conflict of interest that I can think of there.

Q328 John Austin: You mentioned the GSK incident to the chair. Have there been other occasions when pharmaceutical companies have tried to influence you in some way?
Ms Letts: When you are running a patient organisation this word “influence” bears a little bit of examination. Of course, another word for “campaigning” is “influencing”, and we are all involved in influencing. That is what you do when you meet with people, so of course any company that one is dealing with wants one to understand their point of view. I have been sometimes what could be called a bit bloody-minded in resisting it. Anyone who tries to influence me will probably get a counter-productive reaction from me. I am not very susceptible to that kind of approach. The important thing is that what you have to have in your mind is who is it you are there for, who it is you are working for. What I always ask myself is, what is going to be in the best interests of the patients whom I am ultimately here to speak or work for? I believe, as I think you have alluded to already, that the best interests of the patients who I have always worked for, those people with long term conditions, are served by maintaining a dialogue with pharmaceutical companies because those companies make products on which in many cases people depend, sometimes on a day-to-day basis and sometimes periodically but they make those products and it is important to remain in contact with them. That is what I believe. I do not believe that it means you have to adopt lock, stock and barrel the agenda of the pharmaceutical company. You have to go into such relationships knowing full well that they have a commercial imperative, and that is what one would expect in the world that we live in. If you are clear about who you are there for and, as I said, what your non-negotiables are, then I think you can conduct a fairly robust dialogue. I am certainly aware, in the time I have been doing this, because I have both seen and been given explicit feedback, of having influenced companies themselves and persuaded them that it is not a very good idea to try to capture a patient organisation, for example.

Q329 John Austin: The difficulties for some organisations have been explained. Some organisations are more cuddly than others and more easy to raise funds for. Some conditions it is more difficult to raise funds for. If there were no funding from the pharmaceutical industry what sort of impact do you think that might have on the patient’s voice generally?
Mr Prior: Some would really struggle. Some patient organisations would close altogether and then support would not be available to people living with those conditions. For some, like us, there would be a bit of a hit but it would not be anything tremendously significant, so there would be a range of different effects. Then organisations would be more open to influence from other directions. If I can give you an example of this, our main interest is with people affected by psychoses and over the last five or 10 years there has been a major debate about two different classes of anti-psychotic medication—an old class which was cheaper and a new class which was more expensive—and obviously the pharmaceutical companies wanted to sell the new class and there was very clear direct evidence from surveys that we conducted of NHS agencies that government agencies wanted to control the prescribing of these because they were more expensive and cost was a major factor restricting prescription. The way we tackled that was by going
out to people who were taking medications on a very large scale and surveying them about their experiences and the benefits and disbenefits that they found. We produced a report which was presented to NICE and actually was the line that NICE very much followed, which was not to say, “New drugs good, old drugs bad”. It was to say, “They have both got benefits and side effects. The range of side effects is different. People need an informed choice in order to arrive at the best treatment for them”. That was possible only through the most intense job of trying to raise absolutely neutral funds. We could not touch government funds because they were biased against spending more money. We could not touch pharmaceutical funds because obviously they would be biased in favour of selling more of the new drugs.

We found there were almost no sources of funding to support that sort of neutral inquiry into the experiences of patients. We were very fortunate to find two trusts, King’s Fund and the Gulbenkian Foundation, which were prepared to support it, but even then it came with strings. I think the strings were right. The King’s Fund’s condition was that a full data set of the survey must be published on our website, and good on them for insisting on that. That is the sort of influence I like, but it is incredibly difficult and simply removing pharmaceutical funding would damage patient organisations and the work that they do. Replacing it with government funding would create disproportionate influence from one party. We need a more balanced approach. We need to see more charitable trusts contributing to this field, but we also, as patient organisations become more influential, need to defend their position—and I think this is in our own interests—by introducing standards. Governments or regulatory agencies should fund these developments under umbrella bodies for patient organisations. Patient organisations would then be expected to adhere to publication of interests, accountability, showing how they are controlled, how they get the views of their beneficiaries, before their evidence is taken seriously by bodies like NICE or the CSM, or indeed by the media who are all too prone to report the controversial comment rather than the one that is well-founded in evidence from large numbers of people with that condition.

Paul Flynn: We already have the umbrella body, of course. The problem with it is that it cannot enforce its recommendations. There is no way of monitoring what is going on and it is described as being a distant dream, the possibility that it can impose any sanctions. The evidence is that only 26% of the UK groups that were surveyed recently had any kind of conflict of interest statement on this. There is no disagreement with the Long-Term Medical Conditions Alliance’s guidelines and aims. There is also a problem with the Charity Commission because the suggestion that they have absolute control is another fallacy. In a letter to me they said that under the Charity Accounting Regulations there is no general requirement for charities to disclose the sources of their donations and the kind of control they have is very weak, as I mentioned in my written statement. We do need some kind of tightening up on this. They said that the requirements to provide information on the source of donations are less stringent than those relating to the expenditure of a charity. There is a great dispute about those charities and patient organisations saying they have no choice but to accept money that is given to them and those who very successfully resisted money that they thought was tainted because it was intended to influence their policies.

Paul Flynn: I believe that if we did see withdrawal of all the funding, it would liberate the patients’ organisations, give them a new respectability and credibility, and would certainly help those who have properly resisted all funding from pharmaceutical companies over the years and have led the campaigns to expose the dangers of pharmaceutical drugs and the benefits of pharmaceutical drugs.

Q330 Chairman: Mr Woolas, could you say a bit about how you became involved? Obviously you are here as a constituency MP and not as a minister. Can you say a little about what has happened in your constituency that made you become involved in this whole area?

Mr Woolas: Thank you for the opportunity to do so. It might be helpful to you and your Committee if I referred you to the Westminster Hall debate of 7 December 1999, column 186, in which I outlined the case of the benzodiazepine campaign. Essentially, my constituency has an estimated 5,000 involuntary addicts to benzodiazepine drugs; that is an estimate from our primary care trust.
Q331 Chairman: Is there some specific reason why that is such a high figure, or would you say that is not uncommon elsewhere?

Mr Woolas: It is not uncommon elsewhere. There are particular reasons to do with the area of Greater Manchester in which my constituency falls, but it is not an uncommon figure. What is perhaps special about my area is that there is a very well-developed support group for the involuntary addicts of benzodiazepine drugs, and that support group has indeed grown up, over the last five years, into what is now a nationwide support group. We have the first primary care trust funded treatment service for withdrawal from benzodiazepine addiction, but we are dependent, as a national organisation, on voluntary funding from individuals. In particular, our efforts to bring legal cases have been hampered by the lack of legal aid, the lack of funding for advocacy, and of course the enormous resources of the particular companies that have provided benzodiazepines over the last 30 years.

Q332 Chairman: Can I ask you specifically: to what extent do you believe that the drug manufacturers were responsible for the current levels of use and the dependence on benzos?

Mr Woolas: That goes to the nub of the problem. I have referred the Committee to two submissions of written evidence to this inquiry: first, from my constituent, Mr Barry Haslam, who has submitted his evidence to you; and, secondly, from a constituent of Clive Soley, Mr Michael Behan. In addition, those two documents provide the historical record of how Wyeth Brothers and Roche in particular we believe in our campaign withheld information showing that the addictive levels of these drugs were much higher than the prescription guidelines stated. Indeed, as you will know, Mr Chairman, I wrote to you on 13 October of this year suggesting that a number of documents that we have become aware of in our research for legal action in this country and in other countries would show, in my view beyond doubt, that that deliberate withholding of the information was intentional.

Q333 Chairman: You feel the Committee could help you in this respect?

Mr Woolas: I think the Committee could be an enormous help if the documents referred to in the memorandum from Mr Behan were requested by this Committee because I believe that would show evidence existed that the addictive effects of these drugs were much greater than was known to the regulatory authorities in this country, and therefore of course to patients. In particular, I believe the statements issued by ex-medical directors of Wyeth—Dr Dipak Malhotra and Thomas Harrv who were responsible for the development of Ativan—show what I am saying is the case.

Q334 Chairman: Can you say a bit more about the initiative by the PCT in terms of helping people with this problem in your area? Has this been funded entirely by the local PCT or has there been some help from national government?

Mr Woolas: The situation is that our campaign does not advocate immediate withdrawal from benzodiazepines. We believe that would be very dangerous. Our campaign is to have the prescription guidelines enforced. Unfortunately, they are not being enforced. There are some 20 million repeat prescriptions in this country. Therefore, availability of facilities for withdrawal treatment from these drugs is extremely important. I would point out that in the evidence that has been presented, the Home Office statistics, the number of deaths by poisoning from benzodiazepine involuntary addiction in this country is 1,800. This is some nine times greater than the number of deaths from heroin misuse. The funding for the withdrawal treatment is exclusively from our primary care trust. The difficulty we have is, of course, that the withdrawal treatment is not a central part of the national drug withdrawal strategy, and nor therefore is it one of the five priorities given to primary care trusts by national policy. In other words, it is a local decision by the board of our PCT to commission a service in conjunction with the North-West.

Q335 Chairman: It is locally funded, basically?

Mr Woolas: It is therefore locally funded but it is government funded, of course.

Q336 Chairman: Barry Haslam, in his evidence on page 6, makes a number of recommendations for action. Mr Haslam has fought hard on this over many years. He writes to me at least once every week and, to his credit, he has worked very hard. I will not go into one of his recommendations, and you will not want that either, which is to sack the Health Minister Rosie Winterton and her special advisers forthwith and appoint Phil Woolas MP in her place. You probably do not want to comment on that and I will not ask you to do so. His first recommendation is that there should be an independent and full public inquiry to be ordered by the Government as a matter of urgency into benzodiazepine, SSRIs and “Z” drugs. Is that something that you personally would support and, if so, how do you feel that might address some of the issues you have raised with the Committee?

Mr Woolas: I support that and it is something that the Government of the Republic of Ireland has undertaken with significant success. There are two reasons for this. One is that to address this issue requires cross-departmental policy co-ordination. Our campaign in particular has lobbied the Home Office on the scheduling of the drugs, that is the rules that pertain to the storage of drugs, because there is a street trade in temazepam in particular. Obviously, that involves the Health Department, the ODPM and a number of government departments in having that policy, which is needed to enforce the prescription guidelines, to give confidence to doctors and patients in the independence of the regulatory authorities, and to provide the treatment that the addicts require. Incidentally, for example, the prison service in its guidelines does recommend this for prisoners, but not for the general public.
Q337 Dr Naysmith: I have been asking questions about the use of benzodiazepine and SSRIs for the last few years. It looks, quite clearly, as if benzodiazepine use is dropping and being replaced by SSR1 use. Is that something on which you have any views?

Mr Woolas: I do not believe that to be true. The number of benzodiazepine prescriptions has dropped slightly, but it runs into tens of millions. There is a fallacy in the Western world that the benzodiazepine problem was addressed in the 1980s, particularly by the high profile campaigns, the That's Life programme and other legal actions. In fact, the prescription guidelines have not been enforced for the past 20 or 30 years. What has happened is that the media, understandably, have paid attention to SSRIs, and Seroxat in particular. Personally, I am supportive of the campaign of Paul Flynn and others but that has not replaced the problem of benzodiazepines; it has supplemented it and, in my view, made it worse.

Paul Flynn: It is alarming that the level of prescriptions of SSRIs has now reached 25 million, which is approaching the peak levels for benzodiazepines. It is so depressing to look at the answers for treating depression, including mild depression, over the past 150 years. The miracle drug for Sigmund Freud, of course, was cocaine, which he used himself and recommended for his patients. Heroin was then introduced as an answer to opium addiction. Then the bromides were introduced; again, those did enormous damage at the time of the First World War. We have gone through a succession of drugs and now the benzodiazepines, the tricycles and the SSRIs have all been introduced as non-addictive drugs with great utility that will be very successful in treating depression and in treating addiction. In fact, all of them have been used as the answers, the cures, to problems that they themselves have created. This is an uncanny repetition of the same mistake being made by the medical establishment over a period of 150 years of introducing cures that turn out to be curses and problems. We now know the difficulties with the SSRIs, which were introduced because they did not have the effects of the tricycles. Those are now being exposed. The awful part of this, and this comes from someone who like most of us has had scientific training, is that we always believed in the integrity of scientific trials but we realise, to our horror, that the scientific trials have been fixed; they have been suppressed; data has been found, as in the Lancet report of April of this year, that the conclusions of the trials were different from the data. We know that organisations as eminent as the MHRA rely not on the data of the trials but only on the conclusions. I believe that a great confidence trick has been perpetrated on the world by the pharmaceutical industry which has behaved in a disgraceful way. I hope the case that is going on in America now about the trials of SSRIs will bring the pharmaceutical industry back to a position where they behave with honour and integrity. There is certainly a wealth of evidence that they are not doing that now.

Q338 Dr Taylor: I do apologise. Mr Austin's declaration of interest means that I have to make one as well. I am one of the Vice Chairs of the Associate Parliamentary Health Group, which is funded by a wide range of industries. This is still dealing with benzodiazepines. I am horrified to hear from Mr Woolas that they are still prescribed in millions. Short-term injections of benzodiazepines are still used for surgical procedures and to enhance local anaesthetics. Are they still prescribed in millions as tablets to patients?

Mr Woolas: Yes, they are. The estimate of the mental health charity MIND is that 1.2 million people in the United Kingdom are affected by addiction to benzodiazepines, including Valium, Ativan and lorazepam.

Q339 Dr Taylor: So these millions of prescriptions are all for the people who are already addicted?

Mr Woolas: That is exactly the point. The difficulty is that because the drugs are so addictive, particularly Ativan, and because the prescription guidelines were not toughened until 1988, some 25 years after the introduction of the drugs, and because even today the prescription guidelines, which essentially limit a prescription to three weeks, are not enforced and because the difficulties of withdrawal from the drug make the problem worse in many cases, the easy solution is for the doctors to carry on prescribing and for the patients to keep taking them. That results in over 20 million repeat prescriptions and over 1.2 million addicts in the country, many of whom are elderly people living in residential and nursing care, but by no means exclusively.

Q340 Dr Taylor: I do want to focus a little more on the fault of the medical profession. I remember that when the first worries about the addictive properties of these came out, I hoped many of us actually stopped prescribing them, but they were prescribed for a long time after the first worries were made known. Should we not be investigating the conduct of the medical profession in going on prescribing after the first hints of trouble were known?

Mr Woolas: Yes, very much so.

Q341 Dr Taylor: I will move on to regulation. Many of you have already said that the charities need strict regulation. Just one point to Mr Flynn: in the table of the charities that are in receipt of funding, in your paper, I think it is fairly significant that those that do not receive funding, apart from MIND, are probably the ones that the pharmaceutical industry would not be able to make any money out of in any case?

Paul Flynn: I think that is probably true.

Q342 Dr Taylor: So it is not that they are declining it because they are very well-minded and good-hearted charities; it is probably because they cannot get it?

Paul Flynn: No, that is not true of MIND, for instance, and YoungMinds as well, another splendid organisation. I believe there are some charities that look like a public relations group for a drug, and I
think we are very suspicious of them. I am not inclined to go into too much detail on this but there are so many of the charities that appear whose only purpose seems to be pushing drugs and emphasising the advantages of drugs. There was an example with a group called In Vivo Communications where they had, as part of disease mongering, a whole group set up to popularise or to identify irritable bowel syndrome as a specific concrete disease. There was a drug available, which has now been withdrawn because it had fatal side-effects, but there was a whole campaign by a pharmaceutical company that was exposed to the public. There were various stages of the campaign. The first was to persuade the medical press and the medical establishment that this was indeed a problem that affected many millions of people. Then part of their campaign was to set up patient organisations in order to push the need for the use of this drug. I believe we have evidence that the pharmaceutical industry, knowing that they cannot in this country advertise directly to the public, used the patient organisations, set them up or used existing ones deliberately to put their case. We know ourselves from the letters we have from individual constituents. Handwritten letters are far more convincing than something from a drug company.

Q343 Dr Taylor: Can I just go back to regulation and pull together all your ideas on regulation because this has to be one of our huge recommendations? I think Mr Flynn mentioned that the Charity Commission, so that is one organisation that should be strengthening its act. Is that right?

Paul Flynn: I made a list of suggestions at the last part of my report, which I will not read to you now, on pages 6 and 7. Many of those are to strengthen organisations like the one represented by the witness here, the LMCA, and other organisations that are certainly benign and have no axe to grind as far as maximising the sale and use of drugs.

Q344 Dr Taylor: It is primarily the Charity Commissioners and the MHRA?

Paul Flynn: Yes. Action has been taken on the LMCA.

Ms Letts: Mention has been made of patient organisations set up by pharmaceutical companies. Such organisations certainly do exist and I think that is one of the reasons why I think we need to have a clearer way through something like the LMCA of being able to establish the bona fides of patient organisation. That would be a great help to the existing ones.

Mr Prior: If I may comment specifically on that, I think the MHRA and the medicines regulatory bodies are probably a better channel than the Charity Commission, which of course has the whole panoply of all sorts of different charities to regulate and is unlikely to have the specific focus on this area that would be needed. I would like the medicines regulatory agencies to have a strategic relationship with patient organisations, not only co-operating with them on regulation, transparency, accountability and so on of patient organisations but also working with them on early indications when problems are starting to emerge with treatments. I do say “treatments” because it is not just pharmaceuticals that have caused problems. Herbal medicines have caused problems, non-medical therapies, technologies and so on, all sorts of things have caused problems. Patient organisations are often aware of the early anecdotal evidence, the buzz that “well they told us this was not addictive but we did not half have problems coming off it”. It can take years, 10 and sometimes 20 years, for that early patient information to be taken seriously by the regulatory bodies. We have to move towards the yellow card system being opened up to direct reporting by patients. Evidence from other countries suggests that that is not a very strong method unless you are proactive about it. I would like the MHRA to have a channel that hears about what we are observing with antipsychotics, whatever it might be—cardiac risks, weight gain risk—and, in view of that, say, “All right, we hear enough news from you on this to fund you to conduct an informal patient survey”. If that comes back saying, “This seems to be a more common problem”, then they go to a full-scale clinical trial to try and lift the lid on that and to shorten this terrible period, this very long period, between the early news and so on. Whilst the other witnesses are saying things that are absolutely true, there is a real problem here. There is even more of a problem on the European front for patient organisations where the sources of alternative funding are almost nil and the European front, of course, is becoming increasingly important in medicine regulation. This is only one of the influences on patient organisations. Certainly, if I were to list the undue and improper influences brought to bear by different funders, government and NDPBs would be at the top of the list, followed closely by non-pharmaceutical corporate interests. Almost all corporate fundraising, apart from the pharmaceutical industry, which is regulated, is direct cause related marketing; it is directly to sell their product. In the course of looking at undue influences, we have to recognise that removing one undue influence from the scene may simply serve to influence the undue influence of other parties. Balance, transparency, accountability and regulation are needed on this across the board. I am astonished by the fact that in joining the Medicines Commission I was required to declare interests in the pharmaceutical industry and nothing else. Personally, I am much more influenced by the fact that I would not be alive without advanced antibiotics than I am by any financial grant to the organisation.

Q345 Dr Taylor: I am extremely worried about writing this report because we have already heard from many witnesses previously that the vast amount of research is funded by drug firms; the vast amount of postgraduate education is funded by drug firms; these patient groups are funded by drug firms. Some of you have actually implied that some of this money is absolutely essential and cannot come from other places. How do we make the compromise?
there possibly an argument, as has been put to us, that if drug firms reduced their prices because they were not spending all the money on these other things, then the drugs would cost less, they would have more money and then things could be government funded. Is that cloud cuckoo land?

Ms Letts: I do not think we would want to be entirely government funded in any case.

Q346 Dr Taylor: I do not mean entirely, but more?

Ms Letts: Sometimes there are just as many pressures, as we have already alluded to, for patient organisations in resisting the pressures that government or NDPBs or other people want to put on them. Therefore, I think it is, as we have said, it is a matter of establishing the bona fides of the organisations and perhaps, through such a process, being able to offer training and support to some of the less well-resourced organisations in how to deal with these influences. I have always believed it does not have to be the case that taking money from somebody means that you have to do what they say. That has not been the case in my experience. You take the money; if they do not like what you did, then you may not get it again but at least you have had it for the time being and you did something that you thought was good with it. If you have the courage of your convictions and say what you believe to be right and do what you believe to be right with the money that you have, then very often you will find that the funders will not go away because in some way you have all moved on and their understanding of your agenda has developed, just as your understanding of their agenda has developed.

Q347 Dr Taylor: You can take the money without being influenced?

Ms Letts: I have actually explicitly resisted pressure from companies and I have not failed to have a grant renewed.

Q348 Dr Taylor: Many of the research doctors who have spoken to us have said that they have not been influenced by the money they have had to do the research, but they admit that other people are influenced.

Ms Letts: That may be the case. I cannot speak for other people. I said earlier on that you have to know absolutely what your objectives are, what your non-negotiables are, what are the things on which you will not compromise.

Paul Flynn: The main problem is that we look at the problems of the planet and find that the third largest cause of death and illness is medical intervention. There is a deliberate campaign by the pharmaceutical industry to medicalise all society and convince us all that we cannot get through life without their support. It is extraordinary that this has been so successful. The great problem is that it has made us a dependency culture. Giving us the idea that there is no answer to our problems except a pill that gnaws away at our self-confidence and our ability to cope in the way we have for thousands of years.

Ms Letts: That is exactly why every organisation that I have been involved in and am involved in puts out the message that drugs are only one part of treatment; they are only one aspect of treatment. In fact, “Ask about Medicines Week”, of which I am a director, has, as a fundamental message of the week, that patients must have the right to participate in the prescription decision and to choose whether to have that drug or whether to have any drug at all or to have some different form of treatment.

Mr Woolas: In our support group I would say that we do receive funding from the state in the form of legal aid, which we have on occasion received. I think I would want to distinguish between state funding and government funding. I think state funding can be independent. The Opposition parties receive state funding. I would say that I would want to distinguish the funding for treatment from the funding for advocacy and support. I think there are ways that we can guarantee independence on that front by a combination of funding that in our case would not involve the pharmaceutical companies.

Q349 Dr Taylor: This is a question for Mr Woolas. For the record, could you tell us the source of your statement that 1,800 patients have died from benzodiazepine use.

Mr Woolas: It is contained in the memo from Mr Behan. The figures are based on Home Office figures. Part of our campaign is to ensure that coroners' and pathologists' reports actually test for benzodiazepines. The media phrase is “a cocktail of other drugs”. That normally refers to benzodiazepines. The figures are contained in the written evidence that I have given quoting the Home Office that resulted from a series of parliamentary questions.

Q350 Chairman: It is sourced in that evidence to us?

Mr Woolas: Yes.

Q351 Dr Naysmith: Given what Richard Taylor and John Austin have said, I had better admit to the fact that I am an officer of the All Party Stroke Group, I have no idea whether that is funded by the pharmaceutical industry or not. Maybe they are, so I had better admit it. I am active on lots of other backbench health groups as well. I want to ask Mr Prior about something he has really referred to quite a lot already, but I would like to clarify it. In your written evidence, you recommend that the drug regulatory process should be opened up to include all stakeholders and you expanded on that a bit.

Mr Prior: I am particularly thinking of people who take the medications and, where people are too ill to speak for themselves, the carers of the people who take the medications. I think it is on the positive side as well as the negative side. I work in a field where for many years people were really trying to treat the wrong problem. They treated the problem that doctors thought was the problem rather than asking...
the people taking the medications, living with the condition, what they saw as the major problem. It is about the positives as well as the adverse effects. We do need more patient/user/carer representation throughout the medicines regulatory system. Of course, once you do that, patient organisations become yet more important. It is additionally important to follow up on the concerns, and there are real problems out there, which can deflect patient organisations. We stand on our track record for transparency and openness on this, but, for every one of us, there is always some other organisation that perhaps is prepared to cut a corner. Regulation defends good patient organisations. It is to the benefit of good patient organisations. We need that additional level of regulation, that transparency and that openness and the balance. When we survey our members about what they see as most important in this field, they do not want the pharmaceutical industry hobbled. They want the development of better medicines with fewer side effects. They also want the development of alternatives to medicines as well. They want a balanced range, but they do not want the pharmaceutical industry hobbled. They do want the patient voice to come through loud and clear throughout the regulatory system.

Paul Flynn: They want the patient voice uninfluenced by donations from the pharmaceutical industry. It is not true to defend the yellow card system, which has vastly under-reported the effect of adverse reactions. It was alarming to hear a government minister recently in a debate defending the idea that the only people who should be on the MHRA and taking on this very important body are people with years of experience in the pharmaceutical industry as they are the only people who could make these decisions when many lay people and others with a scientific background can make the decisions there. I think we have suffered from a preponderance of people on the MHRA over the years with 20 or 30 years in the pharmaceutical industry; their mindset is very different from that of other people who examine these things.

Q352 Dr Naysmith: We have seen quite a lot of evidence that people are pleased with the extension of the yellow card system and it can go further?

Paul Flynn: Yes.

Q353 Dr Naysmith: To pick up on one or two other things that we need to clear up before we finish this morning, over the last three weeks, we have heard a lot about patient information leaflets and their shortcomings. Why has it taken so long for there to be any serious attempt to improve these leaflets? Perhaps Melinda Letts could start?

Ms Letts: I do not know why it has taken so long. I am very glad that there is a serious attempt because I think many of us know the shortcomings of patient information leaflets. I have heard a lot about that over the years, which is why I was very glad to be asked to chair the working group.

Q354 Chairman: Mr Woolas has to leave as he has government duties to perform. We appreciate his attending today.

Ms Letts: They have been compulsory since 1 January 1999. Among the shortcomings are not only the layout and the contents, which as you probably know are heavily regulated, but also the fact that not everybody does get them, even though it has been compulsory, supposedly, since 1 January 1999. There are various problems leading to this, including splitting packs. I find it almost impossible to believe, but apparently it is true, that the reason why pharmacists cannot photocopy them when splitting packs is to do with copyright. I cannot understand why that has not been able to be sorted out by now. In any case, my working group is charged with looking at improving their quality. We have been working for a year and we are focusing on that.

Q355 Dr Naysmith: Are you finding co-operation from the pharmaceutical industry? Do they really want this information to be much more widely available in a readable form?

Ms Letts: It is a little difficult. There are two pharmaceutical industry representatives on my working group. I certainly have not detected any resistance to improving the readability and quality of the leaflets from those members. I am aware that for the industry generally there is a certain amount of apprehension on a procedural and logistical basis, particularly as there are changes that we are suggesting should be introduced now in advance of some legislative changes coming into practice. There is a concern that if we have to change what we are doing at one time, is there going to be another new guideline issued a short time later that is going to make us change everything all over again? The working group is quite clear that the interests of the patient must come first.

Q356 Dr Naysmith: Do you produce drafts of these leaflets to improve them?

Ms Letts: We do not produce drafts. If we did, we would be very busy indeed, I think. The drafts are written by the companies. They do not have to be approved by us either. They have to be approved by the CSM, the Committee on Safety of Medicines, as part of the licence application. Some leaflets have come to us for comment where there are thought to be special cases. For example, in a recent statin that was going over the counter, the leaflet was brought to us for comment, but we are not the body that actually approves them or drafts them or writes them.

Q357 Dr Naysmith: Do you think there has been improvement?

Ms Letts: No. I do not think there has so far. It is far too early to say there has been any improvement. The changes in European legislation are only coming on stream early next year. For example, one thing that is going to happen is that the order of information is going to change.
Q358 Dr Naysmith: You are saying that in some special cases you have seen some examples. Do you think they are going in the right direction or do you think it is too early to say?
Ms Letts: I could not say I was hugely impressed by any of them. What we need is a wholesale improvement. We need these new guidelines that we are working on. One of the important things that is going to come in is a requirement for user testing to take place. That has been mentioned in guidance since 1999 but it has had a minuscule take-up and it now going to become compulsory.

Q359 Dr Naysmith: Why is that? Is there any reluctance to involve users in the testing?
Ms Letts: I really cannot speak for the industry. I am not involved on their side, but I imagine that if it is not made compulsory, then it is simply another stage that they have to go through in this long and complicated procedure of getting an approval. It does not rise to the top of the priority list. I am simply speculating. I really cannot say. It is not something I am responsible for, but I am glad that it is becoming compulsory because it seems an obvious thing to do, if you are writing leaflets for people organisations to be strengthened to defend something I am responsible for, but I am glad that it is becoming compulsory because it seems an obvious thing to do, if you are writing leaflets for people about something as important as their medication, themselves against the insatiable greed of the drug manufacturers use the summaries of communicating about risk, as well as introducing something I am responsible for, but I am glad that it is becoming compulsory because it seems an obvious thing to do, if you are writing leaflets for people about something as important as their medication, themselves against the insatiable greed of the pharmaceutical industry.

Q361 Dr Naysmith: In a way, that is the nub of this whole question. There have been suggestions that the drug manufacturers use the summaries of product characteristics to mislead readers about their products. This might be a question for Melinda Letts. How can this happen when SPCs are jointly referred to, that people often do not understand that these drugs were all sold as harmless drugs that were not made compulsory, then it is simply another stage that they have to go through in this long and complicated procedure of getting an approval. It does not rise to the top of the priority list. I am simply speculating. I really cannot say. It is not something I am responsible for, but I am glad that it is becoming compulsory because it seems an obvious thing to do, if you are writing leaflets for people organisations to be strengthened to defend themselves against the insatiable greed of the pharmaceutical industry.

Paul Flynn: I think they are very resourceful in ensuring that their case gets across. We would all share what I think is behind your questions, the view that the advice given is not adequate and masks the potential side-effects in many cases. They are often written in a way that is not readily understandable to most of the patients who receive them, and certainly they have a long history, which is part of their nature, it is endemic to pharmaceutical companies, to deny the danger, the “addictivity”, of their products. Over the 150 years that I mentioned all these drugs were all sold as harmless drugs that were non-dependent. Every one of them proved to have little utility, be damaging and addictive or encourage dependence in some way. We cannot ignore where we are now with a history of pharmaceutical companies behaving in this way for 150 years. There has not been some change. With new drugs we are still conducting experiments on a massive scale on the public. They might have been tried on animals and trials might have taken place but the whole confidence we have in trials has been undermined by what has happened with GlaxoSmithKline and Seroxat. The duty of all of us I believe, and I am sure it will come out in your report, is to make a stand for organisations to be strengthened to defend themselves against the insatiable greed of the pharmaceutical industry.

Q360 Dr Naysmith: This will probably be the last question. There have been questions about the reliability of summaries of product characteristics. I know you have strong views on these, Paul.
Paul Flynn: From listening to what has been said, it is revealing—and I think we are all used to this—that the person who actually writes the documents is the one who has the power and it is the pharmaceutical industry that writes these documents now. Then there is approval by the CSM. What is significant is that neither the CMS nor the MHRA nor the industry has exposed the scandals that we have had and the dangers of the terrible side-effects. Recently drugs have been exposed by programmes like Panorama. One patient organisation, not one in the pay of the pharmaceutical industry but MIND, did the heroic job on the MHRA by resignation on this, together with groups elsewhere in the world. We have to look at the position we are in where the might of the pharmaceutical industry is enormous, where their tentacles of power go through the whole of the medical establishment, including the regulatory bodies and into the patient organisations. We need a stronger voice and transparency to defend the patients’ interests.

Q362 Dr Naysmith: You have made your case very strong.
Mr Prior: Leaving aside the specific cases where evidence has been concealed or distorted or whatever, I think it is also true to say that no amount of pre-marketing studies on medications will reveal what the large-scale use, once they are on the market, will reveal. We need to be much more ready to go out proactively to check for side-effects in the first couple of years of marketing and be prepared to hear those messages and proactively ask people, “What are you experiencing?” There is a deeper malaise here. There is a myth, particularly in the British public that I do not find elsewhere in the world, that there is one set of nice, clean, effective drugs with no side-effects and there is a nasty set of toxic stuff that evil pharmaceutical companies adopt and peddle to us. This is a complete myth. There is nothing that you take by way of a drug which does not have risks attached to it. All drugs carry some benefits and some adverse effects. We can know some of that before things are marketed; we can know a bit more afterwards, but everybody has their own body and their own mind and will have different experiences. We need to enter into this with a much greater degree of scepticism.
Ms Letts: I simply wanted to add, in response to your question, that one of the things the working group is looking at is improving the readability guideline and introducing much better ways of communicating about risk, as well as introducing some supplementary information about side-effects, for precisely the reason that Cliff Prior has referred to, that people often do not understand that there are likely to be side-effects with anything that you take. With my 13 years background of working...
for people with long-term conditions of one kind or another, what I have to bear in mind all the time is that for many of those people it is a matter of having to weigh up the benefit of the drug against the side-effects that they may have to put up with. The public find it very difficult to understand how to weigh up risk and benefit. We have been looking at that on the working group. I do think it is relevant here to say, and it is one of my recommendations to this Committee, that patients should have the absolute right to inspect the evidence that led the regulators to license the drugs in the first place. It is wrong that that is not the case.

Chairman: May I thank you, Ms Letts and gentlemen, for a very interesting session. We are most grateful for your co-operation.

Memorandum by the Depression Alliance (PI 54)

I will pursue the SSRI Working Group issue elsewhere. In the meantime, I do have quite strong views on the issue of industry funding of the voluntary sector so, for what it’s worth, I’d like to share these with you and the Select Committee.

In an ideal world, I can see why some would say that it would be preferable if the sector were independent of funding from any area of industry (as opposed to just the pharmaceutical industry). To my mind, there are four essential flaws in this argument. First and foremost, certainly mental health charities are not fortunate enough to exist in an ideal world. We have to make do with the real one. In the real world, there is a paucity of government funding (for example our core grant is not sufficient to pay one member of staff), grant-making trusts prefer project funding, our cause is not popular with the public in general, so we do not have the broad base of untied funding that is the life-blood of the sector. In short, corporate sector funding helps us to provide services that—without it—we would not be able to provide, and it underpins our overheads.

Secondly, there is an argument that by accepting industry funding, the sector in some way becomes “in the pay” of that industry. In 15 years working in the sector, I have encountered one example of this. It was not in the health sector and the company involved was not a pharmaceutical company. It was actually one of the largest corporate givers in this country—and the donation was refused out of hand. I have never been asked for anything in return for a donation from the pharmaceutical industry. In fact, the contrary is true, as I have frequently found myself undertaking, for example, a piece of awareness-raising media work that—had I been a consultant—a company could reasonably have expected to pay for. The simple fact is that the strength of the mental health charity is its independence. Without that independence, our voice would hold no sway—it is in no-one’s interests to dilute our independence.

Thirdly, there is a very tight legal framework determining what freely offered donation a charity can and cannot refuse. This is enshrined in the basic concept of “Charity”, as defined in the Heads of Charity which have stood for, I believe, over 400 years. Charity Trusteeship brings with it a fiduciary duty not just to manage a Charity’s funds, but to maximise its income. Despite what some (invariably wealthy) charities would argue, a charity cannot simply refuse an untied donation. There are strict conditions that need to be met. I believe that more attention should be given to those charities that pursue so-called “ethical” fundraising policies in flagrant disregard of Charity Law. My own organisation, Depression Alliance, accepts monies strictly in accordance with Charity Law, and our guidelines for accepting industry funding are in the public domain.

Fourthly—and to mind critically—those that would have industry funding disallowed would have us miss a tremendous opportunity and would see us do an inexcusable disservice to our beneficiaries. Each of the parties to the industry/charity relationship has tremendous strengths. And corresponding weaknesses. The company has a wealth of research, of marketing expertise, of business acumen and of opportunities for communication. The charity tends to be service-user driven. It has detailed knowledge of its field. It is likely to have a much longer involvement in its core area, at a greater level of detail, than any company. These types of factors present opportunities to build strong relationships of great benefit to the consumer of charitable services—and the consumer of industry’s products. Because, ultimately, they are one and the same person.

For the above reasons and given the above safeguards, I am totally in favour of corporate funding of the charity sector. I believe any argument to the contrary is naive. More seriously, I believe that it would see limited the amount and quality of services we in the sector are able to deliver to our beneficiaries and that is diametrically opposed to the notion of
Memorandum by Multiple Sclerosis Society (PI 25)

1. INTRODUCTION

About MS

1.1 MS is a condition which affects the central nervous system (the brain and spinal cord). Its effects include problems with mobility and speech, extreme fatigue, pain, continence and cognition. With many people diagnosed in their twenties or thirties, employment or other useful occupation is a key issue in their lives.

1.2 There are an estimated 85,000 people with MS in the UK. There is currently no cure.

About the MS Society

1.3 With nearly 45,000 members the MS Society is the largest organisation in the UK representing and working for those affected by MS. We estimate that we represent over one-third of all people with MS in the UK.

1.4 We provide a range of services to people affected by MS including helpline, website and information services, and personal support through our network of 360 local branches. We fund both scientific and service improvement research, and provide pump-priming funding for such things as MS nurses.

1.5 Provisional figures for 2003 indicate that the Society's income was £28 million. The broad division of income was £12 million donations, £8 million legacies, £8 million grants and other income. Details of contributions received from pharmaceutical companies in 2003 are given in Annex A.

2. SUMMARY

— The MS Society values its relationships with the pharmaceutical industry, which we believe in help us achieving our charitable objectives.

— Any financial arrangements between the Society and the pharmaceutical industry are conducted within a clear and transparent framework.

3. DISCUSSION

3.1 As an organisation our role is to support people affected by MS and represent their interests. Our relationships with people affected by MS and other stakeholders depends crucially on our independence. It is important that we are both independent of all outside interests and perceived to be so.

3.2 We have been aware for some time of the need for particular transparency in our relations with the pharmaceutical industry. In 1999, after a lengthy consultation with pharmaceutical companies and other MS charities the Board of the MS Society approved a document Relations between the MS Society and the Pharmaceutical Industry, which forms the basis of our interactions with the industry. A copy of the document is at Annex B.*

3.3 Our relations with the pharmaceutical industry are generally constructive. Most differences tend to be small scale, resolved informally and in private. However, we do not shy away from a more public approach if we believe it to be necessary. In 2000 we reported a manufacturer of MS disease-modifying drugs to the Medicines Control Agency (MCA) for what we believed to be a breach of the Medicines (Advertising) Regulations 1994. The issue related to advertising promoting access to drugs which seemed to us to constitute direct to customer marketing. In the event the MCA concluded that the nature of the advertisement in question was not covered by the advertising regulations.

3.4 We have in the past published a statement on our relationship with pharmaceutical companies and the detail of donations received from them. We did not publish this in 2002 (though the full details of the nurse scheme mentioned in Annex A were made public through a press release at the time of its launch). However, in view of the increasing interest in the relationships between medical charities and the pharmaceutical industry we intend to reintroduce this section in our 2003 Accounts.

Annex A

Money received from pharmaceutical companies in 2003

— We received donations of £100,000 from Serono Pharmaceuticals Ltd and £100,000 from Biogen Ltd to help fund the MS fast-track nurse scheme. This scheme provides pump-priming for MS nurse posts, and the Society itself has contributed £100,000 to the fund. A further company, Teva Pharmaceuticals, is involved in the scheme, but its £100,000 contribution was not received until 2003. These three companies are manufacturers of disease-modifying therapies for MS. (The fourth manufacturer, Schering, has opted not to be involved in the scheme.) Nurses funded through the scheme are employed by the NHS, work with all people with MS—not just those

* Not Printed
receiving disease-modifying therapies—and do not promote any particular product. In this
arrangement the Society essentially acts as an independent intermediary with most of the money
flowing direct to the NHS, apart from a sum retained to provide specialist education for the nurses.

— We received a donation of £101,000 from GlaxoSmithKline to part fund a £140,000 three-year
project at Oxford University (the balance of the project costs are met by the Society). Loss of nerve
fibres in the central nervous system in MS is irreversible and determine impairment. The project
will investigate the extent of nerve fibre loss in people with MS and whether there are compensatory
mechanisms for fibre loss that may be increased by drug treatments.

Small donations from pharmaceutical companies totalling £502 were also received.

Annex B

RELATIONS BETWEEN THE MS SOCIETY AND THE PHARMACEUTICAL INDUSTRY

STATEMENT OF POLICY

Following consultation with this industry and other MS charities this policy was approved by the MS
Society Board of Trustees October 1999.

RELATIONS BETWEEN THE MS SOCIETY AND THE PHARMACEUTICAL INDUSTRY

1. Background

1.1 The MS Society has relationships with many different sectors of business and industry as a routine
part of its work on behalf of people affected by MS. It is often a customer, sometimes a partner or contractor,
and also benefits from gifts in cash or in kind. In all these relationships, the Society aims to behave ethically
and to the standards expected of a prominent charity; it works within the law.

1.2 The pharmaceutical and allied industries (referred to as the “Pharma Industry” in this paper) at
present constitute the only sector of business with an interest in the same unique group of people for whom
the Society works. This policy statement, the result of extensive consultation, sets out the guidelines within
which the Society will work. It is intended to:

— Assure the Trustees that the Society is operating within the constitution.
— Enable the Chief Executive to make decisions as necessary.
— Clarify the Society’s position to its members, the Industry and the public.
— Facilitate clear and unambiguous relationships between the Society and the Pharma Industry.

1.3 Everyone who works for the Society, whether paid or as a volunteer at national or local level, is
expected to observe these guidelines, as is the staff of the Industry. In addition, the Industry is requested to
ensure that consultancies and contractors it retains adhere to them.

1.4 The Pharma Industry is a sector of business with which the Society has only begun to work since the
licensing of the first disease-modifying treatments for MS. While it aims to work to the same standards in
all circumstances, special attention is required for these relations.

1.5 In addition to other factors, specific UK and European laws regulate the Industry, while the MS
Society operates under charity law. The Industry works under particular constraints over promoting
prescription-only medicines to the public, while the Society’s constitution emphasises education and
information. Both the Industry and the Society accept the law and regulations for licensing and use of
pharmaceutical products.

1.6 The Industry is concerned with the health and well being of people with MS, but is of necessity
concerned with selling its products to the NHS and must provide a return to investors. As a charity the
Society works solely for the benefit of people affected by MS and no other interest; its independence is central
to its work. Linked to this is the Society’s public reputation which it safeguards strenuously.

1.7 The paramount consideration for the Society in its relations with the Pharma Industry will always be
the benefit or disadvantage that could result for people affected by MS.

1.8 These guidelines cover the following areas:

— The basis of partnership.
— Research, information and publications.
— Government, the NHS, the medical and allied professions.
— Endorsement and promotion of products and services.
— Support of healthcare workers.
— Financial and other material support.
2. The basis of partnership

2.1 The MS Society values co-operative relationships with the Pharma Industry, to foster effective and accurate communication between people affected by MS and the companies whose decisions will affect their treatment.

2.2 We consider that partnership is based on openness and integrity. It is expected that the Society and the Industry will each share full and timely information about initiatives that bear on the other. Where this is limited for reasons of individual, legal, commercial or other confidentiality, each will ensure that the other is made aware of this. Any information provided and accepted in confidence will be treated on that basis.

2.3 The interests of people affected by MS will be best served if the Society and the Industry have a partnership of equals. We recognise that successful partnerships are based on mutual benefit, and consider that each party should make efforts to ensure that it understands goals and internal culture of the other, as well as the external pressures.

2.4 Serving the interests of people affected by MS often requires the Society and the Industry to work together on policy development and practical initiatives. Neither the Society nor the Industry should assume the other’s support without explicit agreement, formal or informal.

2.5 The MS Society acknowledges the Industry’s need to make profits which serve the interests of investors and provide for investment in future treatments. However, the marketing agenda of the Industry is not necessarily the same as that of the charity, and the Society’s support for marketing activity should not be taken for granted.

3. Research, information and publications

3.1 The Society welcomes information from the Industry of relevance to people affected by MS and to the Society’s research or policy programmes. In general the Society prefers to deal with information subjected to peer review and in the public domain.

3.2 Where the Industry seeks access to the Society’s beneficiaries, members or supporters this will be by communication and invitation to participate from the Society; lists are not made available. Each proposal is considered separately and the Society’s time and resources are taken into account.

3.3 The Society aims to ensure that people affected by MS are able to rely on the best available evidence in reaching conclusions about their treatment. It supports systematic, scientific investigation including clinical trials where these will reduce uncertainty, though it does not regard placebo as the only acceptable form of control.

3.4 The Society is committed by its constitution to seek publication of research on MS. Where the Society is in partnership with the Industry publication of results is always expected, but the Society also encourages the Industry to publish the results of all research.

3.5 The Society is prepared to enter partnerships with the Industry in research projects, providing support as appropriate; a range of involvement can be considered from advisory to co-funding.

3.6 In all research involving people affected by MS, investigators are expected to adhere to the canons of ethical and good clinical practice including voluntary informed consent, as well as prevailing law. The Society is a member of the Association of Medical Research Charities and observes its research policies.

3.7 The Society has an interest in epidemiology and population-based research. Because of its extensive databases, the Society may be able to give particular help with such projects, subject to appropriate safeguards for individuals and their privacy.

3.8 The Society has particular concern that the interests of people with MS are adequately recognised when they participate as volunteers in clinical trials or other human research projects, and is always prepared to advise the Industry on this.

4. Government, the NHS, the medical and allied professions

4.1 The Society and the Industry share the common goal of increasing the resources available for the treatment and management of MS. There are circumstances in which the Society will wish to work with the Industry to influence the policy of government and the NHS, or the attitudes and practices of the professions. Clarity in goals and methods is expected at the outset and at stages during joint work.

4.2 Where the Society is working with the Industry to influence policy and practice it will always be prepared to disclose this. It will not be acceptable for either partner to obscure the involvement of the other.

4.3 Media or other public relations initiatives in pursuit of shared goals are likely to impact on the work and standing of the Society or of the Industry. They should therefore be discussed as early as possible within the limits of proper confidentiality, and note taken of any reservations expressed by either party.
5. Endorsement and promotion of products and services

5.1 The Society supports the availability of the widest range of treatments, and of informed choice by patients in consultation with their doctors. Treatments may include medicines, complementary and/or alternative therapies, lifestyle changes, surgical or other interventions as well as non-therapeutic products.

5.2 In line with its general policy, the Society seeks to ensure that its beneficiaries have the most authoritative and balanced information available on which to base their choices. It encourages the Industry to co-operate in making this available.

5.3 The Society avoids endorsing individual products. Reference in the Society’s publications or information services to a particular product by generic or trade name, or acceptance of advertising where permitted, does not constitute approval or recommendation of the product.

6. Support of healthcare workers

6.1 The Society is willing to co-fund health professional posts in collaboration with the NHS and/or the Industry, through its MS Nurse Fund or other channels as appropriate. We will not support posts that are part of the marketing strategy of the Industry.

6.2 To qualify for the Society’s support, any post must have an agreed job description that makes clear the benefit expected for people affected by MS. The post holder must be available to the client group agreed and be free from bias in principle and in practice.

7. Financial and other material support

7.1 The Society welcomes financial and other material support from the Industry for its work, so long as the Society’s charitable status and independence is not compromised. In addition to the effects upon the goals and programme of the Society, the overriding consideration will always be the potential benefit or disadvantage to people affected by MS.

7.2 When possible, the Society prefers financial support to be provided via consortia of two or more companies. Where associated with a publication or event, the Society will acknowledge support. It will always be prepared to disclose support even where there is no ready vehicle for making this public.

7.3 The Society recognises the ambivalence of attitudes towards the Industry among NHS workers, policymakers and the medical profession, and regards the risk of adverse publicity as grounds to decline or return donations, grants or other payments.

7.4 The name, marks and reputation of the MS Society are its property and may only be used by the Industry with the Society’s explicit agreement. In no case will it agree to their use in order to give one company market advantage over another.

7.5 The staff of the Society are subject to strict rules on acceptance of gifts and hospitality. The Industry is asked to ensure that it does not lead staff to break these rules accidentally or intentionally; to do so would lead to a rupture in relations.

7.6 The Society’s national headquarters in Scotland and Northern Ireland, its regions in England and Wales, and its branches and local units throughout the UK should not be approached by any company without the prior approval of the Chief Executive. If direct approaches are received from these units of the Society, the Industry is asked to first clear them with the Chief Executive.

Annex C

MONEY RECEIVED FROM PHARMACEUTICAL COMPANIES IN 2003

We received donations of £100,000 from Serono Pharmaceuticals Ltd and £100,000 from Biogen Ltd to help fund the MS fast-track nurse scheme. This scheme provides pump-priming for MS nurse posts, and the Society itself has contributed £100,000 to the fund. A further company, Teva Pharmaceuticals, is involved in the scheme, but its £100,000 contribution was not received until 2003. These three companies are manufacturers of disease-modifying therapies for MS. (The fourth manufacturer, Schering, has opted not to be involved in the scheme.) Nurses funded through the scheme are employed by the NHS, work with all people with MS—not just those receiving disease-modifying therapies—and do not promote any particular product. In this arrangement the Society essentially acts as an independent intermediary with most of the money flowing direct to the NHS, apart from a sum retained to provide specialist education for the nurses.

We received a donation of £101,000 from GlaxoSmithKline to part fund a £140,000 three-year project at Oxford University (the balance of the project costs are met by the Society). Loss of nerve fibres in the central nervous system in MS is irreversible and determine impairment. The project will investigate the extent of nerve fibre loss in people with MS and whether there are compensatory mechanisms for fibre loss that may be increased by drug treatments.

Small donations from pharmaceutical companies totalling £502 were also received.
Memorandum by GeneWatch UK (PI 18)

SUMMARY

1. GeneWatch UK is a not-for-profit policy research group concerned with the science, ethics, policy and regulation of genetic technologies. Our aim is to ensure that genetics is used in the public interest. Our submission relates to the role of the pharmaceutical industry in the promotion of the concept of “genetic predisposition” or “genetic susceptibility” to common diseases.

2. **Key points:**
   
   — Within a few years, the availability of genetic tests could significantly expand the market for “preventive” medication to healthy people identified as “genetically susceptible” to a wide range of diseases.
   
   — The regulation of genetic tests is critical to controlling this expansion and ensuring genetic tests and associated medication are used only when they are of benefit to health. Currently, companies are not required to supply any clinical data relating to the tests they sell. Most “genetic susceptibility” tests are not validated and are misleading and of limited utility. Advice and medication based on test results may therefore be harmful to health.
   
   — Some tests are already on the market “direct-to-consumer”, mainly sold by relatively small US biotech companies. The pharmaceutical industry plans to begin using genetic tests to expand the drug market within the next two to three years.
   
   — The pharmaceutical industry favours a medical approach to the “prediction and prevention” of disease because it profits from the sale of preventive medication. Alternatives, such as public health measures, have been neglected: steps should be taken to redress this balance.

INTRODUCTION

3. “Seven month-old Tiffany could one day benefit from Roche’s visionary approach to individualised healthcare . . . Roche is committed to integrating resources in the field of genetics and genomics to find new individualised solutions that address pre-dispositions **long before an ailment even starts.**” [Emphasis added]. Roche “Predisposition” Movie. Available on: [http://www.roche.com/home/divisions/div_dms/div_dms_pred.htm](http://www.roche.com/home/divisions/div_dms/div_dms_pred.htm)

4. Historically, the practice of medicine has involved the diagnosis and treatment of disease, whilst public health measures have attempted to reduce the incidence of disease in a population. Increasingly, medication is now prescribed to reduce risk of future illness. Selling medication to treat risk factors rather than diseases is immensely profitable for the pharmaceutical industry: for example, statins (to lower cholesterol levels) are now the biggest selling prescription drugs in the world.23

5. The definition of the “at risk” population to be treated has a major influence on the relative benefits and risks of preventive medication, its costs to the Treasury and the industry’s profits. Until now, the medical profession has played a major role in deciding who is offered preventive medication via doctors’ interactions with individual patients and via professional bodies which have established international guidelines for tests such as those for blood pressure and cholesterol levels. However, the role of the pharmaceutical industry in influencing guidelines for lowering cholesterol has recently sparked controversy.24 The involvement of the medical profession in determining “at risk” populations for treatment is also changing with, for example, the approval of over-the-counter sales for statins.25

6. Genetic “predisposition” or “susceptibility” is a new means to identify “at risk” populations. As genetic testing becomes more widespread, it is important to consider how the “genetically susceptible” will be defined and who will be given preventive medication.

GENETIC SUSCEPTIBILITY

7. Common diseases are complex and most cases are influenced by multiple genetic factors; a significant environmental/lifestyle component; and interactions between different environmental, genetic and other biological factors.26 Social and economic factors also influence risk. Much genetic research effort is now largely directed at common “polymorphisms” rather than rare mutations. Polymorphisms are common

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genetic variations, each of which can occur in between 1% to 50% of the population. It is unlikely that there is a simple relationship between common genetic variations and the risk of common disease. However this complexity is rarely reflected in reports of genetic discoveries.

8. Some important considerations in using genetic test information to define “at risk” populations include are listed below.

9. The large number of genetic variations that exist. A Single Nucleotide Polymorphism (SNP) is one type of polymorphism which occurs when only a single nucleotide (chemical letter) in the DNA sequence varies. There are 100,000 to 300,000 SNPs in the coding parts of the human genome. Tests which identify polymorphisms have potentially staggering implications for the number of people who might be advised to take preventive medication. For example, suppose a panel of 22 genetic tests each identified 5% of the population as “at risk”. If the whole population took this panel of 22 tests, statistical analysis shows that 1/2 of the population would have at least one “at risk” test result. If the predictive value of the tests is low, most of these people would not benefit, and might be harmed, by taking preventive medication.

10. The poor predictive value of genetic polymorphisms. Tests for “genetic susceptibility” to common diseases typically have limited predictive value: many people with the “high risk” genetic variation do not get the disease and many people without it do. This results in large “numbers needed to treat” to prevent one case of disease.

11. There is poor reproducibility of associations between genes and common diseases. One recent study found that only six of 600 published associations between genetic variations and common diseases had been shown to be robust. Another paper could confirm only nine out of the 55 most studied associations. Strong associations between genes and diseases found in small, early studies were typically not confirmed by larger, later ones, which found either a weak association or none at all. Most genetic researchers do not validate their findings using independent data.

12. That inherited genetic risk factors are not amenable to intervention. The aim of preventive medication until now has normally been to reduce the identified risk factor (eg lowering blood pressure or LDL cholesterol). The effect of the medication on the risk factor is normally assessed in clinical trials, limiting reliance on epidemiological studies. Inherited genetic risk factors cannot be changed. This means patients remain at “high genetic risk” for life. Assessing the utility of the intervention and/or the appropriate timeframe for medication then becomes considerably more difficult. Dealing with statistical confounders in epidemiological studies becomes a major problem.

13. That genetic tests are easily marketed but complex to interpret. Most tests can be performed on DNA collected with a simple mouth swab and posted to a laboratory without the involvement of medical professionals. Genetic test kits are now being developed that might provide an instant read-out in a doctor’s surgery, a pharmacy or in a person’s home. For complex diseases, which depend on the interaction of many complex factors, a test result is likely to be misleading in the absence of other clinical information (such as family history) and professional interpretation.

MARKETING STRATEGIES

14. Genetic tests can be marketed over the internet: in High Street stores, pharmacies or other retail outlets, such as sports centres; via alternative healthcare providers, private GPs or private hospitals; or via the NHS. There is no regulatory oversight or requirement for counselling.

15. Genetic tests which claim to identify genetic susceptibility or predisposition to disease are already being sold via the internet, often accompanied by advice to buy associated products (usually nutritional supplements). Most of these tests are marketed in the US but some are available via a few private GPs and alternative healthcare providers in Britain. Professional bodies such as the American College of Medical


Genetics (ACMG) oppose direct-to-consumer sales of genetic tests on the grounds that they are potentially harmful. The ACMG states: “Potential harms include inappropriate test utilisation, misinterpretation of test results, lack of necessary follow-up and other adverse consequences”.

16. One UK company (Sciona) was forced to withdraw genetic tests combined with dietary advice from the Body Shop in 2001, following criticism from leading scientists. One US company continues to sell tests for genetic susceptibility to heart disease, osteoporosis, immune disorders and some cancers in the UK via individual complementary health practitioners, together with recommendations for supplements and medicines. Two health supplements companies (Health Interlink and Nutri Ltd) have marketed these tests in the UK but no longer feature them on their websites. In the US, other companies sell genetic tests which claim to identify susceptibility to obesity and addiction and several companies use genetic tests to market supplements and skin creams.

17. Genetic tests, reaching the market far earlier than new treatments, can provide a means of generating “near term revenue” from patented gene sequences. Most patents claiming DNA sequences are for research tools or “diagnostics” (genetic tests). Patent claims are always based on early studies (prior to publication), so most of the genetic associations in patent claims will not be robust.

18. So far, relatively small companies have been marketing genetic tests “direct-to-consumer”. However, this will soon change with the involvement of the pharmaceutical industry, which may market tests with or without medical involvement. Companies such as GlaxoSmithKline have recognised the potential to expand the pharmaceutical market to healthy people identified as “predisposed” to future illness.

19. The multinational pharmaceutical company, Roche is the world leader in the diagnostics (medical tests) market. Roche aims to market genetic tests for “predisposition” to common diseases along with lifestyle advice or medication. Roche has a licensing agreement with the Icelandic biotech company DeCODE to discover and commercialise these genetic tests. They plan to market a genetic test for risk of heart attack within two to three years. However, their published evidence for this test has been criticised as weak by other scientists.

20. In some cases, genetic tests may be valid and useful for some people, but inappropriate for widespread use. Mutations in the BRCA1 and BRCA2 genes are associated with a significantly increased risk of breast and ovarian cancer and are helpful to some women who have an unusually strong family history of breast cancer. Widespread testing is not recommended because mutations are rare; the risk associated with them is uncertain in the absence of a strong family history; and the options to reduce risk are limited (the main

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43 “Diagnostic Tests in Clinical Practice” by Sue Glennie DipION, ND, 22 June 2002, On behalf of Health Interlink Ltd.
48 www.health-interlink.co.uk.
49 www.nutri-online.co.uk.
one is to have a prophylactic double mastectomy). The company Myriad which holds the US patents on these tests has been strongly criticised for running a misleading advertising campaign in the US which implies that the tests are suitable for every woman. 65, 66, 67, 68, 69, 70, 71, 72, 73, 74

US REGULATION: THE ROLE OF THE PHARMACEUTICAL INDUSTRY

21. “Beyond the rare Mendelian subsets, genetic influences in common diseases are likely to be conditional on the environment. Testing for these low penetrance susceptibility genes is likely to be of limited clinical utility”. European Society of Human Genetics, 2003. 75

22. In the US, the Secretary’s Advisory Committee on Genetic Testing (SACGT) reported in 2000 76 and recommended that four criteria should be used to assess the benefits and risks of genetic tests: analytical validity; clinical validity; clinical utility and social consequences. Analytical validity is how well the test measures the correct sequence of DNA, which depends on laboratory methods and quality assurance. Clinical validity refers to the accuracy of the test in diagnosing or predicting risk for a health condition, which depends on its sensitivity, specificity and predictive value. Clinical utility depends on how useful the test is for deciding who should be offered a particular health intervention. Even if a test is valid it is unlikely to be useful if there are better ways to decide who should be given a particular medicine (eg a different type of test or means of diagnosis), or if health advice (such as advice to stop smoking or eat healthily) should be the same for people with both positive and negative results. The SACGT recommended that the US Federal Drugs Agency (FDA) should be responsible for the review, approval, and labelling of all new genetic tests that have moved beyond the research phase.

23. Current practice in the US is that tests that are packaged and sold as kits to multiple laboratories require pre-market approval or clearance by the FDA. This means that the FDA will in some cases make an assessment of the clinical validity of the test (but not its clinical utility). A major loophole exists because tests that are not supplied as kits but provided as “clinical laboratory services” receive no such assessment. The FDA has the authority to regulate these so-called “home brew” tests but chooses not to do so.

24. Most genetic susceptibility tests currently sold in the US are “home brew” tests. One genetic test kit, marketed by Roche, has been approved by the FDA, to assess inherited risk of developing blood clots in the veins (venous thrombosis). 77 The link between Factor V Leiden mutations and venous thrombosis (its clinical validity) is relatively well established and this is now one of the most commonly performed genetic tests in US labs. 78 However, the test is controversial because its clinical utility is poor. It is not clear that patients with mutations should be treated any differently than other patients. 79

25. The FDA is still considering the SACGT’s recommendations. However, the SACGT has been disbanded and replaced by a new committee which includes a representative from Roche. 80 Roche has made an alternative proposal, which would involve weakening existing FDA oversight of genetic tests. 81, 82 The Roche proposal would limit FDA assessment of genetic test kits to the analytical validity of the genetic test:

no clinical data would then be required. Roche argues that its proposed approach: “... would be ideally suited for emerging markers, such as those likely to be used for personalised medicine, in which solid claims for predictive ability might take years to develop”.

UK POLICY AND LACK OF REGULATION

26. In Europe, there is no regulatory assessment of any clinical data relating to genetic tests. Legislation covers only analytical validity, not clinical validity or clinical utility. The relevant European legislation is the Medical Diagnostic Devices Directive (93/42/EEC, as amended) and the In Vitro Diagnostic Devices Directive (98/79/EC). The latter is implemented in the UK via the Medical Devices Regulations 2002 SI2002/618.

27. The Regulations deal principally with the award of a “CE” mark to “relevant” devices which meet the required standards as assessed by one of the “Notified Bodies” approved by the Medicines and Healthcare Products Regulatory Agency (MHRA). The Regulations apply to genetic test kits sold for use by clinical laboratories and as self-test kits, but there is some uncertainty about their application to commercial testing laboratories, and also about whether “lifestyle” genetic tests (which give health advice but may not refer specifically to diagnosis or prevention of disease) fall within their scope. The main limitation is that, at best, they cover only analytical validity (ie whether or not the correct DNA sequence is identified) and require no clinical data to be supplied regarding the predictive value or utility of any test.

28. The Human Genetics Commission (HGC) has considered the issue of the sale of genetic tests direct to the public. It published its report Genes Direct in April 2003. The report covers only direct-to-consumer sales, not sales via private medical practice or the NHS. The HGC concluded that “most genetic tests that provide predictive health information should not be offered as direct genetic tests” and that companies wishing to sell genetic tests should have to “convince a regulator that the test is suitable”. However it provided no credible mechanism for this process to take place. The HGC recommended that the MHRA should oversee the wider issues such as clinical validity, clinical utility and the advice given to customers. However, the HGC opposed giving the MHRA the necessary statutory powers to undertake this task. Because current assessments of analytical validity are undertaken by “Notified Bodies” the HGC has neither the necessary structure, remit or resources to assess the clinical validity or utility of genetic tests.

29. Last year’s White Paper on genetics in the NHS stated that the Government would consider the HGC’s conclusions and “respond in due course”. No Government response has yet been published.

30. Some mechanisms do exist to assess genetic tests within the NHS, however there are a number of significant limitations. The UK Genetic Testing Network (UKGTN) seeks to improve fair access and quality of testing for genetic disorders and will soon require all UK labs providing tests for the NHS to be accredited. However, its remit does not cover the analytical validity or utility of “genetic susceptibility” tests. If UKGTN’s remit were to be expanded to include common diseases, due consideration would need to be given for the need for transparency and for an open and inclusive process that can deal with the usually poor evidence base and limited predictive value of this type of test.

31. The National Institute for Clinical Excellence (NICE) recently published its guideline on “Familial Breast Cancer”. GeneWatch welcomed the NICE guideline, which rightly recognises that BRCA1 and BRCA2 genetic testing is only appropriate for a small proportion of women who are from high-risk families. This responsible approach contrasts favourably with the US situation where these tests have been widely advertised on television and in magazines. However, it is unlikely that NICE will be required to make a detailed clinical assessment of the evidence base for all genetic tests in the future.

32. The National Screening Committee (NSC) has assessed the evidence for a number of proposed genetic screening programmes. For example, genetic screening has in the past been advocated for an inherited risk of blood clots (Factor V Leiden) and the blood condition haemochromatosis, but studies have now shown that genetic screening for these conditions is not useful because of the low predictive value of these tests. The NSC has rightly concluded in both cases that there is no evidence to support a screening programme, even in relatives of patients. However, this assessment applies only to screening programmes and does not amount to an assessment of the use of this or other tests in clinical practice in the NHS.
33. The role of the NSC may be undermined in future by the proposal in the Government’s White Paper to consider the genetic screening of every baby at birth “to produce a comprehensive map of their key genetic markers, or even their entire genome”. This “barcoding babies” proposal is highly controversial and extremely unlikely to be of any benefit to health.

34. In addition to the lack of regulation, a number of broader policy issues need to be addressed. These include those listed below.

35. Cost-effectiveness of genetic “prediction and prevention”. With the whole population potentially “at risk” and eligible for preventive medication, the cost implications of “genetic susceptibility” testing have been described as “staggering”.

36. Pros and cons of alternative prevention strategies. There is some evidence that many people dislike preventive medication and prefer alternatives, such as lifestyle changes. Population-based preventive measures (such as banning tobacco advertising, increasing tobacco taxes or tackling smuggling) are generally more effective than individually targeted measures.

37. Impacts on public health. Genetic testing may wrongly imply that a only a minority of the population with “bad genes” need to stop smoking or eat a healthy diet. For example, testing smokers for “genetic susceptibility” to smoking-related diseases could mislead them about the risk of smoking and convince some people that they do not need to quit. This is why the tobacco industry has been heavily involved in funding academic research into “genetic susceptibility” to lung cancer, despite the fact that twin studies show there is no significant inherited component. Similarly, the current rise in obesity is not caused by an increase in genes for obesity, but by over-eating and lack of exercise. Although some rare genetic forms of extreme obesity are known, so far none of the dozens of genetic factors that have been linked to “normal” obesity have been confirmed.

38. Impacts on health inequalities. Health inequalities continue to play a significant role in life expectancy in the UK and elsewhere. An over-emphasis on genetic risk factors can divert resources from addressing the major social and economic determinants of ill health.

39. Advertising. In the US, direct-to-consumer advertising of prescription-only drugs focuses on fears of death or disability to sell preventive medication. Although such advertising is banned in Europe, there are no controls to prevent or restrict the advertising of genetic tests, which also provide a potential mechanism for the “marketing of fear”.

96 Rose, G (1985), Sick Individuals and Sick Populations, London.
IMPARTS ON RESEARCH

40. “[Public health] problems are exacerbated by the concentration of funding on biomedical research and the failure to confront and work with vested interests, which promote and sustain unhealthy behaviour patterns”. Robert Beaglehole, WHO, and co-authors, 2004.108

41. “The dearth of [public health] evidence is not unrelated to the lack of funding of public health intervention research—with funding from research organisations and the private sector heavily directed towards clinical, pharmaceutical, biological and genetic research—and the lack of a clear and coherent set of Government priorities for the public health research which does exist”. Derek Wanless, 2004.109

42. Public health research has been neglected despite its enormous importance in reducing the incidence of disease. The Health Development Agency found that not more than 0.4% of academic and research output is relevant to public health intervention research. During March 2000 and October 2000, no MRC-funded projects were relevant to public health topics.110

43. Important gaps in health research reflect biases within the health research economy which mean that research that is unlikely to be profitable or is of little scientific interest tends to be neglected.111 Health priorities and the pharmaceutical industry’s priorities are not necessarily the same. Public research funds tend to follow the research investment strategies set by industry, rather than the needs of the health service or public health. The Government’s new Science and Innovation Investment Framework makes a welcome commitment to ensuring that the publicly-funded research base responds to the needs of public services as well as the economy; and to improving public engagement in science and technology issues.112 However, in contrast to meeting the needs of business, the Framework does not identify ways in which the needs of public services should be identified and addressed.

44. Derek Wanless has warned that a possible consequence of the low status of public health research is that “pharmacological solutions might become the focus of primary prevention with considerable financial implications”. Wanless states: “Substantial investment, or reprioritisation, is necessary if this imbalance in research funding is to be addressed”.

CONCLUSIONS AND RECOMMENDATIONS

45. “Within the next 10 years I believe we will see: . . . Genetic testing, symptomatic and pre-symptomatic, for a variety of common diseases such as colon cancer and many mental illnesses. Within the next 20 years there will be in addition: Full integration of genetics, diagnostics and medicines in developed countries. Fully developed “predictive medicine”. Pre-symptomatic treatment in developed countries . . .”. Sir Richard Sykes, former Chairman, GlaxoSmithKline.113

46. The pharmaceutical industry is gaining increasing influence over the definition of “at risk” groups who are eligible for preventive medication. The larger the “at risk” population, the bigger the potential profits. Preventive medication is clearly beneficial in some circumstances. However, there has been a remarkable lack of public debate about the trend towards treating increasing numbers of healthy (“pre-symptomatic”) people (most of whom will never get the predicted illness) and the alternatives, such as more investment in public health.

47. The marketing of genetic tests for “predisposition” or “susceptibility” to common diseases is expected to expand significantly over the next few years. Many tests are likely to be accompanied by “individualised” advice to take medicines or supplements (“pills for the healthy ill”). There are currently no regulatory controls to prevent misleading marketing or advertising, either “direct to consumer” or via the medical profession. The sheer number of genetic variations and the large number of spurious published associations means that it is virtually impossible for most medical professionals to make their own assessments of the clinical validity or utility of genetic tests.

48. GeneWatch UK recommends that the Committee addresses the following questions in its cross-examination of potential witnesses:

   — What are the proposed marketing strategies of the pharmaceutical companies for genetic tests and associated health advice and medication?

   — What steps do the Department of Health and the MHRA plan to take to control and regulate genetic tests? Will an independent assessment will be made of the analytical validity, clinical validity, clinical utility and social consequences of each genetic test?

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— Will clinical data be required and will assessments be transparent and involve public consultation mechanisms?
— Will the Department of Health or the MHRA restrict the marketing of genetic tests, including direct-to-consumer sales and advertising?
— What role will the Government and regulators play in preventing people from being misled about their future health?

49. GeneWatch UK also recommends that the Committee gives urgent consideration to the need to:
— Establish an independent body to regulate genetic tests or give the MHRA the statutory powers to fulfill this role, including the powers to withdraw misleading tests from sale.
— Require this body to assess the clinical validity, clinical utility and social consequences of each genetic test via an inclusive, open and transparent process.
— Ban direct-to-consumer sales and advertising of genetic tests because medical involvement is necessary to properly interpret genetic test results.
— Recommend that a thorough assessment of the existing evidence on predictive genetic testing is made to inform future policy decisions (including numbers needed to screen and treat to prevent one case of disease, and potential costs).
— Redress the funding bias against public health research by recommending increased public and democratic involvement in setting medical research priorities.

Memorandum by Insulin Dependent Diabetes Trust (PI 30)

INTRODUCTION

The Insulin Dependent Diabetes Trust is a registered charity offering information and support to people with diabetes and their families. The Trust formed in 1994 as a direct result of the adverse effects experienced by a significant number of people to synthetic insulin made by genetic modification, introduced in 1982.

Synthetic GM “human” insulin was introduced into the market without long-term safety data and as shown in the Cochrane Review,114 without scientific proof of advantage over existing purified animal insulins with their long history of safety and efficacy. Nevertheless, the significantly more expensive synthetic GM insulin became first line treatment for insulin requiring diabetes and the adverse effects experienced by at least 10% of patients (30,000) have been largely ignored or disputed by both the medical profession and the regulatory authorities.

The vast majority of patients have not, and are not, given the treatment choice of animal or synthetic GM insulin which should be theirs by right and nor have they been provided with information about the risks and benefits of all insulin types so that their choice is informed.

It is difficult to find an explanation for this situation which may have an effect on the health of patients, on their ability to have an informed choice of treatment and on the overall cost of diabetes to the NHS. We believe that in part the explanation must be due to the influence of the pharmaceutical industry.

In their conclusion, the Cochrane reviewers114 expressed concerns that the story of the introduction of synthetic GM “human” insulin might be repeated by contemporary launching campaigns to introduce pharmaceutical and technological innovations that are not backed up by sufficient proof of their advantages and safety. It is for this reason that the Inquiry may wish to consider this “story” as an example of the influence of the pharmaceutical industry over health outcomes and health policies.

THE CONDUCT OF MEDICAL RESEARCH

We are concerned about the quality of industry sponsored research. The Cochrane Review of animal and synthetic GM “human” insulin showed no evidence of benefit and a lack of research to compare mortality and diabetic complication rates which are very important issues for people with diabetes wishing to make treatment choices. However, it also showed that the research that was carried out was “methodologically poor”. Yet despite this poor quality research, lack of evidence of benefit and no long-term safety data, synthetic “human” insulin became first line treatment with over 84% of patients transferred to it, too often for no clinical reason.

Our concerns were compounded in 2004, when a further Cochrane Review comparing the more recently developed insulin analogues with synthetic “human” insulin, also showed that the research was “methodologically poor”. As many as 81% of the studies were sponsored by the analogue insulin manufacturers themselves and the remaining studies had no sponsor stated. Insulin analogues are now taking over as first line treatment so no lessons have been learnt.

From this we have concluded that the quality of industry research has not improved and nor have the demands of the regulatory authorities become more vigilant in requiring better quality research.

From our experience, we have to raise the following points:

(a) the quality of studies carried out by the pharmaceutical companies wishing to market and promote a new drug;
(b) the lack of independent studies to inform decision making and the bias that may be introduced, especially publication bias that is likely to occur if the majority of the studies are carried out by industry who are unlikely to publish negative studies;
(c) the quality and efficiency of the marketing approval process whereby drugs are approved for use on the basis of largely poor quality research;
(d) the post marketing surveillance system which does not appear to require evidence from research carried out independently of the pharmaceutical industry; and
(e) in view of the lack of evidence of benefit of synthetic GM insulins, it is surprising that NICE has never evaluated insulin prescribing, assessed cost effectiveness and issued guidelines on insulin prescribing.

Our concerns are summarised by Edwin Gale, Professor of Diabetic Medicine in Bristol, writing about the marketing of troglitazone, a Type 2 diabetes drug which had to be withdrawn for safety reasons six weeks after gaining marketing approval in the UK:

“Big pharmaceutical companies see clinical studies as a means of satisfying the regulators and promoting sales, not of providing information. Published reports are not designed to help clinicians persuade us to use the new agent effectively: they are selected and slanted in such a way as to persuade us to use the new agent. Hence the huge amount of junk literature of irrelevant and badly reported studies with misleadingly optimistic titles. No one will ever know how many people it (troglitazone) killed, perhaps between 200–1,000, yet the culture of secrecy protected the industry from full and timely disclosures of the mounting evidence of risk.”

THE PROVISION OF DRUG INFORMATION AND PROMOTION

1. Advertising and promotion

While direct to consumer advertising of drugs (DTCA) is not allowed in the UK, we are concerned at the subtle ways in which industry circumvents this situation to reach the general public. We cite the following examples:

— Using the press and celebrities to indirectly advertise. For example, the press covered TV chef Anthony Worall Thompson cooking for the staff of Novo Nordisk to launch their new analogue insulin Levermir.

— Industry sponsorship of medical charities occurs frequently and while the agreement may be for sponsorship and not endorsement of their products, the perception of the charities’ membership may well be different and the products seen as acceptable and even preferable by the charity associating itself with the company. Examples include an advertisement in Readers Digest May 2002 Diabetes UK supported by Novo Nordisk and the Sexual Dysfunction Association advertising in the March/April edition of consumer magazine, Balance has with Pfizer prominently on an advertisement.

— The direct marketing to patients of insulin injection devices that can only be used with a particular company’s insulin brand indirectly advertises and promotes the use of that particular insulin. (Complaint referred to and upheld by the ABPI complaints body)

2. Influencing and advertising to physicians

We are concerned at the close links between industry and the medical profession. After failing to obtain recognition of the adverse effects to synthetic GM insulin, some patients attempted legal action against the manufacturer Novo and attracted media attention as a result of sudden unexplained deaths. Novo employed a public relations company to defend the safety profile of genetically modified human insulin. They recommended a reactive strategy of a issues/crisis management programme that spanned three years and

117Crawley Observer. 30.6.04 Top chef cooks at town firm.
involved media training of company headquarters staff and UK medical spokespeople. The litigation collapsed and the PR company’s description of the results was that Novo’s reputation remaining intact among patients, health professionals and media, that sales continued to grow and the medical professionals accepted that human insulin has an excellent safety profile. While such action may have been in the best interests of the company and the promotion of their insulin, it has to be noted that the insulin could not be defended on the grounds of scientific evidence. It also demonstrates that there was unacceptable influence used to influence the medical profession and patients in favour their product.

To further quote Professor Edwin Gale\textsuperscript{118} on the issue of troglitazone, but which could equally apply to synthetic GM insulins: “Not one physician stood up to say that the evidence base was inadequate and that no drug for diabetes is worth dying for . . . Our profession did nothing to protect the public. No one wants to remember troglitazone. It is treated as an unfortunate aberration of the system. It was not. It was a consequence of the system. Finding that out certainly changed my life.”

3. Selective advertising

Industry stops advertising the drugs they no longer wish to promote in favour new more expensive drugs. While this is understandable from the company’s perspective, it adversely affects patients being given an informed choice of treatment or alternatives if they experience adverse effects from the new product. For example animal insulins have not been advertised to physicians for many years and there is a perception amongst physicians and healthcare professionals that they are no longer available as a result of which they misinform patients.

4. Pharmaceutical company promotional materials

Promotional materials to medical and nursing staff affect prescribing habits. A survey\textsuperscript{119} examining the influences on 227 diabetes specialist nurses showed that regardless of their lack of legal status to prescribe and patients’ right to a an informed choice of treatment, 96% felt that they predominantly chose the insulin type. While this choice was primarily influenced by their personal experience of a given insulin type, the second influence was literature and pharmaceutical promotion of a particular insulin type and notably not scientific evidence of benefit.

5. Local pharmaceutical contracts

In some areas drug prescribing is influenced by prescriptive protocols and local pharmaceutical contracts for the exclusive use of a particular insulin brand. While this may reduce overall costs, it removes the right of choice from both patients and doctors.

6. The provision of drug information can be incomplete

We are concerned that in the UK patients and physicians are not provided with full information about risks and benefits and that this must in part be due to the actions of both industry and the regulatory authority in the UK.

Patients and physicians involved in diabetes care receive restricted information compared to the United States.

For example: Journals in the US make reference to the potential carcinogenic effects of insulin analogues in advertisements to both patients and professionals patients\textsuperscript{120} but in the UK published journals have less information and do not include the potential for carcinogenic effects.\textsuperscript{121, 122} The result is that treatment choices of both physicians and patients are less informed and there could be long-term health damage. The lack of this information cannot be explained as a matter of commercially sensitive information as all insulin analogues have this potential.

Professional and patient education

We do not believe that pharmaceutical companies should be involved in patient or professional education as they have a vested interest in promoting their own products or company name. In our experience, industry’s record to date in the provision of the required high quality evidence to inform treatment decisions leaves much to be desired as has been demonstrated by the issues raised throughout this document.

\textsuperscript{118}Professor Edwin Gale. Diabetes Digest; Vol 2 Number 4, 2003.
\textsuperscript{119}Practical Diabetes International; Sept 2003 Vol 20 No 7.
\textsuperscript{120}Diabetes Health, June 2004.
\textsuperscript{121}Practical Diabetes, July/August 2004.
\textsuperscript{122}Diabetic Medicine, July 2004.
If industry wish to be magnanimous and support patient education programmes, then a system should be devised whereby they can donate to a central fund that then allocates funding to specific education programmes not necessarily in a specific company’s particular section of the market.

WITNESSES: Mr Jim Thomson, Chief Executive, Depression Alliance, Mr Glynn McDonald, Head, Policy and Campaigns, MS Society, Dr Helen Wallace, Deputy Director, GeneWatch UK and Ms Jenny Hirst, Co-Chairman, Insulin-Dependent Diabetes Trust, examined.

Q363 Chairman: We express our thanks to the second group of witnesses for your co-operation with our inquiry. Could you each briefly introduce yourselves to the Committee?

Mr Thomson: I am Jim Thomson and I am Chief Executive of Depression Alliance. In the interests of declarations of interest, I should start by making one and that is that although I have been with Depression Alliance for three years, in my immediate previous incarnation I also came into contact with the pharmaceutical industry. I was Director of Fundraising and Marketing for the largest anti-vivisection organisation in this country. Part of my role there was to play an active part in undercover investigations into that industry and its suppliers.

Ms Hirst: I am Jenny Hirst. I am Co-Chairman of the Insulin-Dependent Diabetes Trust and as such I am a volunteer with no conflicts of interest.

Mr McDonald: I am Glynn McDonald, Head of Policy and Campaigns at the Multiple Sclerosis Society. I am also a trustee of the Disability Alliance. The Multiple Sclerosis Society provides the secretariat for the All-Party Parliamentary Group on MS.

Dr Wallace: I am Helen Wallace, Deputy Director of GeneWatch UK, which is a not-for-profit organisation whose aim is to ensure genetic technologies are used in the public interest. Our funding at the moment is largely charitable foundations.

Q364 Chairman: I think several of you were here for the earlier session. You will probably be aware of some of the written evidence we have received and you will have had a chance to look at that written evidence. You will be aware of something mentioned in the previous session, the suggestion that patient organisations are the ground troops of the pharmaceutical industry. I do not know whether any of you feel that that description applies to your organisation?

Mr McDonald: No.

Mr Thomson: My organisation has spoken to you several times in this and previous sessions. I do not recognise the organisation from anything I have heard, so, no.

Q365 Chairman: To be fair to you, may I give you the opportunity to respond to Paul Flynn’s comment. As you are aware, he was talking about the specific SSRIs issue and suggesting that there had been a courageous campaign pursued by MIND, who receive no contribution from any company, but silence from SANE and Depression Alliance who accept donations. Would you all respond to that? Is that an unfair criticism?

Mr Thomson: I would love to respond to that. He says in his memorandum that there is worldwide alarm because of the effects of SSRIs. There is not worldwide alarm but there is an investigation ongoing in this country, which I believe is going to report back soon. There was alarm caused by the so-called heroic (I think that was the word he used) coverage by Panorama. May I say for the record that I do not find it particularly heroic when a programme goes to air and the principal resource offered to people that it is going to alarm is a helpline that has been shut for a month. I spent all day the previous day before that programme on Panorama went out trying to get Panorama to put another resource up there and not to broadcast a number that had shut, but there we are. He further says that there has been silence from SANE and Depression Alliance who accept donations. As he well knows, there has not been silence from Depression Alliance. In fact I have written to Paul Flynn on four occasions and he has written back to me on a number of occasions. I gave up the correspondence when it became clear that the points I was making about the role of a charity as opposed to the role of the regulator were falling on deaf ears. It is not Depression Alliance’s role to campaign in that way. In fact, a political campaign of that type is strictly prohibited under charity law. We have not been silent.

Q366 Chairman: You would strongly refute his argument that your organisation has in some way been compromised on this issue?

Mr Thomson: On five separate occasions, one in person and four in writing, I have asked Mr Flynn to provide one piece of evidence of where my organisation has been in any way influenced by the pharmaceutical industry and he has been unable or unwilling to do so. In fact, for the purposes of the Committee, I have brought a copy of everything that we produce here and I repeat that our turnover is

Q367 Chairman: We discussed in the previous session the difficulties that some organisations have in functioning without support from the industry. Mr McDonald, what impact would it have on your organisation if the resourcing you receive from the industry was no longer available?

Mr McDonald: The effect would not be so much upon our organisation as upon people with MS. May I explain the way in which we receive money from the pharmaceutical industry? Our turnover is
about £28 million a year. We are involved with a scheme which receives donations from three manufacturers of disease-modifying drugs for people with MS where those companies each put in £350,000 over three years, which is matched by £350,000 from the MS Society. We act as an independent administrator for that money. It goes direct to the NHS to fund MS nurses. That arose out of the risk-sharing scheme for provision of disease-modifying drugs. The Department of Health wanted the industry to contribute towards development of infrastructure for delivering those drugs. At the request of the Association of British Neurologists and the UK MS Specialist Nurses Association, the Society stepped in and offered to act as an independent broker for that money to put a gap between individual companies and individual nurses. If that money was withdrawn, the effect would not be on our organisation because we do not actually benefit from that money directly; it would be on people with MS who would have less access to MS nurses.

Q368 Chairman: Do you think that more could be done to develop that kind of principle whereby there is not the direct connection between the patients' organisation and the company? Have you other ideas on how that might evolve?
Mr McDonald: I think what causes some discomfort, and there are numbers of specialist nurses around, is the idea that there might be direct link between those individual practitioners and individual companies. We were quite happy to act in the role which was requested of us, to act as an independent intermediary. If I can give you an example of how that works, we receive the money from the companies; there is then an advisory panel which decides where the money should go. There is a bidding process and a panel decides in which areas that money should be allocated. There is no drug company representation on that group, and so there is no suggestion that nurses are being put in areas where the drug companies see an opening for their pharmaceutical company. Equally, we would expect it if it was something being done entirely independently by a pharmaceutical company. We do not want publication of all results of research. We want publication of all results of research.

Q369 Dr Naysmith: This question is to Helen Wallace. The issues that GeneWatch is concerned with tend to be technical and have a different kind of applicability to what we have been talking about this morning, the side-effects and so on, and very laudable they are. Do you think they are of concern to any other patient organisations? Have any other organisations come in behind you on that?
Dr Wallace: Yes. We have done some work with the Consumers' Association, for example, on the direct marketing of genetic tests to members of the public. Our particular concern and the issue I have raised in my submission is about healthy people; it is not so much about patients but about disease mongering, if you like, to people who are told they are at risk of becoming ill in the future. One of our concerns is that there is not an organisation really that will represent the views of those people in government policy or in regulation and that we therefore need to consider new mechanisms to get the broader public involved in this debate.

Q370 Dr Naysmith: have you ever come across any opposition from patient organisations or consumer organisations to the kinds of thing that you are doing with the idea that you might be blocking progress for them or their supporters?
Dr Wallace: We have been criticised by one of the patient organisations, the Genetic Interest Group, yes, for work that we have done.

Q371 Dr Naysmith: What sort of group is that?
Dr Wallace: They represent groups of people with genetic disorders mainly, a collection of different charities. They do play a role in a lot of consultative meetings and they do take pharmaceutical industry funding.

Q372 Dr Naysmith: Do you think the pharmaceutical industry has any role to play in this kind of negative criticism?
Dr Wallace: I can certainly say that the industry is not happy with the kinds of things that we are advocating in terms of regulation of genetic tests. They have told me, of course, that they are opposed to increased regulation of genetic tests. I am not aware of any action that they have specifically taken to try to prevent us from raising these issues.

Q373 Dr Naysmith: Could I turn to Mr McDonald and mention something from your submission? The Society states: “Where the Society is in partnership with the industry, publication of results is always expected.” Why do you think that is so important?
Mr McDonald: That is purely for reasons of transparency. With any research which we as an organisation finance, and at the moment we have about £12 million of research commitments, it is an absolute that all the results of those trials or research projects are published. We would expect that to apply if we did any joint work with the pharmaceutical company. Equally, we would expect it if it was something being done entirely independently by a pharmaceutical company. We want publication of all results of research.

Q374 Dr Naysmith: Would you take that as far as terminating your partnership with a pharmaceutical company if it refused to publish something, and publish something in a timely way as well?
Mr McDonald: In practical terms, that would happen before any joint work took off if it became apparent that there were any kinds of restrictions on publication. Once we had set out an agreement, if it then appeared that there was a reluctance to publish, we would not continue with that arrangement.

Q375 Dr Naysmith: Turning to Jenny Hirst now, you have been quite critical in your submission and you suggest that the commercial influence of the industry and the culture of secrecy in UK drug regulation
leads to “largely poor quality research”. What do you mean by that? Can you justify that statement? Why is the research of poor quality?

**Ms Hirst:** Relying on the evidence of the Cochrane reviews, which we certainly class as independent and good quality reviews, for insulin, for instance, the genetically-produced insulin, at least 80% of the research was funded by the drug industry and both Cochrane reviews have shown that it was methodologically poor. It has not looked into the long-term effects of the insulin and obviously for people with diabetes that is key. It concerns us that this sort of research has been relied upon for the approval of drugs and for people to make decisions upon.

Q376 Dr Naysmith: Yet there have been some amazing advances in using different forms of insulin in diabetes compared with even 10 or 15 years ago.

**Ms Hirst:** Have they, in fact? There is really not the evidence to show that. What we have actually got now are genetically-produced insulins where there is no evidence to show that they are better or more reliable, but they are far more expensive. The cheaper animal insulins, which have a long history of safety, are not even advertised and doctors and diabetes specialist nurses tend to think that animal insulins are not available any more because they are not advertised, again an influence that the drug companies are having.

Q377 Dr Naysmith: Would you tend to say that these influences are such that drug regulation is failing to protect and promote patients’ health? Is that a statement you would agree with? If things were better regulated, it would be better for your patients?

**Ms Hirst:** Yes, and I am unhappy about the relationship between the drug companies, the MHRA, and the role that patients cannot play in all of that.

Q378 Dr Naysmith: How would you rectify the situation? What would you expect your organisation and other patients’ organisations to do to improve this? What would you be able to do?

**Ms Hirst:** What would we like to be able to do? We would like to be better represented within the regulatory authorities; to ensure that there is greater transparency; to be allowed, as it were, to look at the research properly; to have access to the yellow card scheme and the adverse reaction reports and be able to report. I realise that that is supposed to happen, that patients are going to be able to report, but I think patients need all of that information. They need to be able to access it if that is what they want.

Q379 Dr Taylor: May I go on along that tack just for a moment? You are content that there is no advantage of the genetically-produced insulin over the others and the only rationale for them is that they make more money for the drug firms? Am I overstating you?

**Ms Hirst:** You are over-stating me. A wide variety of insulins need to be available to suit all needs, but what we have now got is increasing pressure from the industry to make us believe that the genetically-produced ones are better for everybody, which I do not believe.

Q380 Dr Taylor: You would agree they are better for some people?

**Ms Hirst:** They are for some people, but not for everybody.

Q381 Dr Taylor: What is the incidence of the inability to take the genetically-produced insulins?

**Ms Hirst:** What we know is that 30,000 people, which is about 10% of people requiring insulin, are still using animal insulins but I come back to the evidence. The research has not been done so we do not know. There have never been long term comparative trials, for instance, to show the difference in people.

Q382 Dr Taylor: Has any work been done on why these 30,000 cannot take it?

**Ms Hirst:** No, and that is even worse, is it not?

**Dr Taylor:** Yes, it is.

Q383 Dr Naysmith: There is also the question that, if you are using pig insulin, you run the risk of organisms which might be there in the animal insulin which will not be there in the genetically produced stuff.

**Ms Hirst:** There is no evidence of that at all. Animal insulins are as highly purified as the so-called human insulins.

Q384 Dr Taylor: “Disease mongering” is a very good phrase because we seem to be in a position where patient awareness groups, illness awareness groups, are fostering the climate where one could get into a situation? What would you expect your organisation to do in that situation? What would you comment on this?

**Dr Wallace:** Our particular concern is that is likely to expand in future. There is a definite shift towards treating risk factors rather than diseases and clearly that can be beneficial in some circumstances, but what we are seeing with proposals to use genetic tests in particular to expand those risk groups is a system in which the tests themselves are not properly assessed. There is no mechanism to assess whether or not the test is useful or not. There is no mechanism to assess whether or not the test is useful to decide who should take a particular medicine. There is no mechanism to assess whether or not the test is useful.

Q385 Dr Naysmith: There is a definite shift towards treating risk factors rather than diseases and need to take medication. There is clearly an interest from the pharmaceutical industry in using these types of tests to expand the market for medication.
Q385 Dr Taylor: Your submission is a great help. You have told us the questions to ask potential witnesses. You have made a whole string of recommendations which I think we will certainly follow up. Does anyone else want to come in on the disease mongering?

Mr Thomson: This is something that is often mentioned in the context of depression. I would like to establish that context because, without harping back to Mr Flynn’s evidence, I had a conversation earlier on—Dr Naysmith was in the room at the time—about the incidence of depression and its status. Mr Flynn mentioned then that in his view there was a handful of people in this country suffering from serious depression and the rest were the worried well, created either by the pharmaceutical industry or by me and my evil organisation. I would like to correct that and to establish the context for the illness. Mr Flynn also mentioned that the WHO predicts that by 2020 depression will be the third biggest burden on health services worldwide. He misquoted because it is the second biggest by 2020. It is a serious, enduring mental illness and my organisation certainly does not need to disease monger to realise the job that we have on combating depression. I wanted to establish that, in the view of the Committee, there is a reason for me being here and that reason is that the condition exists.

Dr Naysmith: Mr Thomson referred to a meeting that took place in the House of Commons. I was indeed in the room but I think I had a position somewhere in between him and Mr Flynn, which is occasionally the case.

Q386 John Austin: On the depression issue and the role of your organisation and its relationship with the pharmaceutical industry, can I ask whether your Alliance accepts that there is some risk of dependence on SSR1 anti-depressants and whether you have alerted your membership to that risk or are you more fearful of dissuading people from taking medication?

Mr Thomson: Absolutely not. We support all therapies being available. We publicise information about all therapies fairly equally. Our most recent publication was on cognitive behavioural therapy which is a non-pharmaceutical intervention.

Q387 John Austin: Have you specifically issued warnings about the possible risk of dependency on SSRIs?

Mr Thomson: I have brought all our publications with us and one of them is called Depression and Antidepressants. That issue is specifically covered in that publication so it is quite wrong to say that we have not alerted people to that risk.

Q388 Dr Taylor: Certainly diabetes is one thing that you do need to be aware of and promote. Have you any comment?

Ms Hirst: Yes. People with diabetes are prime targets for drugs for cholesterol, obesity and blood pressure. I do have concerns that the easy way out is to take a pill, whereas to eat sensibly and exercise, the standard line, is vital. I do worry that pills will be pushed as an easy option. I think we all worry about that.

Mr McDonald: There are tight and specific diagnostic processes around MS. It is not something which is susceptible to disease mongering.

Q389 Dr Taylor: Can I go back to Helen Wallace? Obviously the genetic approach is going to be good for some patients. Could you tell us the sorts of groups that it is going to help?

Dr Wallace: There are examples already of genetic tests obviously in use in diagnosing genetic disorders, which is clearly beneficial, but there are familial forms of some common disorders, familial cancers, and the most obvious example is the BRCA test associated with risk of breast cancer, which can be useful to some women from high risk families who want to know their risk. That is why we are arguing for regulation. I am not saying that these tests are bad in general. There will be some circumstances where they are useful to some people but they are going to be much more questionable for use in the general population across the board.

Q390 Dr Naysmith: Because of misuse of inadequate information now, things are being marketed too soon. As someone who has studied genetics in the past, it seems to me it will be possible one day, I suspect, to identify individuals who will benefit from specific treatments and drugs. It may be multifactorial in lots of ways and polygenic as well but we will get there one day. Would you agree that it is possible that we will get there one day?

Dr Wallace: I would agree that the number of useful tests will expand. The jury is still out and in some ways it is not totally relevant to the decision about assessment but, as to what extent it will be useful, say, to scan the genomes of everybody in the population, I would argue that there is enough data already on some diseases to show that that is not going to be useful, for example, for trying to find out who is genetically susceptible to lung cancer. We know there is not a significant genetic component to that disease and I think the potential has been generally exaggerated. In terms of regulation, it is irrelevant what side of that debate you come down upon because you can still agree that the tests should be assessed.

Q391 John Austin: You suggest in your evidence that this focus on drug based and diagnostic approaches may lead to reduced funding for other health issues. Do you think there is a role for patient organisations to help the government and other agencies in putting the genuine contribution of the pharmaceutical industry into perspective in relation to other interventions like leading healthy lifestyles and other public health measures? Is there a danger that there may be a switch of resources away from public health measures?

Dr Wallace: Yes. If we look at the situation at the moment as analysed to some extent in the Wanless reports and in work by the Health Development Agency, a very tiny proportion of medical research
is spent on public health interventions so the Health Development Agency found something like 0.4% of research output in terms of publications was looking at those very important public health interventions which, as your Committee knows from its reports on obesity and tobacco, are the things that are going to make the difference. The reason for that is that funding tends to follow the priorities of the pharmaceutical industry and of patients that need treatment and not look at these other priorities in terms of prevention. I would argue it is not so much patient groups but perhaps new mechanisms to involve the broader public in decisions about research that would help to counter that. There has been a step towards that in the new science strategy that has been published, which does advocate public involvement, but it advocates public involvement very much at the end of the pipe to look at how new technologies might be applied and what the risks are. Many organisations, including ours, are arguing we should shift that involvement upstream to make decisions about research funding and what the priorities should be that involve the public as well as scientists.

**Q392 Dr Taylor:** You all represent a number of patient organisations. Have you ever felt that financial dependence on the pharmaceutical industry has produced adverse effects?

**Mr Thomson:** The interesting thing there is financial dependence. It implies a passivity in the relationship and we are in no way passive in our relations with—I hesitate to use the words “the pharmaceutical industry” because I have no encounters with the pharmaceutical industry. I have encounters with a number of companies who are in competition with one another. This idea that it is an industry that is seeking to influence me I do not recognise. The reality is that in an ideal world we would probably like to rely, which we do, on far less funding from companies within that industry but unfortunately my organisation exists in the real world, not the ideal one. Government’s core funding of our organisation does not pay the rent on the building, let alone any staff, the lights etc, and it is not a grand building. In fact, one year it was voted the ugliest building in London. The fact is that we do rely on that but we are very careful in those relationships and we do not accept money from the pharmaceutical industry; we aggressively seek it. There is a fundamental difference because that gives us an equality within the relationship.

**Q393 Dr Taylor:** Would you agree with the witness in the last session who said she was quite confident she was not influenced?

**Mr Thomson:** We have two separate policies on fund raising, one generally, which I will not bore you with because the core of it is repeated in the second one, which is regarding funding from the pharmaceutical industry.

**Q394 Chairman:** If you could leave that with us, that would be excellent.

**Mr Thomson:** What it points out is that as a charity we are bound by what we can and cannot accept. If there are no strings donations, there are only two very tight conditions under which we can turn down a donation. That pertains to other organisations as well in the charity sector. I do wonder why that question has never been asked of people who overtly broadcast the fact that they do not accept any industry funding because that leaves their trustees quite liable.

**Q395 Dr Taylor:** As a charity, you have to accept donations?

**Mr Thomson:** There are two conditions under which we can turn them down. Those conditions are if there are strings attached or if, by accepting it, we would prejudice other funding areas so if it would blacken the name of the organisation. Were we to only be accepting money from one company I would feel quite happy about turning it down on that basis because we would be seen to be favouring one over another. We do not do that and I am quite happy that we do not risk the charity’s name by accepting those moneys.

**Ms Hirst:** I would totally agree that a charity can grow, develop and reach more people if it accepts pharmaceutical industry money, but we are set up with a deliberate policy of not accepting pharmaceutical industry money. That is because we have problems with industry and its influence. We also felt that in order to represent the people we do represent we could only do that if we remained independent. You cannot criticise the pharmaceutical industry and specific drug companies and take their money at the same time, or I do not feel you can, and we as an organisation do not feel you can. The other point that we feel quite strongly about is that it is how the public see you which is that you can be as independent as you like and make judgments you like if you accept pharmaceutical industry money, but if you see adverts that are for a charity alongside a major drug company the general public on the whole think there is an link and you are giving approval to a product, not something any charity should do.

**Q396 Dr Taylor:** Where does the bulk of your funding come from?

**Ms Hirst:** People and legacies, the general public. I fully accept that that limits us and we never did set out to be Diabetes UK as employing 164 people. I still think that charities like us can do a worthwhile job without accepting pharmaceutical industry money.

**Mr Thomson:** By accepting or seeking, as we do, pharmaceutical industry funding we are then gagged and not able to launch campaigns that would adversely affect the income of those companies. Our most recent campaign does exactly that. We had a conference last week looking at the issues around parallel trade, counterfeiting and online pharmacies, all serious topics. One of the outcomes from that conference which was covered in The Telegraph on Monday this week is that we will be lobbying industry to look at tamper proof packaging of their
products and that will cost the pharmaceutical industry a great deal of money, running into several billion dollars no doubt because they will have to retool all their production facilities to produce their medicines in tamper proof packaging. That is an issue of patient safety and that is where we are coming from. The fact that it adversely affects companies that fund us is neither here nor there in terms of patient safety. That is what we need to do, so we do it. If we compromise our funding, so be it.

Q397 Dr Taylor: The MS Society is obviously a very large society that needs a lot of money. Do you think you have been influenced? Tell us about the beta interferon episode.

Mr McDonald: I would agree with Jenny that as a voluntary and membership organisation one of our most prized assets is our reputation for independence. In terms of the relationship with the pharmaceutical industry that rests on three things. The first is transparency. Our accounts set out where money has come from, from individual pharmaceutical companies. The second is our code of practice which is appended to our evidence and freely available. The third is in terms of accountability. We have 45,000 members, 30,000 of whom have MS which means that over a third of all people with MS in the UK are members of our society and we are accountable through an elected board to them. On the access to beta interferon campaign, that has to be set in the context of our overall activities: millions of pounds’ worth of our own research commitments, 350 branches across the UK, a helpline, £1 million of individual support grants every year. That is the context for our activities on beta interferon. It is probably worth me going back over some more figures which were not included in the evidence. In the two years to the decision on providing the disease modifying drugs the MS Society received a total of £18,000 from manufacturers of those drugs, set against an income in those two years of £53 million.

Q398 Dr Taylor: It is a very small amount.

Mr McDonald: It is a very small amount. There was a reference earlier to voluntary organisations being described as the ground troops of the pharmaceutical industry. We are not that but we would unashamedly be regarded as the ground troops for people with MS. It is on that basis that we undertook the campaign for access to beta interferon, to put those people on an equal footing with people with MS who lived in France or Germany, where those drugs are readily available.

Dr Wallace: The industry operates at a bigger level than the level that came up in the earlier questions in terms of selecting who gets money in the first place. We have talked about whether individuals are affected in terms of how they respond to industry pressure, but those organisations and those individuals are selected as part of an industry strategy to promote its own aims. For example, it is perfectly legitimate for patient charities to campaign for earlier access to new medicines and that is something which coincides with the pharmaceutical industry’s interests but that kind of work will inevitably get more funding from the industry than work that is against the pharmaceutical industry’s interests. I think that is really where the system gets distorted and where the priorities get distorted, rather than in individual caving into pressure or that kind of development.

Q399 Dr Taylor: You would agree tighter regulation is needed?

Dr Wallace: Yes.

Q400 Dr Naysmith: How can you achieve the balance that we were just talking about between informing sick people of, say, a new medicine and making sure that people know about it and get its benefits and inadvertently increasing the number of the worried well who are not depressed? I know people can feel unhappy and miserable periodically and not necessarily be clinically depressed. That was the basis of the conversation we were having in the House of Commons a few weeks back. How do you get the balance right?

Mr Thomson: I am not sure I understand the question.

Q401 Dr Naysmith: You have new products and people recognise that they are useful and functional and have a benefit to confer for people who suffer from a disease but at the same time you could convince quite a lot of people that they would be happier if they were on this product as well if you were not careful. Is it not a problem?

Mr Thomson: I suppose it could be. I fail to see how, in what we do, it would be an issue because what we are predominantly doing is raising awareness of a condition which I hope we all accept exists. I can see how raising awareness of that issue by definition is likely to convince people that they have it, but that is for the doctor’s diagnosis to confirm.

Q402 Dr Naysmith: None of these people are rushing along to see GPs with bits of paper off the web or what they have read in The Guardian or The Telegraph saying, “I think this applies to me. Can I have some of it?”

Mr Thomson: I hope they do because it is a vastly under-diagnosed condition. On average, it takes nine visits to the GP in this country to get a diagnosis of depression. There is a legitimate job there to raise awareness of the symptoms. There are 2.9 million people with a diagnosis of depression in this country. There are several million more who probably have that condition and have it undiagnosed, largely because of the stigma still surrounding the condition. In terms of what we produce, the link between new treatments is way further down the line and any new treatment, once it had been approved by regulators, would come into our literature and stand or fall alongside all the other treatments. We do not recommend any treatment at all.

Dr Wallace: One thing that would help would be to involve a wider constituency of people in decisions that are made. For example, NICE is starting to do that with its consultative panel. Then you would
involve not only the people who are at risk and get ill but also the people who have been told they are at risk and do not get ill, often a much larger number of people. You would change the interests, if you like, of the people informing the decisions.

Q403 John Austin: I want to come back to the regulatory process. Clearly it is in the interests of the pharmaceutical industry to get its new products on the market as quickly as possible. In that they may be aided and abetted by pressure from patient organisations and patient groups. Over the last decade, do you feel there is any evidence that patients have been put unnecessarily at risk by an acceleration of the process?

Ms Hirst: Yes. I do not think there is sufficient evidence to warrant the speedy acceptance of some of the drugs. I accept that with certain conditions getting a drug on the market as quickly as possible is essential but if we take the insulin issue there is no urgency about getting a new insulin onto the market, so why does it go through the regulatory process quite so fast without, in my view, the evidence being strong or being looked at sufficiently?

Mr McDonald: In terms of the disease-modification and finding therapies for multiple sclerosis, the issue is not so much the idea of risk with things being brought to the market quickly but of the possible long term benefits. This is why we have the 10 year monitoring scheme which is agreed with the Department of Health. There is an issue around drugs which are licensed on the basis of relatively short term evidence, if they are going to be used in some cases for decades. That 10 year monitoring study which is underway at the moment is intended to look at the longer term benefits in addition to the shorter term benefits which have been demonstrated for those drugs, but obviously it also has the benefit that, if there are risks attached to taking the drugs over a longer period than is usual in clinical trials, that will tend to emerge from that study as well.

Mr Thomson: There are two parts to the question. It is not something I have considered before but, off the cuff, the condition I represent is one which, if left untreated, will lead people to kill themselves. I would be in favour, as long as due diligence is observed, if there is a new treatment which is effective, and I would want to see it on the shelves as soon as possible and being in a GP’s armoury. Where Mr Flynn and I agree—those are not words I have ever said before—is that, once a drug is in use, I would like to see regular monitoring of it and we leave ourselves open to criticism as a society if we do not implement that, certainly in the first few years of its introduction. I agree with him also that the yellow card scheme in the vernacular is a bit of a pup. I think it is the regulatory body’s responsibility to ensure that ongoing monitoring carries on. The regulatory body is woefully under-resourced. How many people work in the MHRA to police this activity? 60 odd? It is preposterous.

Ms Hirst: I support that. If there was proper monitoring over the long term, a lot of concerns would go away. It is the fact that a drug comes onto the market and then what happens? We often talk about long term benefits, forgetting that all drugs have long term risks as well and I think that is key to having proper monitoring.

Q404 John Austin: Some drugs and therapies will react differently with different people. A drug which is very beneficial to one group of patients may cause severe harm to others. Does a patient organisation have to be particularly wary of the influence of the pharmaceutical industry in those circumstances and perhaps need to bring pressure on the pharmaceutical company to present that remedy as a therapy of last resort?

Mr Thomson: We are almost coming back to the issue of patient information leaflets. I would support a crystal mark or a far simpler method of producing patient information leaflets that a patient with that condition can read and understand. The litigious nature of the business is such that these patient information leaflets run to several pages. Companies are forced to produce them in that way. I have some Neurofen here which I had to take earlier on, having over indulged after the Arsenal match last night. The patient information leaflet in that would dissuade me from ever taking it and yet I take it routinely because I digest the information and take it with a pinch of salt. Antidepressants are powerful medicines and I would like to see sensible patient information on there that people understand and can use to exercise choice. It is simply not there at the moment.

Q405 Dr Taylor: I was so interested that you said you thought it was society’s responsibility to monitor for side effects after the explosive sales when drugs are released, because so far everybody has told us that they thought it was industry’s responsibility in that phase immediately after the preliminary release, when it is released to the wider population. How should society do this?

Mr Thomson: Society is probably wrong. I think it is your responsibility. Once a drug is approved for use and licensed, you may well want to involve industry because they are likely to have the data but, as we have heard, that data is often called into question so I think it is the regulatory body’s responsibility to ensure that ongoing monitoring carries on. The regulatory body is woefully under-resourced. How many people work in the MHRA to police this activity? 60 odd? It is preposterous.

Q406 Dr Taylor: Do you think there should be a limited release to begin with, limited prescribing? If it is a really major advance like the anti-TNF drugs, they are only allowed to be prescribed by NICE guidelines and by limited people, whereas something like Vioxx was released to everybody.

Ms Hirst: We did have at one time—I do not know whether it still exists—a post-marketing surveillance body which was independent. It seems to me that it would be unrealistic to expect drug companies to be
open, above board and totally transparent in monitoring their own products. I am sorry if I sound cynical but I really do think that is unrealistic. An independent body like that could monitor.

Chairman: Can I thank our witnesses for a very helpful session? We appreciate your cooperation with our inquiry. Thank you very much.

Memorandum submitted by Barry Haslam (PI 76)

PERSONAL HISTORY

I am an ex-Senior Accounting Technician, now aged 61 years. From 1976 to 1986 I was G P prescribed benzodiazepine drugs eg Librium, Valium, Ativan. At the peak of my iatrogenic addiction in 1985, I was ingesting 30 mgs of Ativan daily (the equivalent of 300mg of Valium) (Para 1)

As a direct result of the above “medical treatment”, the period from 1976 to 1986 is a complete blank. I have no memory of family life (I have two daughters), no memory whatsoever of my 10 year coma. (Para 2)

I am now permanently brain damaged (Ref 1) and suffer from brain atrophy, cognitive defects, hypothyroidism, neuro pathway pain—right side of body, semi-deaf in both ears, mood swings, violent headaches, narrow airways disease, chronic fatigue syndrome and aggression. (Para 3).

Despite the above, I love life. I love my wife, family and grandchildren. I have been re-born. (Para 4)

For the past 14 years I have been Chairman of a drug support group—Oldham (Tranx). I have counselled thousands of people both in this country and abroad over the last 18 years, all done voluntarily. I have written articles for the local and national press via interviews, (Ref 2) and on TV. I have written a report on benzodiazepine drugs for the European Commission (Ref 3), and presented the report in February 2004 to Mr David Byrne, The Health Commissioner in Brussels at the request of Euro MP Mr Chris Davies. (Para 5.)

In addition I have worked closely with Mr Phil Woolas MP Deputy Leader of The House of Commons, and Oldham PCT . . . (Ref 4.A,B,C.) The result being that from August 2004, Oldham will have a benzodiazepine drug withdrawal service for legal drug addiction. We have 5,200 long term benzodiazepine drug addicts in Oldham and need a large increase in funding from Government to fully address the problem. (Para 6)

1. Patient use and Past Consumer of Benzodiazepine Drugs

See Paragraphs 1–3.

2. Drug Innovation

Barbiturate drugs were replaced partly by the Benzodiazepines. The World Health Organisation (WHO) in 1964 said “that barbiturates and Benzodiazepines could have been expected to produce dependence of substantially the same kind”. (Para 8)

The medical profession welcomed the benzodiazepines as an alternative drug of treatment due to easy overdosing with barbiturates and alcohol resulting in death, (Para 9)

However, benzodiazepines cause suicidal ideation (Ref 5) and many deaths by suicidal poisoning as illustrated clearly by Home Office statistics (Ref 6) of 761 deaths between 1990–96 (Excluding 1994). (Para 10)

3. The Conduct of Medical Research

Medical research by the drug companies eg, Roche and Wyeth were in the main short term trials of a few weeks only. Yet both these drug companies actively promoted their products of Valium and Ativan for long-term treatment of patients. In essence, the patients became human guinea pigs (Ref 7 A./B) both in terms of length of enforced addiction and in excessive recommended dosage. (Para 11)

DUTY OF CARE! Was the producer (Wyeth) in possession of evidence about the performance of their drug which if it had been passed to the prescriber would have caused the prescriber to modify his prescribing behaviour? The dosage recommendations are clearly excessive for Ativan eg the equivalent of up to 40 mg of Valium daily dosage for mild anxiety. (Para 12)
In Canada and the USA 0.5 mg Tablets of Ativan were available unlike in the UK where only 1 mg and 2.5 mg tablets were available. Indeed such is the strength and short half life (leading to addiction) that Professor C Heather Ashton of Newcastle University advocated that 0.25 mg and 0.125 mg tablets be made available for Ativan tablets. (Para 13)

4. The Provision of Drug Information and Promotion

In April 1967, the ABPI published the 3rd edition of its Code of Practice for Member Firms. Both Roche and Wyeth were members. (Para 14)

They include:

“Methods of marketing must never be such as to bring discredit upon the pharmaceutical industry” (Para 15)

“Information furnished to the medical profession about a medical speciality product must be accurate and balance and must not be misleading either directly or by implication” (Para 16)

“Claims for the usefulness of a product must be based on an up to date evaluation of all the evidence and must reflect this evidence accurately and clearly” (Para 17)

“Communications on medical specialities must reflect an attitude of caution”. (Para 18)

“Observance of the Code is a requirement of membership” (Para 19)

Clearly Roche and Wyeth broke the Code of Practice and clearly did not give a damn for the recipients of their drugs. They rode roughshod over principles all the way to their bank. (Para 20)

On 5 March 1980, (Ref 8) Roche (Producers of Librium and Valium) wrote to all GP’s and consultant psychiatrists a “Dear Doctor” letter. Clearly, they were concerned about their market share and a fall in profits and went on the offensive. Dr John Marks (a former Roche employee), whose thinking was in line with the 1980 CRM (Ref 9) systematic review of the benzodiazepines decision, to fudge the report on benzodiazepines. “The number dependent on the benzodiazepines in the UK from 1960 to 1977 has been estimated to be 28 persons”. This lie was printed despite approximately 350 million prescriptions being issued during this period. Dr Marks, a few years later, revised his opinion on the true addictiveness of benzodiazepines. This came too late. The pattern was set and the damage done, all due to the criminally inept yellow card ADR System. (Para 21)

Watts 1972 cited in Parish 1973 pp 30–31 “The patient must be warned that tablets are only to help him over the crisis. Longer courses are very hazardous and likely to provide drug dependent patients. When their use was accepted in our area as a reasonable form of treatment, so many people were on tranquillisers that a partner suggested we might as well put Chlordiazepoxide (Librium) into the tap water” (Para 22)

Wyeth issued deliberately misleading advice re data sheets from 1974—1981–82. “It is advisable to avoid abrupt discontinuation of Ativan as some sleep disturbance MAY result. This applies especially when high doses have been given for prolonged periods.” (Para 23)

“The dependence potential of the benzodiazepines is low but this increases when high doses are used, especially when given over long periods.” (Para 24)

The date of the first warning in UK data sheets was 1984–85 yet the USA data sheet warned of possible physical and psychological dependence to Diazepam in 1971 and Canada 1973. (Para 25)

“Little is known regarding the efficacy of safety of benzodiazepines in long term use”. The date of the first warning in the UK Valium data sheets was 1984–85. (Para 26)

Roche admitted to the US Senate hearings in 1979 that it had NOT itself undertaken or sponsored any research into dependence. Roche has deliberately or otherwise altogether omitted any reference to the development of “tolerance in data sheets for Valium. This could be expected to cause prescribers to seriously underestimate the risks of dependence involved with this drug. (Para 27)

5. Regulatory Review of Drug Safety and Efficacy

The 1980 CRM’s (Committee on the Review of Medicines) “Systematic Review of the Benzodiazepines” states: “This report further observed that sleep laboratory studies show most hypnotics tend to lose their sleep-promoting properties within three to 14 days of continuous treatment. There was little convincing evidence that benzodiazepines were efficacious in the treatment of anxiety after four months continuous treatment” (Para 28)

I could take members of the Committee to Oldham people who have been benzo addicts for 20–40 years so much for efficacy! The only reason they are still taking their drugs is to keep withdrawal symptoms to a minimum (Para 29)

The UK Regulatory Authority MHPRA (Ref 10), just like its predecessor (MCA) is far too closely linked, almost incestuously so, to the drug industry. A completely new organisation, independent and with new Parliamentary powers and chaired by Mr Charles Medawar, needs to be set up as a matter of urgency. (Para 30)
6. **Product Evaluation Including Assessments of Value for Money.**

How do you start to put a monetary value on human suffering, loss of freedom, loss of employment, loss of memory, loss of family and loss of your soul to these mind altering drugs called benzodiazepines? (Para 31)

Home Office statistics from 1990–96 (Ref IOA) (excluding 1994) show that benzodiazepine drug deaths by poisoning equal 1,810 compared with 291 heroin deaths, and 43 deaths from cocaine. Surely Class “A” drugs are more dangerous—or so the Home Office Minister Mr David Blunkett (Ref 11 A/B) tells us! (Para 32)

If people taking tranquillisers did not drive (Ref 12), there would be an estimated 110 fewer road deaths and 1,600 fewer accidents each year. (Para 33)

The Economic and Social Costs of Mental illness, Policy Paper 3 produced by 13 the Sainsbury Centre for Mental Health (Ref 13), in June 2003 estimated that the economic and social costs of mental illness for England 2002–03 totals £77.4 billion. When you consider that benzodiazepine drugs mimic mental health symptoms in addiction and withdrawal modes, and these drugs produce paradoxical symptoms, eg insomnia, depression, rage, anxiety and aggression, just what part of that £77.4 billion cost is directly and indirectly caused by benzodiazepine drugs? (Para 34)

The BMJ, June 2004 stated that 10,000 deaths per year were from bad reactions to medication side effects at a cost of £466 million per year (Para 35)

Trust me I’m a Doctor, but at what cost to the nation! “The health of my 14 patient will be my first consideration”—(Ref 14) The Declaration of Geneva Hippocratic Oath, 1948. (Para 36)

I estimate that total deaths caused by benzodiazepine drugs from 1959 to 2004 are 18,450. (Para 37)

7. **Recommendations for Action by the Government or Others**

(a) An independent full Public Inquiry to be ordered by Government as a matter of urgency into mind altering benzodiazepine, SSRI and “Z” Drugs. (Para 38)

(b) To completely change the UK Regulatory Authority under its present set up (as per para 30) (Para 39)

(c) To sack the Health Minister Ms Rosie Winterton MP, and her special 15 advisers forthwith. Appoint Mr Phil Woolas MP (Ref 15) (Presently Deputy Leader of the House of Commons) in her place and ex-addicts of benzodiazepine drugs, who are the real experts, as special advisers. Mr Woolas would be a master of his brief on benzodiazepine drugs, unlike Ms Winterton who has not got a clue, and has relied far too heavily on her special advisers on benzodiazepine drug matters of importance. (Para 40)

(d) for government to adopt in its entirety the recommendations for European Best Practice Guidelines of Beat The Benzos Report (Ref 16) “A call for EU guidelines on the prescribing of benzodiazepines, Europe’s most harmful drugs” by Barry Haslam, 7 October, 2003 as a matter of urgency to the victims of these drugs. (Para 41)

(e) The Government to explain to the nation just why benzodiazepine drugs have been so freely and criminally prescribed in Britain when, under the 1991 Chemical Weapons Convention, drugs such as Valium or other calmatives would be outlawed. This protocol prohibits any chemical which can cause death, temporary incapacitation, or permanent harm. (Ref 17) (Para 42) So it’s in order for Valium to be considered by the MOD as a chemical weapon and banned under the Chemical Weapon Convention, BUT—GIVE IT TO UK PATIENTS—THAT’S ACCEPTABLE? (Para 43). Go tell Mr. Blair I have found his weapons of mass destruction, they are in Britain NOT Iraq, they have been hidden since 1959 and are called benzodiazepines. (Para 44)

(f) For Paul Boateng MP (Ref 18) (now Chief Secretary to the Treasury) to honour his pledge of 25 April, 1994 to Barry Haslam and loosen the treasury purse strings for services and compensation when he said “Clearly the aim of all involved in this sorry affair is the provision of justice to the victims of these drugs (Ativan)” (Para 45)

(g) Drug companies, Roche and Wyeth, producers of Valium and Ativan respectively, should be urgently investigated by the DTI and Serious Fraud Squad, into corporate fraud and corruption. (Para 46) Roche and Wyeth should also be the subject of Police Authority investigations into charges of Corporate Manslaughter and other criminal acts. (Para 47)
(h) With regard to legal benzodiazepine drug addiction (1.2 million UK addicts long term), the Department of Health’s record for services is a disgrace, abysmal and heads should roll. There is not one UK designated benzodiazepine drug withdrawal clinic at the present time. This despite 45 years of producing these neuro-poisoning chemicals and 45 years of super profits for the drug companies. (Para 48)

Professor C Heather Ashton of the University of Newcastle states (Ref 19)

“Facilities for benzodiazepine dependent people need to be developed. Detoxification units dealing with dependence on alcohol and illicit drugs, are not appropriate for prescribed benzodiazepine users who have unwittingly become dependent through no fault of their own. Such places usually withdraw the drugs too rapidly and apply rigid contract rules which are quite unsuitable for benzodiazepine patients struggling with withdrawal symptoms.

Much needed are clinics specialising in benzodiazepine withdrawal where clients can receive individualised, flexible, understanding and supportive counselling. At present only too few voluntary support groups (Ref 20) valiantly strive to fill this gap with minimal finances. Proper financing would also allow provision of residential accommodation where clients in need could go for short breaks in a supportive non-hospital atmosphere at crucial times during their withdrawal process”. (Para 49) Psychiatric units are completely the wrong environment and setting to withdraw legal drug addicts (iatrogenic). This procedure adds insult to injury. Benzodiazepine drug addiction is a chemical addiction problem, not a mental health issue. In my opinion, this has been deliberate Department of Health Policy to cover up the shortcomings of the Medical Profession and Government. (Para 50)

Legal benzodiazepine addicts get their “Fix” from their doctors. If this was not the case and they had to rob to feed their habit! Then the resulting chaos would make illegal heroin/cocaine addiction look like a “tea party”.” (Para 51.)

A no fault compensation scheme for benzodiazepine drug injured victims should be funded by the manufacturers. Such a scheme exists in New Zealand for all drug injuries. Failing this, Government could slap a “windfall tax” on the manufacturers themselves, thereby obtaining optimum funding for compensation and finally putting in the required withdrawal and support services the benzodiazepine legal drug addicts so desperately need and deserve. (Para 52).

REFERENCES
8 “Dear Doctor” letter from Roche, 5 March 1980.
17 The Observer 26 May, 2002.
INTRODUCTION

Ativan is a highly addictive and dangerous benzodiazepine drug. The more inaccurate and defective are the warnings issued with such a drug then the more dangerous that drug becomes.

The purpose of this submission is to draw the attention of the Health Select Committee to the benzodiazepine scandal and to its architects the pharmaceutical manufacturers John Wyeth and Hoffman La-Roche (Roche Products). These manufacturers introduced a successful mass benzo addiction trap into this country. The trap was based on the provision of inadequate and defective drug safety warnings to the public and prescribers.

Those defective warnings remained in place until 1988 by which time a benzodiazepine addict population had been created.

The benzodiazepine addiction problem and the commercial success of the drugs has continued ever since. A stream of unwary patients is initiated into drug addiction by trusted doctors. Meanwhile, the Government has tinkered in the face of an enormous problem, and is misled by a flawed system of advisers, experts and regulators.

My perception is that of a sufferer of a benzodiazepine drug injury. My experience and the theme of this submission is that the pharmaceutical manufacturers have introduced and openly operated a psychotropic drug scandal with impunity.

They are confident that their influence is so strong that they possess a complete defensive shield—in the legal system, in the regulatory system and the Government Departments and can never be held accountable for their actions.

Application of the Terms of Reference

The first section of the submission, parts 1 and 2, address “the provision of drug information and promotion”.

The second section, parts 3 and 4, address “regulatory review of drug safety and efficacy”.

I am willing to give oral evidence.

My name is Michael Behan and I took the benzodiazepine Ativan from 1981–87 on prescription from my GP in the belief that it was a medicine.

Upon discovering that Ativan was a drug, I withdrew to a zero dose over six months. I suffered side-effects whilst ingesting Ativan and severe withdrawal symptoms during the tapering period. Many of these symptoms have persisted ever since, particularly neurological and muscular-skeletal symptoms, and I now believe that they represent permanent damage.

I was a litigant in the benzodiazepine litigation against the benzodiazepine manufacturers John Wyeth (Ativan) and Roche Products (Valium, Librium, Mogadon). I became a litigant-in-person in the High Court and the Court of Appeal. I subsequently petitioned the House of Lords and the ECHR. In connection with this I privately researched all aspects of the benzodiazepine for three years in The British Library, the Royal Pharmaceutical Library and the WHO and UN Libraries. I contributed to the Panorama special “The Tranquilliser Trap”. I am assisting solicitors in Ireland in their Ativan litigation and acted as a researcher for the continuing Scottish Mogadon case against Roche Products. I was a founder and a Director of the charity “Beat the Benzos”.

In these phases, as involuntary benzodiazepine addict, litigant, researcher and campaigner, I have encountered the pharmaceutical industry in several different ways. I have divided these experiences into four parts and draw my own conclusions.
1. **Litigation**

   The domination of the legal process by the pharmaceutical companies.

2. **Research**

   The drug companies own documents show the UK benzodiazepine scandal to be the intended outcome of the manufacturers—mass addiction.

3. **Regulation**

   The processing and issuing of the Benzodiazepine Drug Licence by the CSM/MCA is suspect.

4. **Government**

   Control of psychotropic drugs has been infiltrated by regulators, advisers and self-styled experts who promote the agenda, the ideas and the products of drug manufacture to the detriment of public health.

**SECTION ONE THE PROVISION OF DRUG INFORMATION AND PROMOTION**

**Benzodiazepines**

The Problem

Benzodiazepines are highly addictive. Ativan is one of the most addictive drugs known to man, a three year withdrawal (tapering of dose to zero) from the prescribed dose may be necessary, 12 months withdrawal is common. Benzodiazepine addiction is a physical addiction. The nervous system becomes reliant on the benzodiazepine chemicals, which replace natural chemicals in the nervous system. If the benzo chemicals are removed or reduced the nervous system cannot operate properly. The natural chemicals may regenerate slowly or not at all. Furthermore, benzodiazepines are poisonous. They insidiously poison the body and its organs.

While the dangers of benzodiazepines are enormous, their efficacy is limited. They do not cure anything. Benzodiazepines can only suppress the symptoms of anxiety and only for a short period. The Data Sheet recommendation is for a prescribing period of 2–4 weeks in total.

As the efficacy of benzodiazepines decrease, addiction can already be setting in. Also, paradoxical reactions can start to appear, the drug produces the conditions it attempts to treat such as anxiety, insomnia and anger. These are the first stages of the Tranquilliser Trap.

The current number of benzo addicts in the UK is estimated at one and a half million although no official figures exist. Many more people are ingesting benzos and are on their way to addiction. Many other ex-addicts have withdrawn but remain damaged. There is no treatment for benzo damage. Post-benzo sufferers are often left to struggle alone, stigmatised and excluded by the Health Service that made them ill.

1. **Benzo Litigation**

   Benzo victims are often told by Government letter writers at the Home Office, Department of Health, MHRA, etc to seek compensation through the courts for any injury they have suffered. In fact, this is an impossibility. The pharmaceutical companies dominate the courts and the legal process with their power and money.

   I was a litigant in the benzo litigation against the manufacturers John Wyeth and Brother and Roche Products. The litigation ran from 1986 to 1996 with a peak of 17,000 complaints. The plaintiffs alleged that the manufacturers were negligent in failing to give adequate warnings of the dangers associated with their products. The manufacturer delayed and complicated the proceedings to the point that the Legal Aid Board could no longer meet the expense of the litigation. Each side spent more than £35 million yet not one minute of court time was spent on the merits of the case; the time and the money was spent on technical motions and procedural wranglings. Under pressure from the defendants the LAB withdrew funding from the litigation.

   The defendants then successfully applied to the court for a strike out on the basis that the Plaintiffs would be unable to continue without funding and legal representation. The Legal Aid Board was disbanded in the wake of the benzo litigation and re-constituted as the Legal Services Commission with a new set of regulations designed to exclude the possibility of any similar litigation occurring again.

   The failure of the benzo litigation gave the pharmaceutical companies the green light. They had demonstrated they could not be brought to trial and that the evidence against them would not see the light of day. In reality, the consumer has no protection in law against pharmaceutical companies or rogue drugs.
Powerful commercial corporations should not be immune to liability. Such potential liability acts as an incitement to developers of new products to ensure that their product is safe, this is a valuable counterbalance to the temptation to make fast profits.

**Recommendation**

My recommendation here is a no fault drug compensation scheme for sufferers of drug injuries.

Secondly, the Government should set up an independent prosecuting authority to take on the pharmaceutical companies when necessary. It is unrealistic to expect a firm of solicitors to be able to take on the might of a multi-national. When convicted the pharmaceutical companies should pay proportionate fines in order to provide a deterrent.

2. **Documents**

The benzodiazepine manufacturers have pretended that the litigation collapsed because the drugs were safe and the case was weak.

In fact, the evidence of negligence against the manufacturers was overwhelming and their defence was a fraud that never had to be tested. The benzodiazepine scandal is the outcome of a deliberate strategy by the manufacturers. Mass benzodiazepine addiction is not something that just happened, it was the intended result of a world-wide benzo strategy devised by Wyeth and Roche.

Wyeth and Roche released co-ordinated information on benzo’s in each country according to the strength and vigilance of the regulatory authorities in that country. Ativan first appeared in the UK in 1972 with warnings well below the level of information in the possession of Wyeth. The minimal warnings and the exaggerated indications for Ativan increased prescribing and therefore sales and profits for Ativan. The addictiveness of Ativan works a ratchet effect. Any unwary patient who is prescribed Ativan for a month or more can become an addict for decades and thus a steady customer for Wyeth drugs.

Wyeth deliberately issued defective information on Ativan in their UK Data Sheets. This defectiveness can be shown by collating and cross-referencing Wyeth’s own documents:

(i) clinical trials;
(ii) worldwide Wyeth Benzo Data Sheets;
(iii) Wyeth benzo adverts in USA medical journals;
(iv) information provided by Thomas Harry, Wyeth Medical Director and Whistleblower.

(i) **Ativan Clinical Trials**

The Wyeth Ativan Clinical Trials were poor quality and short term; none provide reliable evidence that Ativan is safe, several of the Ativan trials report what were to become the classic Ativan problems.

The earliest Ativan trial sponsored by Wyeth was conducted in a US prison in 1970 and is by HW Elliot (1). This was a one-tablet only, one day trial. Subjects are reported with:

- EEG modification to alpha rhythms;
- “minimal” changes in cardiovascular reflexes;
- being unable to repond to their spoken names;
- unable to walk;
- instantly falling asleep;
- amnesia;
- post treatment depression of CO2 response;
- unable to complete a test because of fear;
- EEG—loss of alpha rhythm, burst of spindles; and cardiovascular problems.

Cross-referencing this trial with the 1974 UK Ativan Data Sheet (2) shows Wyeth withheld vital safety information from the Data Sheet. Omissions from a Data Sheet are a simple but effective way of sabotaging the mechanism for drug safety put in place by the 1968 Medicine Act.

De Buck 1972 trial “Clinical Experience with Lorazepam” (3) is also Wyeth sponsored. This trial reported epileptic seizures in two patients (of 30) when withdrawing from Ativan after three weeks ingestion. Epileptic seizures are an extreme withdrawal symptom and were clear warnings of the highly addictive nature of Ativan.

The appropriate warning for a specific Adverse Drug Reaction (epileptic seizure) that the De Buck trial should generate does not appear in the UK Ativan Data Sheet. Neither does an appropriate high level addiction warning.
The deeper question consequently arises—did Wyeth provide the CMS/MCA with all available safety information when they applied for an Ativan Product Licence? My answer is most definitely not but, as long as Wyeth’s Ativan Drug Licence Application remains secret, Wyeth will deny any wrong doing. A DLA application is the country’s most secret document, and it remains secret in perpetuity.

These discrepancies—between the trial results and the Data Sheets—are not administrative details or secretarial problems. The withheld trial results correspond closely to the injuries suffered ever since by unwary ingesters of Ativan.

The discrepancies are at the heart of a multi-million pound drug swindle perpetrated in the UK by Wyeth. It is a swindle that has condemned 1000’s in the UK to the misery of Ativan addiction and the slow incurable poisoning of their bodies organs and nervous systems.

Up until now Wyeth have escaped responsibility by hiding behind the shield of a supposedly all powerful “right” to commercial confidentiality.

Recommendation (during enquiry)

I strongly recommend that the Health Select Committee root out the truth by subpoena of the DLA for Ativan, in particular the Summary Basis of Approval (SBA) which is the section dealing with safety as opposed to commercial information.

(ii) Wyeth’s Benzodiazepine Adverts

Oxazepam (Serax), Wyeth’s first benzo, was launched in the USA in 1965. All benzodiazepines are analogues of one another. This means they are not just similar to one another but closely similar. Any warning or information provided for Oxazepam (Serax) is applicable to Ativan. Particularly when Ativan is 20 times the strength of Oxazepam (Serax).

Oxazepam (Serax) prescribing information (FDA approved) is provided in a Wyeth advert in Psychosomatics September 1965 (4), one of a series of advertisements that appeared in USA Medical Journals. The nightmare list of side-effects associated with this low-strength earlier product can be compared with the innocuous warnings (CSM/MCA approved!) provided by the UK Ativan Data Sheet nine years later in 1974.

Similarly, when Ativan itself was launched in the USA in 1978 it was done so under a different higher-level set of warnings (JAMA 1978) (5).

Ativan is described in the USA as a potent and dangerous compound. Ativan is described in the UK as clean, mild and efficient. US consumers and prescribers have proper addiction warnings, pregnancy and lactation warnings, liver function warnings, etc. Generally, it can take 10 or 15 years for safety warnings to travel from the USA to the UK Data Sheet.

(iii) Wyeth’s Ativan Data Sheets

The origin of drug information in the UK is the Data Sheet. It is a legal document required by the Medicine Act 1968. Wyeth consistently issue a lower level of information on Ativan in the UK Data Sheet, lower than the information provided in the equivalent year Data Sheet for Ativan in the USA, Canada or Australia. I have provided copies of 1978 Ativan Data Sheets (6) for the Committee to examine—and I have complete Ativan Data Sheets collection for those countries.

Recommendation (during enquiry)

Senior Directors of John Wyeth should be summoned before the HSC to explain these safety information discrepancies and to take responsibility for the results of these discrepancies.

Recommendation (during enquiry)

Unpublished clinical trials for Oxazepam (Serax) and Ativan should be subpoenaed from John Wyeth.

(iv) Whistleblower Statements

During the benzodiazepine litigation, two ex-Wyeth Medical Directors made detailed and incriminating statements against their former employers. They are Dipak Malhotra and Thomas Harry (7) who was responsible for the development of Ativan. Thomas Harry states clearly and consistently that Wyeth were fully aware of the problems with Ativan and that for commercial reasons they did not warn doctors or patients.

These statements were taken by my former solicitor Graham Ross. So far this document has been swept under the carpet and ignored by Government and regulators.
Recommendation (during enquiry)

That Graham Ross (8) and the original Thomas Harry statements and authentication be subpoenaed by the HSC.

3. The Ativan Licence

My submission is that Wyeth did not tell the truth when they made their Ativan Licence Application. Furthermore, the licensing procedure that was applied to the benzodiazepines, and in particular to Ativan, was not the vigorous assessment procedure that has been claimed by the CSM/MCA. Far from it. Most of the benzodiazepines—Valium, Librium, Mogadon—were on the market before the Medicine Act of 1968. These drugs were issued “Licences of Right”. The Licences of Right were a registration procedure and involved no assessment of safety or efficacy. Assessment was deferred to a future review by the CRM. Significantly, those reviews did not occur until 1983/84. By then the damage was done, the huge benzo addict population had been created and still exists to this day.

The first application for a full Benzo Product Licence was for Ativan in 1972. The relevant safety requirement was that the drug should be no less safe than other drugs indicated for the same condition (ie, the existing benzos). This was not an objective standard, it was a comparative standard and it was a comparison to Roche’s benzodiazepine products that had not yet been assessed for safety themselves. As Ativan had secured a full Product Licence it was not even subject to the future CRM review. Can it be said that Ativan was ever fully assessed for safety by the licensing authority?

The senior members of the licensing authority have what has been quaintly described as a conflict of interest—they receive large amounts of money from the drug companies they regulate. In 1996–97, for example, 10 members of the CSM/MCA declared financial links with John Wyeth and Brother.

Wyeth is a subsidiary of American Home Products. In the 1970’s the USA Securities Exchange Commission offered US corporations an amnesty from prosecution in return for disclosure of corrupt payments. American Home products (9) declared from 1971–75 corrupt payments of $3.4 million in 41 different countries by their subsidiaries and divisions.

AHP’s auditors, Arthur Andersen, submitted form 8K in 1975:

“These payments were intended to further business with government agencies or to obtain action on necessary government clearances”. (Item 13).

“Non-commission type payments were made in a number of countries to foreign government employees primarily in connection with the granting of required government approvals”. (P4).

Recommendation (during enquiry)

That Wyeth and the MHRA should be questioned on all aspects of the Ativan Licence application, its truthfulness and the process applied. That Wyeth be questioned on involvement in corrupt payments in the UK.

Recommendations (for actions)

That the MHRA be disbanded. That it should be replaced with an independent body. That clinical trials should be supervised by an independent body. That there should be no retainers from the pharmaceutical industry to regulators. There should be significant lay membership and an end to secrecy.

Wyeth have plenty of form when it comes to avoiding regulatory control and manipulating information on safety and efficacy. Dr Rheinstein of the FDA in the United States wrote a regulatory letter to Wyeth-Ayerst in 1989 telling them they had an “intolerable record of compliance with the law” (on drug promotion). (10).

Wyeth-Ayerst had “in case after case . . . disseminated promontional materials that are clearly false and misleading” indicating a “general and wilful disregard for legal and regulatory limitations upon drug promotion”.

Dr Rheinstein told Wyeth-Ayerst that a 1989 advert for the heart drug Cordarone was “clearly intended to minimise the hazards of the drug and emphasise the drugs efficacy”.

Dr Rheinstein’s Office of Drug Standards issued 18 notices of violation to Wyeth-Ayerst concerning drug advertising and labelling in 1988–89.

In 1999, AHP had to pay $4.85 billion compensation in the “Fen-Phen” litigation to 5.8 million ex-users who suffered heart-valve damage. The drug was marketed through Wyeth-Ayerst, it was linked to serious lung disease and leaky heart valves. Wyeth-Ayerst were found to have concealed this information. Settlements included medical care and monitoring for the victims, paid for by the manufacturers. (11)

Also in 1999, Wyeth Laboratories were convicted by the Supreme Court of New Jersey of failing to warn adequately of side-effects associated with the contraceptive device Norplant.
4. **Government Control of Psychotropic Drugs**

In 1997, the campaign group “Beat the Benzos” was formed by Barry Haslam, Phil Woolas MP, myself and others. We hoped that if we brought the benzo problem to the attention of the Government that appropriate action would be taken across the various government departments. There has been no action. In my opinion the strength and influence of pharmaceutical companies extends into Government.

Ministers come to the complex subject matter of psychotropic drugs as lay people and move on regularly, this produces an over-reliance on advisers who are presumed by Government to be unbiased. There is no balance or brake on these advisers. The Government takes advice on the psychotropic drug problem from people who help to sustain the problem, namely the psychiatric profession, specialised prescribers of drugs. The psychiatric profession has both feet firmly in the camp of the manufacturer with whom they share the common desire to extend the use of psychotropic drugs.

The advisers on psychotropic drugs claim possession of “The Science” and that thereby Ministers can believe that their policies are underwritten by science. “The Science” they possess is actually information emerging from the pharmaceutical companies and the clinical trial system—also known as “The Evidence”. The psychiatrists claim the exclusive ability to understand and interpret this information and they insist that it is true. What anyone else says, for example the patient or ex-patient, is excluded as “anecdotal evidence” as opposed to their “scientific evidence”. The government experts define their own expertise. They create a monopoly for their own extreme viewpoint. The policy outcome is a non-policy of minimum regulation and inaction, the ideal environment for drug addiction to take root and spread.

In our case the “Beat the Benzos” group attended a meeting in April 2003 with the Home Office Minister Bob Ainsworth MP. We asked Bob Ainsworth to consider re-scheduling and re-classifying benzodiazepines and he invited us to prepare a submission (12) to the Home Office Advisory Council on the Misuse of Drugs (ACMD), which we did. The submission was referred to the Technical Committee of the ACMD which is chaired by Professor David Nutt, a key Government adviser and regulator. The ACMD was set up by and derives its power from the Misuse of Drugs Act 1971. The Act states (Section 2) that class and schedule are to be determined by the drugs level of misuse and the harmful effects to the public thereby caused.

We submitted that on any relevant criteria benzodiazepines are one of the most harmful of drugs and are wrongly classified and scheduled. Example of criteria that are used in the submission are:

(a) the number of benzo related deaths;
(b) the number of people affected 1.5 million +;
(c) the magnitude of addiction;
(d) the duration of addiction;
(e) the social cost of benzo addiction; and
(f) the suffering of addicts and its immorality.

It emerged that in fact the original scheduling (1986) and classifying of the benzos was not based on a risk assessment. The concern in 1986 was to conform with international legal obligations created by a UN Convention.

The ACMD has not so far carried out, in fact, a risk or safety assessment of the benzos. We received a refusal letter from the Home Office in April 2004.(13). The ACMD do not respond to any of the evidence arguments or suggestions put forward in the submission. The ACMD make an assertion that re-classifying and/or re-scheduling benzodiazepines would be likely to be ineffective in curtailing their misuse but gave no reason.

Professor Nutt has financial links with John Wyeth. In the 2001 CSM Declaration of Interest, Nutt declares an “Honoria” and a non-personal grant from benzo manufacturers John Wyeth. He did not declare that interest in his dealings with us.

Professor Nutt chaired a recent CSM/MCA/MHRA review on SSRI’s which found them to be safe. He was later revealed by the Guardian to have financial links to Glaxo Smith Kline, as had two out of three of the other members of the review committee.

Professor Nutt sets out his own position on benzodiazepines in his paper “The Psychopharmacology of Anxiety”. (14). Professor Nutt recommends prescribing practices that directly contradict:

1. CSM advice and addiction warning.
3. The Department of Health stated position.

Professor Nutt advocates treatment for 6–10 weeks, six months, one to two years and life-long use—“some patients appear to require maintenance benzodiazepines”.

In this medical paper, Nutt also takes the trouble to present the manufacturers account of the litigation. Nutt wrongly claims that “it was decided by the presiding judge that the case for benzodiazepine dependence causing real damage has not been made”.

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At the original meeting with Bob Ainsworth and in a letter dated 11 July 2003 from the ACMD, it was
directed to us that our submission would be assessed by a point scoring system that would measure levels
of harm. Professor Nutt did not apply that system. I have requested the minutes of the ACMD Technical
Committee meeting of 2 October 2003 but have been refused for “reasons of confidentiality”.

The processing of our ACMD submission on benzos followed the pattern of benzo drug regulation set
by the CSM/MCA. The case against drugging is not addressed, it is ignored and avoided by bureaucratic
manoeuvering. There is extreme secrecy and no engagement between the regulator and consumer. The
complete absence of a safety assessment is revealed. Power and control is concentrated in the hands of
Professor Nutt, an all powerful benzo-enthusiast who claims expertise and is in the pay of the
manufacturers.

Recommendation for enquiry

To examine Professor Nutt. That the scheduling and classification of benzos be properly assessed by an
independent and open process.

Beat the Benzos final attempt to change the benzodiazepine status quo was a meeting with Health Minister
Rosie Winterton in 2003. We outlined our concerns and suggested solutions. Rosie Winterton asked for
more information and told her advisers she had not been kept informed or had been wrongly informed of
the situation. However, the arrangement was unexpectedly ended in January 2004 when we received a letter
that shut the door in our face and re-affirmed Department of Health policy. That policy is:

(a) To exclude any consideration of benzo damaged people for aftercare by setting the parameter “the
main focus is to prevent addiction in the first place”.
(b) To provide no research into and no treatment for benzodiazepine injuries.
(c) To ignore the problem, there is no quantification, no figures, no statistics.
(d) To claim withdrawal facilities are available when they are not.
(e) To blame over-prescribing on GP’s and psychiatrists as if these employees are nothing to do with
the Department of Health. The Department of Health makes no effort to enforce benzo prescribing guidelines. As long as guidelines are not enforced prescribers will continue to over-
scribe in dosage, in time and by polypharmacy.
(f) To pretend the benzo problem is a mental health problem—it is not, it is a problem of physical
drug addiction and drug toxicology.

Chief spokesperson and letter writer for the Department of Health, and this policy, for the last several
years has been Dr Anna Higgit who styles herself as Senior Policy Adviser on benzodiazepines. It is a policy
of denial and inaction which provides the perfect environment for psychotropic drug addiction to flourish.

The pharmaceutical industry have created the benzodiazepine problem and have left it in the lap of the
Department of Health. The Department of Health will not tackle the problem because:

(a) The Department of Health has been compromised by years of denial and cover-up.
(b) Tackling the benzo problem involves confronting the pharmaceutical industry which they will
not do.
(c) The apparent cost of tackling the benzo problem appears massive—benzo withdrawal facilities,
medical treatment and compensation payments—but is not massive when calculated against the
social cost of benzo-addiction.

Melanie Johnson MP, Minister of Health has registered a financial contribution of £20,000 from Hoffman
La-Roche. (15).

Recommendations for Action

1. Establishment of benzo withdrawal facilities nationwide including clinics, self-help groups and a
help line.
2. Prescribing guidelines to be enforced.
3. Compensation for benzodiazepine injuries with no-fault compensation scheme.
4. Prosecution of negligent manufacturers by a government agency.
5. Medical research into benzo injuries and after-care for victims—alternative, non-drug treatment.
6. An independent and open licensing procedure.
7. Education of the medical profession on psychotropic drugs.
8. New government experts, adviser and regulations.
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Michael Behan
Beat the Benzos

30 August 2004
Memorandum by Professor Patrick Vallance (PI 106)

PERSONAL STATEMENT

I am Professor of Clinical Pharmacology and Head of Department of Medicine at University College London. The Department is one of the largest and most research active in the UK, and has responsibility for teaching medical students. The research funding income of the Department is in excess of £13 million per annum with about 2% coming from industry. My personal research group is funded largely by grants from the British Heart Foundation, Wellcome Trust and MRC. Clinically I am involved in general medical practice, cardiovascular medicine and clinical pharmacology. Until recently I was chair of UCLH Trust Use of Medicines Committee, the body that determines prescribing policy and the drug list for the Hospital. I have published on evidence-based medicine and the need for rational policy in relation to drug use, and was a member of the editorial board of Drug and Therapeutics Bulletin (Consumers Association) until a few months ago. Earlier this year I joined the main Research Advisory Board of GSK and am the only person from the UK on this board. I am an Honorary Officer (Registrar) of the Academy of Medical Sciences. I was asked to submit this memorandum in an individual capacity and I am not representing any of the above institutions.

1. NEW DRUG TREATMENTS HAVE RADICALLY IMPROVED HEALTH CARE

1.1 Despite concerns about the rate and extent of innovation within the pharmaceutical industry, it is clear that new drugs have been introduced that have had a major impact on the health of patients and the organisation and delivery of health care. Examples include the introduction of streptokinase and other “clot busters” for the treatment of heart attack (25% reduction in death rate), ACE inhibitors for heart failure (the first treatment to produce a major effect on survival), statins to lower cholesterol (effective in everyone but most useful in those at highest risk), anti-TNF antibody treatment for rheumatoid arthritis (altering the outlook in a particular unpleasant disease), treatments for HIV (that have turned a death sentence disease into a chronic condition), several new drugs for epilepsy, and drugs for impotence. Industry also explores therapeutic areas that are sometimes ignored by the medical profession.

1.2 In each of these examples the introduction of new effective treatments has also led to changes in the way clinical services are organised and delivered within the NHS. For example, the treatment of heart attack used to involve a three week stay in hospital with little effective intervention and the administration of toxic ineffective agents (lignocaine), but now the stay is around five days and the outcome is considerably improved. Clinical services for impotence were virtually non-existent until the development of sildenafil (Viagra).

1.3 It is also worth noting that the introduction of new drugs leads to academically-driven experimentation in new indications. Examples include current studies exploring the potential of statins to reduce inflammation and improve outcome in autoimmune conditions, the use of sildenafil for treating pulmonary hypertension, or the use of rituximab (a B cell depletion therapy designed for treatment of leukaemia) for rheumatoid arthritis.

1.4 The contribution of industry to health care can also been seen in the generation of effective vaccines. Very recent examples include vaccines against viruses that cause cervical cancers and progress in developing vaccines for malaria.

Conclusion

Effective interaction between academia and industry has led to innovation, improvement in health outcomes and development of health services. Some of the most significant advances in health care have come from industry funded trials or trials undertaken in partnership between industry and public funders. Once drugs are available clinical researchers explore new indications, such “off-licence” use of drugs has been an important part of innovation.
Recommendation

Interaction between academic clinicians and industry should be open, transparent and appropriately recognised by both sides.

2. SOME NEW DRUGS DO NOT OFFER SIGNIFICANT ADVANCES OVER EXISTING TREATMENT

2.1 Alongside these examples of major successes many drugs have been introduced that offer little advantage or are simply variants of existing products. These agents are granted a marketing authorisation on the basis that they are better than placebo, not because they offer an advantage over existing options. Industry will try to maximise profits from their developments, including those that may only offer marginal advances. Marketing is clearly effective.

2.2 Some high profile “failures” have been related to innovative products. For example, rofecoxib (Vioxx) is a member of a new class of drug and an innovative product. Its effects on cardiovascular events were not predictable prior to the clinical trials.

2.3 Some disease areas are over-represented in drug development whereas others are ignored (for example antimicrobials). Commercial considerations are key determinants of priority areas for industry.

Conclusion

There is no doubt that commercial interests determine the priorities of industry. “Me-too” drugs can make substantial profits and innovative drugs may have unexpected effects that make them risky to develop. Many doctors do not understand that the marketing authorisation simply means that the drug is more active than placebo.

3. CLINICAL TRIALS IN THE UK

3.1 Many of the clinical trials that have identified major clinical benefits and changed practice have been funded in part or full by the pharmaceutical industry. Examples include the 4S study showing that statins improve outcome after heart attack, the ISIS-II study showing that streptokinase and aspirin reduce death by nearly 50% after heart attack, and the UKPDS study that demonstrated how diabetes should be managed.

3.2 It is also clear that some studies funded by industry have been more helpful to marketing than to advancing clinical care. Common flaws include the use of inappropriate comparator drugs (sometimes used in doses lower than appropriate), assessment of surrogate markers of disease that do not relate well to clinically relevant end points, the use of composite end points that make it difficult to assess which end point has really been changed, the use of inappropriate safety markers or drug-specific quality of life assessment tools.

3.3 It is important to note that design flaws are not confined to trials conducted by industry, although there is a concern that some of the design flaws in commercial studies may be conceived to exaggerate benefit or obscure access to the clinically important result.

The pharmaceutical industry will pursue drugs that provide profit and will want to design studies that maximise the chance of doing so. Does this objective distort the general research agenda and reduce capacity for other research?

3.4 First it is important to consider funding. The majority of funding for clinical trials comes from industry. It has been my experience that other funding agencies may contribute to joint funding with industry, but are often unwilling to fund in full the cost of large scale clinical trials. This means that it is easier to fund a trial of a new medicine than it is to ask questions about the efficacy or safety of existing therapeutic options, or to fund therapeutic trials of non-drug interventions. The underlying reasons include the logistic difficulty in mounting a large clinical trial, the huge costs involved, and the priorities of funding agencies and their advisory committees which may (often rightly) favour spending money on more basic discovery research rather than applied clinical trial research.

3.5 Second there is a perception that the funding of commercial studies uses up capacity and thereby reduces the opportunity for undertaking other research. There is little evidence to support this view. In the UK a very low percentage of patients are enrolled in clinical trials and the experience of the cancer trials networks shows that recruitment can be increased substantially provided infrastructure is in place. There is a shortage of appropriately trained clinical investigators in the UK, and this reflects lack of investment in clinical research and problems with clinical training pathways (outlined in a recent report from the Academy of Medical Sciences “Strengthening Clinical Research”). This deficiency affects both commercial and non-commercial studies.
3.6 Third there is the issue of duplicate research. In many instances the evidence base is not reviewed in a systematic way prior to starting a clinical trial. Many small studies are funded that apparently show promise for a new drug or intervention but each individual study is too small to be persuasive or definitive. There must come a point at which another small study designed to investigate a therapeutic effect is either redundant because the answer is already available, or unnecessary because it will not produce the definitive answer that is required. In my opinion these are matters that funding agencies and ethics committees should consider very carefully before approving a study. At the very least, the patient information sheet should indicate clearly the realistic likely impact of the study.

Conclusion

Industry supports and develops areas of interest to itself but it is wrong to assume that industry is solely to blame for the lack of research in certain unprofitable/unfashionable areas or that industrial trials exhaust capacity for research. Rather, there is a lack of infrastructure to undertake research within the NHS, a failure to develop robust mechanisms to identify research priorities for the NHS and inadequate funding for this type of clinical research. The NHS should be a knowledge-based organisation and requires substantial investment in R&D.

Recommendations

The NHS infrastructure for clinical trials needs to be improved. The example of cancer networks suggests that it should be possible to increase substantially the clinical trials capacity and number of patients involved in studies. This will need investment in clinical trials networks, development of trained clinical investigators, simplification of the regulatory burden placed upon clinical investigators, and a change in culture within the NHS. These needs have been anticipated in the establishment of the UK Clinical Research Collaboration (UKCRC) earlier this year. NHS Trusts need to have a reward mechanism for engaging in clinical research that addresses NHS priorities.

UKCRC and its disease specific networks will need to scope in a systematic way their specific areas to identify where research gaps lie and which are the key questions of importance to patients, practitioners and the NHS. Where answers are known and no further studies are required, this should be identified and clearly stated.

4. Prescribing Drugs

4.1 There is confusion amongst prescribers about the significance of a marketing authorisation (product licence). It is my experience that many prescribers view the issuing of a marketing authorisation as evidence that the drug has a place in practice and should be available for them to prescribe.

4.2 Once a drug is available its use will increase and it will be used for indications outside the initial licence. This extension of use is an important part of innovation, but only if properly evaluated.

4.3 The existence of Drug and Therapeutics committees, formularies and more recently NICE, adds an additional layer to try to explore and regulate the place of new treatments against current alternatives. However the working of these bodies is complicated by patient pressure groups, clinician pressure and, increasingly, by the need for some NHS Trusts to be seen as offering a “cutting edge” service, which may mean a service that anticipates the arrival of a supporting evidence base.

4.4 Expert clinical opinion or “opinion leaders” in specific disease areas are influential forces on prescribing. Sometimes this is appropriate and makes an important contribution to disseminating best practice. However this is not always the case, and sometimes opinion leaders in specific disease areas benefit directly or indirectly from activities that amount to endorsement of specific products. This can distort prescribing practice.

4.5 Skills for evaluation of therapeutic claims are generally not well developed amongst doctors. It is time consuming to evaluate claims and for busy doctors the time is often not available. Much postgraduate education comes from industry-sponsored meetings.

4.6 Patient groups can exert very significant pressures to make new therapies available within the NHS. This is especially true for diseases in which existing treatments do not exist or are widely considered ineffective. Examples include the patient lobby for the use of interferons for multiple sclerosis, drugs for Alzheimers disease, and some cancer treatments.

4.7 Clinicians wanting the best for their patients are sometimes overly optimistic in their interpretation of phase II studies not designed to prove efficacy. Drugs are made available to patients before there is clear evidence for efficacy in clinically relevant outcomes.

4.8 Once a benefit has been described in the literature, it is very difficult to deny access to the drug. However the nature of the benefit is often not clear. For example, for a cancer drug, “benefit” may be expressed in terms of cure, quality of life, time until death, time until disease progression, reduction in
tumour size, or change in rate of change of tumour bulk. The size of the benefit may vary from clinically important to potentially irrelevant. Similarly, the number of patients that need to receive a given treatment for one of them to benefit may vary from hundreds to only one or two.

Conclusion

There are pressures from industry, doctors and patient groups that mean that drugs are sometimes introduced into routine clinical practice in the NHS in advance of strong evidence of benefit in the target patient population. There is a tendency to give a new drug “the benefit of the doubt” in favour of it being an advance. Once a drug is being used in routine practice it becomes very difficult to gather any meaningful data on effectiveness.

Recommendations

NICE should explore whether defined targets for new treatments could be set in a limited number of disease areas. For example, in the treatment of heart failure NICE might prospectively define the type and size of benefit that would be considered an advance likely to merit inclusion in an NHS formulary. This would have the advantage of helping to define general trial objectives, avoid having to respond to every “advantage” of a new product however small or clinically irrelevant, and would bring academics, clinicians, patient groups and industry into the target setting process before a specific product is considered or even developed. This approach could help guide industry to trials of most benefit to the NHS.

Money currently spent on some new drugs could be better spent on ensuring that where the evidence base is insecure but the potential need is great, the drug is introduced into the NHS only as part of a clinical trial. This will require an improved NHS infrastructure and clinical academic workforce as envisaged by UKCRC. The drug costs could be met from the drugs budget since no more patients would receive the drug than at present, they will simply be evaluated. Designating a small percentage of the NHS drug budget for “Research and Evaluation” would facilitate this process. A similar budget would need to be identified for trials of non-drug interventions.

The public should be informed about areas of “uncertainty” in medical practice and clinical trials to address uncertainty should be commonplace within the NHS. Trial design and results should be in the public domain.

Use of the concept of “Numbers needed to treat—NTN” and “Numbers needed to harm” for given intervention would improve information for prescribers and the public and aid informed decision making.

Medical students need to be trained in evaluation of evidence and this should form a major part of continuing medical education.

More funds should be available for independent postgraduate educational meetings.

Advice given to prescribers, and presentations or publications discussing therapeutic agents should always come with a clear statement about financial relationships and real or perceived conflicts of interest. This is common practice in the best medical journals but needs to be extended to meetings and all activities credited for CPD (continuing professional development).

5. Data Bases for Drug Safety

5.1 Drug safety is evaluated before launch of a product but many effects of drugs only become clear after the drugs have been used by many thousands of patients over several years.

5.2 The NHS data sets collected as part of computerised records provide a unique resource for evaluating drug safety.

Recommendation

Computerised databases of information collected as part of routine clinical care should be used to evaluate drug effects. The UK should develop increased research capacity in this area.

References:


Memorandum by Sir Iain Chalmers (PI 29)

Personal Statement

I am editor of The James Lind Library, a public website explaining and documenting the evolution of fair tests of treatments in health care (www.jameslindlibrary.org). I am also a co-convenor of the James Lind Alliance, a coalition of organisations representing patients and clinicians collaborating to confront important, shared uncertainties about the effects of treatments in health care (www.jameslindlibrary.org/jla.html). I have a longstanding interest in improving the quality of evidence about the effects of treatments in health care, an interest that was prompted initially by realising that I had been harming my patients by relying on “eminence-based” rather than “evidence-based” guidance. I have previously submitted evidence to the committee for its enquiry into the National Institute for Clinical Excellence (NICE). I am submitting this memorandum in an individual capacity. I would be willing to give oral evidence, if the Committee decides that this might be helpful.

Summary of Main Points and Recommendations in This Evidence

Many patients are suffering and dying unnecessarily, and resources for health care and research are being wasted, because of:

1. perverse influences on the clinical research agenda;
2. failure to take systematic account of existing knowledge when planning clinical research;
3. biased under-reporting of research;
4. insufficient public and professional access to trustworthy evidence about treatment effects and information about relevant ongoing research;
5. government-endorshed secrecy about the effects of licensed drugs; and
6. the introduction of inadequately assessed treatments within the NHS.

The pharmaceutical industry inevitably contributes substantially to these serious problems because of the very prominent role it plays in clinical research and information about the effects of treatments.

This unsatisfactory state of affairs can be addressed by:

1. assessing the extent to which the clinical research agenda reflects the priorities of patients and practitioners for developing and evaluating healthcare innovations;
2. ensuring that systematic reviews of existing evidence are the basis for planning new research;
3. requiring public registration of clinical trials with unique identifiers and outlawing biased under-reporting of health research;
4. increasing the capacity for preparing, maintaining and disseminating systematic reviews of the effects of treatments, and for providing public information about ongoing research;
5. promoting public access to the results of all clinical studies of the effects of licensed drugs; and
6. restricting the use of inadequately evaluated drugs within the NHS to the context of controlled evaluative studies, thus reducing unacceptable uncertainties about their cost-effectiveness.

1. Drug Innovation

Over the past half century, better health care has been responsible for between a third and a half of the increase in life expectancy, and an average of five additional years free of chronic health problems (Bunker et al 1994). Compared with all previous eras of health care, this is a remarkable record of success, and drug treatments have made their contribution to it. Indeed, the extent of these achievements over the 50 years before the human genome was sequenced will be the yardstick against which we will come to judge the validity of current claims that the genetic revolution promises even greater benefits to patients.

In spite of these heartening estimates of the effects of health care, the public could have obtained better value for the substantial private and public resources invested in research intended to improve health, particularly during the past 20 years. During this time, very few newly approved drugs have offered worthwhile advantages to patients over previously available options (International Society of Drug Bulletins 2001), a problem that has been noted within the pharmaceutical industry (for example, Horrobin 2003) as well as outside it (for example, Garattini and Bertele 2002).

Over the past two decades, industry and academia have increasingly worked in partnership to promote commercially dictated objectives. This has had perverse influences on the clinical research agenda (Chalmers 2000). For example, most clinical trials relating to osteoarthritits of the knee are commercial studies of drugs. When patients, rheumatologists, physiotherapists and general practitioners were asked to identify their priorities for research, they made clear that they had little need for any more such studies, but instead wanted more rigorous evaluations of physiotherapy and surgery, and assessments of the educational and coping strategies that might help patients to manage this chronic, disabling and often painful condition more successfully (Tallon et al 2000).
Studies evaluating the effects of out-of-patent drugs and non-drug interventions cannot expect to attract support from industry. The opportunity costs of acquiescing in industry’s pervasive influence on the clinical research agenda is that many questions of importance to patients, professionals and the NHS more generally, are not being addressed.

**Recommendation**

Independent evaluations should be commissioned to assess the extent to which research reflecting the priorities of the pharmaceutical industry is promoting or jeopardising the development and evaluation of innovations regarded as important by patients, practitioners and the NHS itself.

**2. The Conduct of Medical Research**

An editorial in the British Medical Journal entitled “the scandal of poor medical research” has called for “less research, better research and research done for the right reasons” (Altman 1994). In part, the scandal reflects the pervasive influences of commercial interests on the research agenda. For example, there is evidence suggesting that some studies sponsored by industry have been designed deliberately to yield results favourable to particular drugs (Djulbegovic et al 2000). This can be done by withholding a comparison treatment known to help patients, or giving comparison treatments in inappropriately low or high doses.

The scandal of poor medical research would be reduced if researchers were required to take systematic account of existing knowledge when planning and reporting their research. Because this job is not done well, patients have been denied treatments which could have benefited them, while other patients have received treatments that were either of no material benefit, or actually harmful (Antman et al 1992).

For example, after reviewing the experience of thousands of patients who had participated in controlled trials of new calcium-blocking drugs given to people experiencing a stroke, a Dutch team found no evidence to support the increasing use of these drugs in practice, or for the large numbers of clinical trials that had been performed (Horn and Limburg 2001). Furthermore, when they subsequently prepared a systematic review of the relevant animal studies they found that these had never suggested that the drug would be useful in humans (Horn et al 2001).

These serious problems would be reduced if all funders of research followed the lead of the Medical Research Council in requiring those seeking support for new research to refer explicitly to systematic reviews of existing evidence, showing that proposed additional research is necessary and that it is building on previous experience. Because research ethics committees have tended to ignore this principle, patients and the public have not been protected effectively from unethical research (Savulescu et al 1996).

**Recommendation**

As a precondition for funding and ethical approval, funders and research ethics committees should be required to ensure that proposals for new research are supported by systematic reviews of existing evidence.

**3. The Provision of Drug Information and Promotion**

Reliable evidence about the effects of drugs on patients depends on systematic reviews of all relevant, unbiased studies. Such systematic reviews are now used extensively by the National Institute for Clinical Excellence (NICE) and in clinical guidelines. The increased amount of evidence being assembled in systematic reviews is a major advance. However, these reviews may overestimate the beneficial effects of drugs and underestimate their adverse effects because the results of some key studies are not publicly available: studies that have not found beneficial effects of drugs, or which have found adverse effects, are less likely than others to be published (Dickersin 1997).

Biased under-reporting of clinical trials kills patients and wastes resources. For example, had all the completed studies of drugs to reduce heart rhythm abnormalities in patients having heart attacks been reported, tens of thousands of deaths from these drugs could have been avoided. To their credit, Dr Cowley and his colleagues in Nottingham pointed out how an unpublished study done there 13 years previously might have provided an early warning of this iatrogenic disaster. “When we carried out our study in 1980”, they reported, “we thought that the increased death rate was an effect of chance—The development of lorcainide was abandoned for commercial reasons, and this study was therefore never published; it is now a good example of “publication bias” (Cowley et al 1993).


**Recommendations**

All clinical trials done within the NHS should be registered publicly at inception, and assigned an International Standard Randomised Controlled Trial Number ([www.controlled-trials.com](http://www.controlled-trials.com)). Pharmaceutical companies wishing to perform trials in the UK should be required to publicly endorse and comply with the Good Publication Practice for Pharmaceutical Companies ([Wager et al. 2003](http://example.com) and [www.gpp-guidelines.org](http://example.com)).

Consideration should be given to introducing legislation—comparable to that in Spain—requiring pharmaceutical companies to publish all results of all randomised clinical trials involving NHS patients.

4. **Professional and Patient Education**

Health professionals and patients alike face an overload of information about the effects of treatments. This problem is compounded by the fact that it is usually impossible to interpret the significance of the findings of individual research studies because researchers rarely set the results of new research in the context of systematic reviews of all other relevant data ([Clarke et al. 2002](http://example.com)).

Welcome support for the training and other infrastructure needed to prepare and maintain systematic reviews has been provided by all UK governments since 1991, largely through the NHS R&D Programme and NICE. The results of these analyses have also been increasingly successfully made available for professionals and patients, for example through the Cochrane Library, The Centre for Reviews and Dissemination, the NHS Health Technology Assessment Programme, NICE, NHS Direct, and the National electronic Library for Health.

In spite of this encouraging progress, however, current levels of support for preparing and maintaining systematic reviews remains dangerously inadequate. Professionals and patients have ready access to only a small proportion of existing evidence about the effects of drugs and other treatments. As systematic reviews of existing evidence are an essential (albeit not sufficient) component of the foundation for informing professional practice, patient choice, and policies within the NHS, support for this work must be increased substantially.

Furthermore, when systematic reviews of existing evidence reveal that there are important uncertainties about the merits of treatments, healthcare professionals and patients should be able to find out more easily whether any ongoing research is addressing these uncertainties, and how they may be able to contribute to these studies.

**Recommendations**

The Department of Health, the Medical Research Council and the medical research charities should increase substantially their current levels of investment in systematic reviews.

The Department of Health should ensure that patient-friendly information about ongoing clinical trials within the NHS is made readily available.

5. **Regulatory Review of Drug Safety and Efficacy**

Continued lack of public access to information about the effects of licensed drugs is incompatible both with current public expectations and with the government’s professed commitment to promoting informed patient choice and rational use of resources within the NHS. Denial of access to information held by the Medicines and Healthcare products Regulatory Agency (MHRA) puts the interests of pharmaceutical companies ahead of those of patients and prescribers. This is particularly indefensible in the light of evidence that regulatory agencies, supposedly established to protect the public, are acquiescing in biased later publication of the information they hold ([Melander et al. 2004](http://example.com)).

For example, after the safety of human albumin solution had been called into question in a systematic review of published and unpublished controlled trials, the Medicines Control Agency (MCA, which preceded the MHRA) refused to disclose the evidence that had led it to grant a licence for the product ([Roberts et al. 1998](http://example.com)). The government colluded with the manufacturers of evening primrose oil in suppressing information suggesting that the drug had no useful effect in eczema. Five years later, the MCA withdrew the marketing authorisation for evening primrose oil on grounds of lack of efficacy, but without revealing the evidence upon which it had based its decisions initially to award and then to withdraw a licence for the drug ([Chalmers 2004](http://example.com)).
Recommendation

There should be easy public access to all information from clinical studies of the effects of licensed drugs, including that held by the Medicines and Healthcare products Regulatory Agency.

6. PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY

During the 2nd World War, a drug was produced which was thought to promote faster recovery from common colds—a substantial cause of lost work and reduced national efficiency. Because of its potential national importance, the Ministry of Supply asked the Medical Research Council to evaluate the drug. The pharmaceutical industry provided supplies of the drug and placebos for this research, and, within a few months, strong evidence had been produced showing that the drug was highly unlikely to have any useful effect (Clarke 2004). This showed how concerted common purpose can reliably answer questions of national importance about the effect of a drug. It is relevant today, and is reflected in the creation of NICE.

NICE exists because the information supplied by pharmaceutical manufacturers to the MHRA is inadequate for assessing the extent to which the costs of drugs represent good value to the NHS. As I noted in evidence submitted to the Committee for its enquiry into NICE, the organisation cannot be expected to serve the interests of the public effectively while it does not have full access to relevant evidence, and while there is continued acquiescence in biased and incomplete public access to the results of relevant clinical research.

NICE cannot make adequate assessments of cost-effectiveness without information about the relative merits of alternative treatments (including drugs in the same class), and evidence gathered after wider use and longer follow up of new products showing their effects on the outcomes that matter to patients. In these circumstances of significant ignorance about the effects and cost-effectiveness of drugs, the NHS should consider adopting recommendations made in respect of the Australian Pharmaceutical Benefits Scheme (Glasziou 1995): promising but inadequately evaluated drugs should be used by the NHS only within the context of research designed to reduce uncertainties about their value, and thus provide the basis for informed choices and decisions.

Recommendation

Selected promising but inadequately evaluated drugs should be used in the NHS only within the context of controlled evaluative studies until enough is known to judge their cost-effectiveness.

14 August 2004

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Witnesses: Sir Richard Sykes, Rector, Imperial College, London, Professor Patrick Vallance, Professor of Clinical Pharmacology and Head, Department of Medicine, University College London, and Sir Iain Chalmers, Editor, The James Lind Library, examined.

Q407 Chairman: Colleagues, I welcome our witnesses to this morning’s session. We are most grateful for your co-operation with our inquiry. I think you are aware that we have two separate sessions this morning, and we will try to keep each session to an hour each. We will keep our questions sharp and ask you for reasonably concise answers. Would you each like to introduce yourselves to the Committee?

Sir Richard Sykes: I am Director of Imperial College.

Professor Vallance: Patrick Vallance, Professor of Clinical Pharmacology and Head of the Department of Medicine at University College.

Sir Iain Chalmers: I am Editor of James Lind Library and one of the co-conveners of the James Lind Alliance, which is a coalition of patients and clinicians trying to influence the research agenda.

Q408 Chairman: Professor Vallance, I gather you have just got off a plane from America. We do appreciate you coming here in those circumstances. Sir Iain, you suggest in your evidence that the pharmaceutical industry has a pernicious influence on the clinical research agenda, and you also criticise publication bias by industry. Could you expand on these observations and perhaps give us some examples of how you feel patient well-being is being affected by these concerns?

Sir Iain Chalmers: If I could start with an example to make a general point: some researchers in Bristol a couple of years ago asked patients with osteoarthritis of the knee and the people caring for them—physiotherapists, rheumatologists and general practitioners—what unanswered questions they would like to see addressed in research, and the answers that they came up with were things like better evaluations of surgical options, better evaluation of physiotherapy, and better evaluation of ways of coping with a chronic, painful condition. When the researchers compared the questions which these patients and professionals had indicated as important with what had been studied in osteoarthritis they found that very few of those questions had been addressed. Rather, yet more placebo-controlled trials of non-steroidal anti-inflammatory drugs were being done. All of the focus groups of patients and clinicians said, “we do not want any more studies of drugs, of pain-relieving drugs.” That is just one example of the way in which research agendas can be distorted by the interests of industry. In fact, in this week’s BMJ there is a report of acupuncture for osteoarthritis of the knee, which is an example of the sort of thing that industry has no interest in at all. So, there are inappropriate questions being addressed in research, or inappropriate from the point of view of patients and clinicians. In addition inappropriate comparators are sometimes being used. For example placebos are being used as comparators when there are already effective treatments, and sometimes inappropriate outcome measures are being used. From a commercial point of view there may be reasons for doing these studies, but they are not necessarily serving the interests of patients and clinicians, rather than shareholders. There is also the problem of the academic influences on the research agenda, some of which I regard as perverse. In this country, one of these is the Research Assessment Exercise, which is done to decide how much of the science budget should go to support particular universities. Within that system there is no encouragement to review systematically what is already known from existing research,
before ploughing ahead and doing new additional studies. There is discouragement of collaborative research, which is often necessary to obtain robust evidence about the effects of treatments. People in particular institutions competing for resources see collaborative research as a threat because it submerges the identity of the institutions, and does not give individuals in institutions the prominence which they think they require. This encourages academics to do small-scale, often poorly-designed, studies. The other, often perverse influence there has been growing encouragement of academia to attract for income-generating research. Take a trial funded by the NHS R&D programme or the Medical Research Council. There may be a certain sum of money to support the recruitment of every patient in the trial, but industry sometimes can offer a bounty for each patient recruited of thousands of pounds. Clearly, people who are wanting to make income for their academic institutions, or indeed their hospitals, may find it difficult to support a study that is addressing an important question (of no interest to industry) that is funded by the MRC or the NHS R&D programme. Those are the perverse incentives that I believe exist. You asked me about the problem of publication bias. This is a very serious problem, and one that I have been wittering on about for well over a decade. I am very glad that Sir Richard Sykes is here at this session, because I want to give credit to those people in industry who, way back in the mid nineties, said that this was unacceptable behaviour. Richard Sykes and his colleagues within GlaxoWellcome did that, so also did Mike Wallace, the Chief Executive of Schering Healthcare. It is quite unacceptable that people should be invited to participate in clinical trials, and then, when the investigators or the sponsors do not like the results, their contribution is not made public. It is a very, very serious problem.

Q409 Chairman: Can I ask the other two witnesses whether they feel their institutions or research groups are influenced in similar ways by the industry in some respects; and, if so, how?

Professor Vallance: I can answer from my own institution. We get a small percentage of our total research income from industry, and it is about 2% in total of research income.

Q410 Chairman: Where does the rest come from?

Professor Vallance: From the Medical Research Council and major charities like the British Heart Foundation. Currently 2% comes from industry. We are probably unusual in that in terms of having a very high percentage of peer-reviewed grant funding. But there is no question that what Iain Chalmers says is correct; that industry will of course pursue drug-related research over and above other kinds of research. The question is, to what extent that distorts the ability to undertake other types of research. One of the problems is that a rather small percentage of patients are involved in clinical trials and there is huge uncertainty in healthcare. There is capacity in the system, but it is not used. I remain concerned that we have not got the capacity issues right, or the infrastructure right to undertake more studies. It does not surprise me that industry will want to pursue studies of interest to itself.

Sir Richard Sykes: Our research budget is £200 million a year; and £20 million of that will come from industry. That is the biggest industrial funding of any university in the UK. Most of that, of course, is in the physical sciences and engineering, not in medicine. However, we live in a knowledge-based economy. The knowledge base is university-based, and we want industry to work alongside universities. If we are going to be competitive in this country, then we have to use our knowledge, our creativity and innovative skills. Therefore, the universities have to play a very important role in that, and we have to have translation of research in healthcare or other areas because that is the fundamental basis now of being competitive. We have to use our knowledge base.

Q411 Chairman: You do not feel that that relationship with industry has a bearing on the objectivity of the work that you do?

Sir Richard Sykes: I think it has to some extent, but again—

Q412 Chairman: In what way?

Sir Richard Sykes: In the way that we have heard already, that industry will want to come in at the front end, doing clinical trials; they will also want to invest in certain types of research. Of course, the academics themselves will not get involved in that research if they do not believe it will benefit them at the end of the day, so how it manipulates is difficult to tell. Certainly, big clinical trials in patients related to the hospitals are certainly being done to generate money. We are being driven to generate money, otherwise we would not be competitive in the world.

Q413 Dr Naysmith: This is really a question to Sir Richard. I agree with what Sir Iain said, and we are really pleased to have someone who has been at the top of scientific research and one of the country’s major companies. We suspect that you will be able to give us quite an insight into what goes on if we can discover the right questions to ask. One of the most important questions facing this Committee in producing the report is to try and find the right balance, if there is one, between business and trading and health priorities and between marketing and evidence-based clinical practice. I am sure you would agree that that is something we all want to do. As I have just said, you have experienced both sides. What do you think of this conflict? How do we get the right balance? You have partly touched on it, but as a more global thing?

Sir Richard Sykes: I think we have carried a lot of baggage from the past, and somehow we have to recognise that those days have gone, or at least they are going away. We have to look forward. If we are going to deal with some of the big problems in
healthcare today, it has to be a partnership between the academic face, the research base, the industry, the NHS. We have to work together to solve some of these big problems. I believe that this has got to be a collaboration today, not a group here, a group here and a group here, and it is all “them and us”. That method will not work.

Q414 Dr Naysmith: How do you get rid of this conflict between trade and health, and how do you make sure that they work together?
Sir Richard Sykes: I think you need a lot of transparency. As Iain said, you need to be transparent, and you need to make sure what everybody is doing, and that the information is there so that we can all share with it and deal with it, rather than having things hidden—“if we do not like the result we put it away and do not tell anybody” —which is totally inappropriate. Transparency is particularly important.

Q415 Chairman: Do you see there is any way of squaring up that transparency with a market system where there is this obvious emphasis on the need to create profits and business incentives; and on the other side the health policy? Do you see that can in any way actually be balanced out so that you can have transparency and also a commercial market operating, which is what the companies clearly want?
Sir Richard Sykes: I do not think there is any conflict at all. If you produce good medicines, whether they are diagnostics, whether they are treatments, whether they are palliatives, curatives, preventatives, whatever they are—if they benefit somebody in society, we should all be very happy. That is the objective at the end of the day.

Q416 Dr Taylor: The phrase “commercial confidentiality” is thrown at us all the time. How do you square that with transparency?
Sir Richard Sykes: There are certain areas where, at the beginning of the research process, there has got to be a degree of confidentiality in terms of intellectual property. Once that intellectual property has been achieved the whole point about intellectual property is to make it available to everybody so that everybody can see what you are doing.

Q417 Dr Taylor: How early in the process should that be done?
Sir Richard Sykes: As soon as you have got the intellectual property filed.

Q418 Dr Naysmith: How do you resolve the conflict that Sir Iain referred to, where you have the situation where people who are suffering from an arthritic condition would much more benefit from physiotherapy or something like that than from another painkiller and another anti-inflammatory, and the companies just put the money into that?
Sir Richard Sykes: If the doctors continue to prescribe analgesics for treating these diseases, so that the market—I do not know what it is today, but it must be billions of dollars for these kinds of drugs—then what do you expect the market to do? They respond to it. That is what I am saying: people have to work together. If you are talking about osteoarthritis, the first thing you need is a diagnostic, because it is a nightmare to decide whether somebody has osteoarthritis or not.

Q419 Dr Naysmith: Where does the transparency come in, then, because you were just following down that because it is the job of companies to generate profits as well as to generate—
Sir Richard Sykes: They cannot generate profits if nobody sells the drug. The companies do not sell the drug to the patient; it is the doctor—the gatekeeper.

Q420 Dr Naysmith: We will come to some questions later on about the role of the industry and marketing the product.
Professor Vallance: Can I make a comment on this? It seems to me that the job of saying which of the trials are missing and what the patients want that are not drug-related trials is a matter for the NHS to set the agenda and to say, “where are the gaps and what should we be addressing in a clinical trial?” It is unrealistic to expect industry to go out and want to do that.

Q421 Dr Naysmith: I think we will come to interesting questions later on related to what the role of the Department of Health should be versus the Department of Trade and Industry and whether it should operate through the Department of Health. I want to move on to something else. I have been very impressed in this inquiry by witnesses who have been able to tell us about the practice of ghost writing, someone else writing papers, sticking their names on a paper that they know very little about. I am sure that Richard, as a scientist, will not think that is a very good idea, but does it happen widely in the industry? I am really talking about clinical trials rather than original research.
Sir Richard Sykes: I am sure it happens because academics are very, very busy people, and they prefer to do research than spend a lot of time writing papers. If the industry puts forward a method of relieving them of that chore, then I am sure that that does happen throughout the industry. That would be true generally. Is it a good idea? I think it can be, as long as everybody is in agreement with what is written at the end of the day, the results and what they are.

Q422 Dr Naysmith: You would never have done it as a scientist, would you?
Sir Richard Sykes: It would never have been within anything that I did as a scientist to do that. I am not a clinical researcher, so I was never informed of that situation.

Q423 Dr Naysmith: How much will the chief executive of a big British pharmaceutical company know about the details of the sort of things we are talking about now, and the kind of research that is
being pursued? Is it seen in terms of one, two or three new drugs progressing, or would you be interested in things like incentives and disincentives for sales representatives and the pressures they face to meet targets; or would you be really interested in producing a drug that benefits humanity?

Sir Richard Sykes: I must make it clear to everyone here that people go to work in the pharmaceutical industry generally—and particularly the researchers—because they really have a mission. They want to discover and develop something that is really going to benefit people, and the young people that go into industry today go with that desire. I have met very few people who did not want to achieve that end. The people working in industry work very closely with academia in the big companies, and they all have one objective at the end of the day. In my opinion, these are not people that are driven by greed, money or avarice; they are driven by the desire to be successful and to do something that is going to benefit people. When you get higher up in the organisation, those objectives change to some extent, but not the people doing the work. As a scientist and a chief executive, I obviously took a lot of interest in what was going on, because that was my desire as well; to make sure that we could develop things that really benefited people.

Sir Iain Chalmers: May I add something on ghost writing and publication practices? One of the developments under Sir Richard Sykes’s regime at GlaxoWellcome was that there was a publication unit headed by Dr Elizabeth Wager, which worked with some people in other companies developing good publication practices. One of the things that came up was ghost writing and gift authorship and so on. They developed good publication practice guidelines for the pharmaceutical industry; they are on the Web. When I wrote to the successor of Sir Richard Sykes, Jean-Pierre Garnier, congratulating him on supporting this activity through the successor company GSK not only did I not get a reply but Dr Elizabeth Wager and her team were sacked. The last time I looked only six companies worldwide had endorsed the good publication practice guidelines. I think it is a very, very serious situation. If companies are really genuine about wishing to improve publication practices then they should sign up to those guidelines.

Q425 Mr Amess: I am sorry if I am repeating things which you have answered already.

Sir Iain Chalmers: I apologise I have not yet given a detailed answer on this. Registering trials at inception is one of the steps needed to tackle this problem of publication bias. It has been proposed at least since 1986 as a way of addressing this problem. Very good progress has been made in some respects. For example, the trials that are funded by the NHS or by the MRC are now all registered on the meta Register of Controlled Trials set up by the publishing company, Current Controlled Trials, which has done an extremely good job. In addition there is a need to uniquely identify trials, in the way that books are identified uniquely. There is an ISBN scheme, which was introduced initially by two publishers, and then became the responsibility of the International Standards Institute. WHO has recently assumed responsibility for developing the International Standard RCTN number. It is a very important initiative which has now has international backing from WHO, and from the International Committee of Medical Journal Editors and from others. In terms of which trials should be added to that register, and indeed for which trials it should be required, I think it is reasonable for industry to say that in the early days of drug development, there are issues of commercial confidentiality that they will want to keep under wraps. However, at the time when studies start to be likely to influence patient care, those studies really do need to be registered prospectively and reported fully.

Q426 Mr Amess: Who would judge that?

Sir Iain Chalmers: One way of judging is to see if the study is randomised. If it is, people are really taking a serious interest in making sure that they are not misled by bias. I would say randomisation would be a good trigger for registration, although it has to be said that drugs are still being licensed on the basis of rather inadequate evidence, looked at from my perspective of uncontrolled case series, particularly in cancer.

Q427 Mr Amess: You mentioned the need for registration of trials at inception. Can you explain to the Committee why you feel that is so important?

Sir Iain Chalmers: Yes. If you wanted to address uncertainties about treatments you want to look at all of the relevant evidence that has been generated, and not just a sample of it, and certainly not a biased sample. Unless you identify, at inception, the studies that are addressing a particular question, you cannot know that you have identified all of the relevant evidence. There are examples of people being harmed, and certainly resources being wasted because disappointing studies have not been published. Trying to identify those studies in retrospect—in the mid eighties we wrote to over 40,000 clinicians around the world to try and flush out unpublished studies—does not work. You need proper registration of these studies so that you have a handle on them right from the beginning.
Q428 Mr Amess: Gentlemen, do you have anything to add to your colleague’s remarks?
Professor Vallance: I agree with what Iain said. The cut-off point in a sense is when a trial is trying to establish a therapeutic end-point, then that should be in the public domain and should be registered. I think that is true for academic and industrial-sponsored trials.
Sir Richard Sykes: I agree.

Q429 Mr Amess: Gentlemen, do you think the current draft regulatory system is adequate? If it is not, what do you think is wrong with it? Might the MHRA take a greater role in addressing the problems of adverse drug events or post marketing clinical trials or, again, do you think it would be better to be handled by some sort of independent authority, if you can think of such an independent authority?
Professor Vallance: There are a number of problems. MHRA, when it licenses a drug, is looking for the effect of that drug over and above placebo very often. I understand why that happens as a regulatory process, and that is in harmony with other places in the world, but it is not a question you want answered in terms of whether you want the drug available in the NHS. That is where NICE comes in. There are some boundary issues that need to be explored, and whether NICE has said in advance the criteria it wants to put in place to say something is a true advance over existing therapies.

Q430 Mr Amess: What is your view of how it operates at the moment?
Professor Vallance: NICE has done a lot of very good things, and in many ways it has worked tremendously well. It is often on the back foot when a trial shows an advance, because it is then left with asking how big an advance it is and whether it means something. The problem is that very often it does not mean very much, but they are always seen as denying—

Q431 Mr Amess: So this links up; it is all written up.
Professor Vallance: Yes, there is an expectation by patients and doctors and others. I would prefer to see at least as a pilot NICE looking at the idea of setting criteria as to what is an advance in a given therapeutic area.

Q432 John Austin: In your evidence you have suggested there is a lot of information on the effects of drugs which is collected in the routine of clinical care. Could that be used as a base for evaluation?
Professor Vallance: There is an immensely valuable database called the GP Research Database, which is routine clinical data collected on five million patients through computerised systems, and that will increase in the NHS. It is an under-utilised resource for looking at drug safety. There is good evidence it is under-utilised, and one of the reasons is that it has been incredibly expensive to access, and just about the only groups that have accessed it in the past have been in hospitals in the USA. UK data of direct relevance to safety in this country has been used mainly by groups in Boston. That database is now owned by the MRHA and it extremely valuable for drug safety, and there will be more of that coming along as NHS computer systems get put into place in hospitals.

Q433 John Austin: What is the barrier now?
Professor Vallance: Cost and to some extent expertise.

Q434 Mr Amess: I do not think you addressed the point about the drugs.
Professor Vallance: The database is a way to get that. You can get a lot of safety information and you can monitor safety much more accurately. I suspect that some of the issues around cost might have been picked up using that database.
Sir Richard Sykes: I think you have to recognise that you can never win at this game. The MHRA or any regulatory agency gets a set of data. Usually you do this through clinical trials with from anywhere between 3,000 and 10,000 patients. If an adverse event is one in 20,000 or 30,000 or 50,000, you are never going to see it. There has got to be a process of making sure you have enough information to give an approval to have the drug into the clinic, but then there have got to be very clear monitoring processes for seeing that drug operate in a true market place, where now you are not selecting the patient who receives the drug but patients of a great genetic diversity are now receiving that drug. That, by definition, will produce adverse events. Remember that these drugs, at the end of the day, must be poisons, otherwise they would not be working. The body is a very complicated organism. It is all connected. If you inhibit one bit, you are going to inhibit something else somewhere else, and that is an adverse event, and that is the risk/benefit relationship at the end of the day. The more information we can get about this, the more we understand about the underlying mechanisms of disease and how those mechanisms are connected to other mechanisms. This will change over the next 20 years absolutely dramatically. That is where we have to make sure agencies like the MHRA are tied in to this modern technology so they can get better, more valuable information, to make better decisions.

Q435 Mr Amess: You think they are the appropriate body.
Sir Richard Sykes: As long as they change and develop with progress, then they should be fine.

Q436 Dr Naysmith: Why should it be better in the future because it has not been all that good in the past? I know it will change with the different scenarios, but you are still going to have to regulate.
Sir Iain Chalmers: I have a slightly different take on your question. It seems to me that unless you establish that a new treatment is either better or cheaper than what is already available, then
worrying about side effects is displacement activity. We need better information, complete information on the effects of treatments and their benefits, in particular if better information about what difference drugs make to outcomes that matter to patients. This is very important because often they are evaluated for licensing in terms of outcomes that are completely meaningless to patients. If we had evidence that a drug is beneficial in these terms, and we can be reassured that there is no evidence that there is no publication bias, then that drug becomes interesting in terms of trying to make sure it does not have any unexpected side effects. The initial problem is the worst one; that we do not yet have good mechanisms for identifying drugs that are useful to patients, partly because of publication bias, but partly because the outcomes studied are either not sufficiently important to patients. I was listening to the Chair of the Psoriasis Association speaking yesterday, who is a lay person. He was saying that the studies of psoriasis do not measure the things that he and other sufferers of psoriasis rate as important, such as itchiness and pain. There are the fundamental earlier problems that we need to address before looking for side effects.

Q437 Mr Amess: To help the Committee in reaching its findings, can you think of a good mechanism?

Sir Iain Chalmers: I do not know how radical this is, but I would propose that there should be a provisional licence given to drugs on the basis of the kind of outcome measures and the type of follow-up that has been done in studies submitted to the MHRA; and that a decision about whether this new drug represented good value for the NHS should wait until there is more evidence about whether or not it affected outcomes that matter to patients.

Q438 Chairman: Is that a model that applies anywhere else in the world?

Sir Iain Chalmers: I do not know.

Q439 Mr Burns: In parallel with your criticism of the industry you have said “denial of access to information held by the MHRA puts the interests of the pharmaceutical industry ahead of those of patients and prescribers”, and you categorise it as “deplorable”. Can you explain to the Committee what exactly you mean by “deplorable”?

Sir Iain Chalmers: Let me give you two examples, both of them relating to pharmaceutical products. One relates to a treatment that has been used ever since the Japanese attack on Pearl Harbour for treating people who were severely burned or otherwise critically ill. The treatment involves giving a transfusion of human albumin solution. Ever since that time, until very recently, there has been no adequate assessment of whether the claim that this was a way of reducing the chances of those individuals dying was substantiated in good evidence. Human albumin solution has been used repeatedly in this country, and it was re-licensed in 1993. Yet a systematic review of all of the studies that provided information about death done in the mid 90s showed no evidence that albumin was helpful, and some worrying evidence that it might be harmful. Furthermore, there are mechanisms through which this harmful effect might be mediated. The reaction of the Medicines Control Agency to this news was to slightly modify the labelling, but to keep confidential the evidence upon which the drug had been re-licensed in 1993. It was not considered in the public interest to allow that to be made public, and I think this is indefensible. If you have a question about a widely-used medical product, which has been used for decades, you need to know what criteria the licensing authority, which is meant to be looking after our interests, has used to decide that the product but it was left to Australia and New Zealand to address the concern. Their study has failed to detect any advantage of this human albumin solution compared to salt water. As you can imagine, salt water is a good deal cheaper! There is some evidence that in a certain sub-group of patients albumin may be harmful, but the worry from the systematic review was not substantiated. However, we have been paying millions and millions of pounds for a way of resuscitating patients which is no better than salt water. That is one example. Another example is so-called evening primrose oil for eczema. This was given a drug licence, but in the early 1990s the Department of Health commissioned a systematic review of the evidence relating to the effects of this drug in eczema. The reviewers did an extremely good job, and included both unpublished data provided by industry and published data. They were unable to find any evidence that the drug was useful in eczema, except “in doctor-assessed itch”—“not patient-assessed itch”. This raises an interesting question! The drug continued to be sold to the NHS, at a cost of about £7 million a year at the time the study was done. However, industry put pressure on the Department not to release the results of the systematic review. Two years ago however the MCA withdrew the licence on the grounds of lack of efficacy; but it did not make available the evidence that had led it first to license the drug, and then to withdraw it. Those are examples of the sort of secrecy that those outside the system have to put up with. That secrecy is not in the interests of the public.

Q440 Mr Burns: Do you think there are ever cases where it might be in the interests of the public to deny access to publication?

Sir Iain Chalmers: I cannot think of examples, but that is not to say that there may not be some. Clearly, one of the problems that epidemiologists face is if they find an association between, let us say, coffee drinking and pancreas cancer, do they report that association and stop a lot of people drinking coffee who enjoy it but who might worry they will get pancreas cancer? There is an issue about not causing unnecessary alarm, but when it relates to licensed products that have been given the go-ahead for marketing in our country to our
population, I just do not think it is consistent with 21st century public values that that information should remain secret.

**Professor Vallance:** I will go one stage further. I do not understand how you can use a drug if you cannot access the information to see if it works.

**Sir Richard Sykes:** If you really wanted a system that works more effectively you would have a regulatory body in terms of approval; then you would have the body that is determining whether you have efficacy and safety; but NICE can only make those decisions once the drug has been on the market for quite some time. Then you can ask those questions. Therefore the data has to be transparent because there is no way you can make the decisions. If they say there is no benefit to be gained from the drug, and the NHS stopped supporting that drug immediately, that would be a better system at the end of the day, but you can just imagine the arguments as to whether there was real efficacy. If you set up NICE correctly, you would be able to do that.

**Q441 John Austin:** The evidence we have had both from the United States and Australia has suggested that only a minority of drug innovations offer any significant therapeutic advance. Would you say that is also the situation in the UK; and do you think the industry does concentrate too much on already there and therefore we will not support it? I do not think it is a time issue; if you go into that area you are going to end up with hopefully a safer and more efficacious drug. Some of the predecessors have been pretty toxic and you cannot access the information to see if it works.

**Sir Richard Sykes:** If you look at the whole history of drug development—and really it started as an industry in this country in the sixties, and the first range of drugs—if you think about beta-blockers for treating hypertension—obviously people recognised that there was a mechanism here to attack high blood pressure, so lots of people get involved in that research because they see the patterns. Once you are down that track and you have invested a certain amount of money, you are going to continue. Again, if you can show safety and efficacy, those drugs get approved. Let us say there are 15 beta-blockers on the market: doctors will put patients on the drug that tends to work for them best, so you are actually doing a genetic analysis on that group of patients by having 15 drugs available to you. Each one of those drugs has a benefit to a certain class of patients, worked out by pure random testing. I suspect. That has been the tradition going forward, so if you go back to the sixties and seventies, we have gone through that period where drugs come out and they are followed by other drugs, because safety and efficacy has been proven in the market place and therefore you know if you go into that area you are going to end up with hopefully a safer and more efficacious drug. This is where I said earlier that the world is now changing. That model will not work any more, and this is why we have seen this paradigm shift in the drug industry and why we read that drugs are not coming out as fast as they used to, and there are no new molecules, because it is going back to basics. It is now trying to understand the underlying mechanisms, and to deal with that right at the fundamental issue, rather than serendipitously moving along the track and then everybody following that track. This is the change that is taking place, and my view is that over the next 20 years we will start to see drugs that will offer real benefit to patients. You will not get a lot of “me too-isms” I suspect.

**Q442 John Austin:** You said earlier that the industry manufactures the drugs and the doctors prescribe them. You have gone through a period of asking why doctors prescribe a particular drug. Professor Vallance, in his evidence, has pointed out that in order to gain a licence a drug does not have to prove it is more effective than existing treatment; it just has to prove that it is more effective than the placebo. Professor Vallance says that not a lot of doctors know that.

**Sir Richard Sykes:** It is not true in the United States of course. The FDA will tend to eject drugs that do not show benefit over existing drugs.

**Q444 Dr Naysmith:** You have used the phrase, Sir Richard, quite a lot, “safety and efficacy” and “approved by the market place”. How long would you give for the market place to bring something both safe and efficacious if you were still in charge of a company?

**Sir Richard Sykes:** I do not think it is a time issue; it is a quantitative issue. You could put a drug on the market like a Cox-2 inhibitor, and in one year you have millions of patients on that drug. If you were treating small-cell lung cancer, you would only have perhaps a few thousand. You have to somehow contain that period on numbers of people treated.

**Q445 John Austin:** Lots of people take RSAs, and some of the predecessors have been pretty toxic and have been marketed very heavily and sold in their millions. When are we going to recognise that?

**Sir Richard Sykes:** If you started from square one now and did that, I would say now within a period of three years you would have a pretty good idea of whether those drugs are safe and efficacious. Remember, it is always a risk/benefit ratio. There has to be a risk. There is a risk with every possible drug.
Q446 Dr Naysmith: I think what the industry is play down the risk and play up the benefits.
Sir Richard Sykes: Yes.

Q447 Dr Naysmith: You said there were 15 beta-blockers.
Sir Richard Sykes: I used an example, but there are probably more.

Q448 Dr Naysmith: It will take a very long time until a doctor finds the right one for the right patient, if he is having three months at a time.
Sir Richard Sykes: Until you get the genome sequence for every individual patient and you can use that information to the best advantage to determine which drug—

Q449 Dr Naysmith: That is not there yet, is it?
Sir Richard Sykes: We are not there yet.
Dr Taylor: For clarification, a doctor does not use all 15.
Dr Naysmith: No, but he was talking about finding the right one for a patient.

Q450 Dr Taylor: I wanted to go back to Sir Iain. You have touched on the final recommendation in your paper. The recommendation was that selected promising but inadequately evaluated drugs should be used in the NHS only in the context of controlled evaluative studies until enough is known to judge their cost-effectiveness. Cox-2 inhibitors probably had some real benefits. If Vioxx for example had only been released on a controlled trial basis to start with, would that have allowed it to be restricted in its prescribing, and then when it was eventually released would that have just delayed the discovery of the side effects? Can you comment on that?
Sir Iain Chalmers: I would like to comment on two issues. People embarking on new studies and reporting new studies do not do a systematic review of what is already available in terms of evidence, and when they have new data set the new data in the context of an updated systematic review. We know now, from evidence published in the Lancet a couple of weeks ago, that had such a process been in operation for Vioxx, then the adverse effects might have been identified as long as four years ago. The first thing to do is to take notice of all the current evidence. At the moment, that is impossible because of this problem of publication bias and because of the fact that academia does not value the process of finding out what is known already, using scientifically defensible methods. That is academia’s problem; it really is. It is their fault. In terms of allowing a drug a provisional licence, there may be some drugs that have been given a licence on the basis that they seem to have an encouraging effect with an outcome patients that patients may not value, but which is seen as relevant. In those circumstances, if you want to find out whether it holds value for the patients, the drug should be released in the context of a further evaluation. For example, the Class I anti-arrhythmic drugs were given to people who had heart attacks to try to prevent arrhythmias because arrhythmias were a risk marker for subsequent premature death. These drugs were very good at suppressing arrhythmias, but they were also pretty good at suppressing life; they killed people. They were licensed on the basis of a surrogate outcome, which patients would not have been worried about, and they came into widespread use. An estimate has been made that during every year in the United States at the peak of their use in the late 1980s they were killing more people than all the Americans who had been killed in the whole of the Vietnam war. That shows an example of the kind of circumstance where it would be important to release a drug or a device or a surgical operation—only in the context of a randomised trial, until we knew more about its worth to the NHS and the patients who use the NHS.

Q451 Dr Taylor: In the case of Vioxx, if everything has been available beforehand we would not have got into this problem.
Sir Iain Chalmers: That is the evidence that was published in the Lancet about three weeks ago, that four years ago we could have known there was a real problem.

Q452 Dr Taylor: Can I go on to picking up side effects after marketing, when there is not that bank of information before. The yellow card system, as we have heard so many times, is not really working effectively. It was Professor Vallance who talked about the GP database. How will that help? Professor Vallance: That, and increasing numbers of databases, as the NHS becomes computerised, will allow you to collect data from everyday practice, for dealing with the issue that Sir Richard raised—the variability once a drug is out there in the real world away from the rather tight setting of a clinical trial.

Q453 Dr Taylor: So one will be able to tie up side effects with drugs.
Professor Vallance: Yes. You can on that system already. You can interrogate it. Of course, it is not randomised and not very good at establishing efficacy, but it is quite good for picking up safety signals, and once a drug is out there in practice it is very difficult to get efficacy data unless you have randomised controlled trials; it is much easier to pick up safety signals.

Q454 Mr Bradley: Do you think the Department of Health is the right sponsoring Government department for the pharmaceutical industry as opposed to the DTI?
Sir Richard Sykes: My view has always been that it should be the DTI. The pharmaceutical industry in this country is a global business, not a national business. The DTI is a global business, but the DoH is not global. Therefore, the DTI should be the sponsor. The only reason that the DoH is the sponsor of the pharmaceutical industry is so that the fox would not eat the chickens!
Professor Vallance: Sir Richard knows far more about this than I do, and I think there is some sense in that, but it is not an area I know about.
Sir Iain Chalmers: I was only introduced to this possibility quite recently, and it does seem very sensible. Clearly, the pharmaceutical industry in this country is a very important part of our manufacturing economy, but I do not see that we should subsidise that industry by buying useless treatments for the NHS, just because they are being manufactured in this country. There is a tussle, and I can see that there is a real debate to be had there, presumably at Treasury level, but the NHS ought to be giving the best possible treatment to patients who use it.

Professor Vallance: Sir Richard will comment on it more, but the percentage of the market involved—

Sir Richard Sykes: It is 4% of the world market.

Q455 Dr Taylor: By pure chance we started this inquiry at the stage when Vioxx and SRI’s problems were coming out, so the inquiry was greeted by the press with a huge welcome; but here we are, we are going to expose all the inadequacies of this desperate industry. Is this just prejudice, and would you make a comment on this, because we have this terribly difficult problem of writing this report and getting it right and not blaming an industry, if it is not iniquitous, and blaming it if it is? Do you have any comments?

Sir Richard Sykes: It is not an iniquitous industry. I think it adds great value, first of all to the UK, the industry in this country. It has been one of the great success stories. It has spun off a lot of bioscience activity in this country, which is still some of the best in the world, and that has been very important because it has been a base for many pharmaceutical companies’ research and development, which is critically important for the economy. Like all businesses, they are private businesses and they have shareholders. They have to provide returns. The industry itself has always been highly regarded, particularly in times of recession. Everybody is sick and the industry has always been a good place in terms of investment. Obviously, like anything else in the world today, it becomes very competitive and once people become highly competitive they are driven to do strange things, so I think that today the industry has got a very bad name. That is very unfortunate for an industry that we should look up to and believe in, and that we should be supporting. I think there have to be some big changes. The industry has got to get back on track and get rid of its bad image by being much more transparent in some of the things we have been talking about, by working closer with other bodies, and being much more interactive with the public. We need this industry; it is critically important. We need it to work with other people, with academia and with industry. I think we have a great opportunity in this country to continue to be leaders in this area of research.

Q456 Dr Taylor: You are almost in a unique position to comment from both sides of the argument, so it is very valuable.

Professor Vallance: My experience of research from the industry is that they want to make innovative drugs and often in areas where there is a need, which is sometimes not recognised by doctors but by patients, such as incontinence and other areas. I think within the research side that is what they want to do. From the marketing side they have a different job, which is to sell whatever they have. It seems to me that part of the response to that is to be much more robust about what we are prepared to buy and pay for, and have our own criteria for what works and is an advantage.

Q457 Jim Dowd: You say industry wants to make innovative drugs. We received evidence, certainly when we were in Australia and elsewhere, that the vast majority of intellectual effort in drug companies is now going into maximising patents, not in developing new drugs.

Professor Vallance: I think the research side of industry wants to create new drugs. If you ask anyone in research, that is what their aim is. The marketing and other side of industry may have other objectives which are about patent extension. Within industry there is exactly that tension that you are exploring here. Most people want to make innovative medicines.

Q458 Jim Dowd: Clinical practitioners are all clear-eyed optimists—

Professor Vallance: No. The basic scientists in industry are striving very hard. They recognise that the real money comes from the innovative blockbuster that beats everything else. That is what their focus and energy is on in terms of drug discovery. Another end of industry is all about making the most money you can from what you already have, and that is where patent extension comes in. That is why we need to be much more robust about what we need and what we do not need, and why we need it.

Sir Iain Chalmers: I would like to separate these two things. One is the influence of industry on the scientific record, which at the moment is indefensible, and sly we are agreed on that. There needs to be a great deal more transparency. The other is the influence of industry on the way that drugs are used. Basically, you are in a market place then, and it is up to organisations like NICE to make sure that the NHS gets good value for money. All sorts of tricks will be used, as marketeers will always use to get people to use their products. There is however such a distortion now in that the things that do get studied, because of the economic power of industry and its influence not just on individual academics, but the whole academic institutions, that some important questions are not being addressed. That is a great shame. If one takes of some of the recent innovations that have come not from industry but from looking at old drugs like aspirin and magnesium sulphate—Epsom salts for the treatment of convulsions of women during pregnancy and devices to help people who are having subarachnoid haemorrhage, which are nothing to do with the drug industry—there are all sorts of important questions
like those that are very relevant to patients using the NHS and which are in some instances getting squeezed out because of this increasingly close partnership between industry and academia. I do not think that is a good trend.

Q459 Mrs Calton: What do you advise your colleagues and students about the influence of the pharmaceutical industry on prescribing patterns?
Professor Vallance: We have a pretty robust course for students, which illustrates very clearly the influences on prescribing. We have a system which we introduced for the students which I was explaining to Iain beforehand, which was rather unpopular when I first introduced it, which is a simple evaluation sheet that they carry around on their ward rounds, and when they see anything being prescribed they go away and ask whether it was a reasonable or unreasonable decision, and what was behind it. That was unpopular. The idea of students challenging consultants about the evidence generated a very interesting culture amongst students.

Q460 Jim Dowd: Was there a high mortality rate?  
Professor Vallance: At student level, those are the things we have done. I think it has changed perceptions of students as to how you evaluate evidence. There is an ongoing problem with many doctors that perhaps they are not trained in evaluation skills, and also, coming back to the point about marketeers, sometimes data is presented in a way that is complex to disentangle, and people find that awkward. I do not think many doctors are well equipped to undertake those analyses.

Q461 Mrs Calton: Would you say the sort of practice that you now have when teaching students is widespread, or is it isolated?  
Professor Vallance: It is patchy. It is becoming more common. I think it could be developed further.

Q462 Mrs Calton: What assessment have you made that the teaching is effective in influencing outcomes?  
Professor Vallance: The evidence we have relates to the questions we set in exams and assessments. I do not have prescribing data to show it is valuable; but do anything about it? Do you still think the issue is that if there is strong evidence, patients and clinicians will take notice.

Q463 Mrs Calton: It would be helpful if we had more evidence that this was a useful activity. Certainly the information we received in Australia was that the influence of the pharmaceutical industry on prescribers was extreme, and that those prescribers were not always aware of the influences.  
Professor Vallance: I think that some prescribers are poorly equipped to evaluate the evidence before them. The way evidence is presented is sometimes extremely complicated, with composite end-points wrapped up as though they all meant the same thing, and relative risk being presented when actually it is absolute risk. Simple things could be done, for example, for every medicine trying to evaluate as best you can—although it is not always easy to do it—the numbers you need to treat to gain a beneficial effect and the numbers you need to treat to get a harmful effect. Those two standardised numbers could be quite helpful if everyone were to “buy in” presenting in that way.

Sir Iain Chalmers: When the evidence is strong and you know that it is strong, you can change practice very fast indeed. For example, I referred a moment ago to treating women with Epsom salts rather than far more expensive drugs when they have eclampsia, because the cheaper drugs are better. That evidence was generated completely outside this country in Latin America, Africa and India, and it changed British obstetric practice overnight. Similarly, a study that was done recently, which raised questions about the use of steroids given to people with acute brain injury, was recently published in the Lancet. It shows that this practice, which has been going on for about three decades, has been killing tens of thousands of patients. I am very clear that that will stop pretty dramatically now. The essence of the issue is that if there is strong evidence, patients and clinicians will take notice.

Q464 Dr Naysmith: I would like to ask a peripheral question to Sir Richard. Going back to Dr Taylor’s question, when you talked about the importance of the pharmaceutical industry to the country and the research that was done and so on. During that you mentioned the importance of university research. I have heard you say in the past that academics in this country, particularly scientists, are very poorly paid, and this is one of the things that—not just pay but conditions of service—which reflects on it. People used to come to this country—firms—to do their research, partly because of what was happening, and it still happens now—I am getting to the punch line! You have been managing director of one of our really important university science orientated universities for a couple of years: have you managed to do anything about that? Do you still think the conditions for young scientists in this country could be improved, particularly if you want a pharmaceutical industry, and have you managed to do anything about it?

Sir Richard Sykes: There has certainly been a big change with this Government. We can go back now to the late 90s. This Government has recognised that there are a significant number of issues within universities in terms of teaching and research, and they have changed that quite significantly. There has been a lot of money put into infrastructure so that you build better laboratories and facilities. There has been more money for paying people better salaries. You can always argue that you need more, but I would say today that the top universities are in a much better condition than they were 5–10 years ago. That is improving all the time, and I know the Chancellor will probably say something else about it again today. There is a recognition that we have to put money into these places if we are going to drive the economy. It is critically important. To me, this is
a very, very big issue. We must keep tracking inward investment on the basis that we do have a very big industry.

Q465 Dr Naysmith: You think there has been an improvement and things are getting better.

Sir Richard Sykes: Yes, there is no question about that. The NHS has stood outside this whole biosciences process, and that is totally unacceptable. This is a jewel in the crown. If we could bring all this together, no other country can do this because they do not have this system. If we could bring all these parts together during a period when there will be some dramatic developments in those areas, then I think the UK becomes a very attractive place for businesses to come and operate.

Q466 Chairman: Do any of the witnesses have anything further to add? Is there anything within our terms of reference that you feel we ought to have covered which we have not covered within this session?

Sir Iain Chalmers: There has not been enough disagreement among your witnesses, and I just want to introduce one note of disagreement! It has been estimated that between a third and a half of the increase in life expectancy during the last 50 years, and an increase of five years of life free of morbidity, has been achieved by what has gone on in healthcare. That is a fantastic record. The promise of post-genome medicine is that is going to do better than that. We ought to take with a little pinch of salt some of the promissory notes that we have had from Sir Richard. I also want to make the point that the smaller the thing you study in academia, the higher your status. People interested in clinical research are way down at the bottom of the pile!

Q467 Chairman: I think I should give Sir Richard the right of reply, especially as he is a Yorkshireman!

Sir Richard Sykes: I think we expect too much. We sequenced the genome a few years ago, and we now have 300 genomes; but what we need is a thousand human genome sequences. That will happen because the technology is changing dramatically. Until we get that information and until we start to collate it and understand what is going on, we are competing against hundreds of millions of years of evolution. We cannot do it in five years. It takes time and it will take 10–20 years to see the benefit of those, but it will come.

Q468 Chairman: Professor Vallance, have you anything to add, or are you happy to sit and let them get on with it?

Professor Vallance: There are things coming through. I agree with Iain about healthcare, but things like treating heart attacks with block-busting drugs—there has been a huge change in practice, and a vaccine against cervical cancer viruses holds out huge promises for the future, so I am slightly more optimistic.

Chairman: Thank you for your evidence. It has been a very interesting session.

Memorandum by Research Councils UK (PI 22)

INTRODUCTION

1. Research Councils UK (RCUK) is a strategic partnership that champions the research, engineering and technology supported by the seven UK Research Councils. Through RCUK the Research Councils together with the Arts and Humanities Research Board (AHRB) are creating a common framework for research, training and knowledge transfer. Further details are available at www.rcuk.ac.uk

2. This memorandum is submitted by Research Councils UK on behalf of three of the Research Councils, and represents our independent views. It does not include or necessarily reflect the views of the Office of Science and Technology (OST). RCUK welcomes the opportunity to respond to this inquiry from the House of Commons Health Committee.

3. This memorandum provides evidence from the Council for the Central Laboratories of the Research Councils, Engineering and Physical Sciences Research Council and Medical Research Council. Each Research Council has presented information on different aspects of the inquiry and therefore submissions have not been cross-referenced.

Council for the Central Laboratories of the Research Councils (CCLRC)—Annex 1.
Engineering and Physical Sciences Research Council (EPSRC)—Annex 2.
Medical Research Council (MRC)—Annex 3.

Annex 1

Submission by the Council for the Central Laboratories of the Research Councils (CCLRC)

1. The Council for the Central Laboratory of the Research Councils (CCLRC) owns and operates the Rutherford Appleton Laboratory in Oxfordshire, the Daresbury Laboratory in Cheshire and the Chilbolton Observatory in Hampshire. These world-class institutions support the research community by providing access to advanced facilities and an extensive scientific and technical expertise.
2. One such facility is the Synchrotron Radiation Source (SRS), the UK’s brightest source of ultraviolet light and X-rays, which is based at Daresbury Laboratory and used for research in materials and life sciences. Industry accesses the SRS via the DARTS service and there has been significant usage of the experimental facilities at Daresbury by the pharmaceutical industry.

3. It is primarily at the fundamental research stage that the pharmaceutical industry uses the SRS rather than at the production stage, although the potential to replicate production processes and monitor reactions in real time is gaining in interest. The characteristics of the X-rays generated by the synchrotron mean that problems which are simply intractable in the home laboratory become routine and researchers are able to collect data more quickly than would be possible using their own laboratory resources. Typical experiments include target identification and lead generation using protein crystallography.

4. Rapid screening of target-lead complexes is becoming ever more important and developments in robotics at Daresbury are aiding this. Further down the chain, the identification and characterisation of drug polymorphs is of utmost importance when protecting intellectual property and for regulatory approval. A new treatment developed by Organon for use in anaesthesia was partially characterised using data from the SRS and it is now in clinical trials both in the EU and USA. All of the income generated by this and other industrial activity on the SRS is used for reinvestment in the facilities of CCLRC to benefit the wider research community.

Annex 2

Submission by the Engineering and Physical Sciences Research Council (EPSRC)

INTRODUCTION

1. EPSRC are the main UK government agency for funding research and training in engineering and the physical sciences, investing around £500 million a year in a broad range of subjects—from mathematics to materials science, and from information technology to structural engineering.

2. The Council operate to meet the needs of industry and society by working in partnership with universities to invest in people and scientific discovery and innovation. The knowledge and expertise gained maintains a technological leading edge, builds a strong economy and improves people’s quality of life.

3. The work of EPSRC is complementary to other research investors including other Research Councils, government agencies, industry and the European Union. The Council actively engage in and encourage partnerships and collaborations across disciplines, boundaries and the world.

4. EPSRC also actively promote public engagement in science, engineering and technology.

THE PHARMACEUTICALS INDUSTRY AND UK UNIVERSITIES—AN EPSRC PERSPECTIVE

5. It is important to recognise that the UK pharmaceuticals sector has been highlighted by the DTI R&D Scoreboard as having an especially high R&D intensity, 14.6% compared with 13.0% internationally, and 2.2% for UK industry overall. It is second only to the USA’s industry in this respect.

6. The Pharmaceutical industry has extensive links with UK Universities. The expenditure on research and development by industry within the pharmaceuticals sector is several times larger than the most generous estimates of the relevant public and charitable research spending in these sectors. The pharmaceutical industry is also a major employer of UK science and engineering graduates and postgraduates. It is inevitable, therefore, that the sector plays a significant role in the development of University research and training strategies.

7. As part of its strategy of engagement with industry, EPSRC visits players across this sector on an ongoing basis to increase its understanding of their businesses and to make industry more aware of the opportunities for active interaction with EPSRC policy and activities. This is in addition to the strong relationships with many companies through community consultation and direct participation by industry in peer review and policy panels, research projects and training. Interactions extend to, for example, the secondment of EPSRC staff to placements in pharmaceutical companies. A summary of our internal Pharmaceuticals Sector Brief, setting out our strategy for engagement with the Sector, is attached for additional information at the Annex 4.

8. EPSRC supports a wide range of research and training activities that underpin the pharmaceuticals sector to a total value on 1 April 2003 of £175 million. Figure 1 (overleaf) highlights collaborative research activities with those companies with five or more current collaborations on the census date.

9. EPSRC currently supports over 700 EPSRC funded grants underpinning the pharmaceuticals and biotechnology sectors distributed cross the UK academic sector. Figure 2 (overleaf) shows the academic institutions with current EPSRC grant support of £4 million or greater relevant to the pharmaceuticals and biotechnology sectors. The Sector is active in a wide range of collaborative research activities including Innovative Manufacturing Research Centres, Faraday Partnerships and LINK Programmes.
10. EPSRC has also established a number of Strategic Partnerships with industry where research is jointly commissioned to address areas of common strategic concern. The EPSRC/GSK Combichem Initiative was one of the first such activities and involved an open call for proposals for research in combinatorial and solid phase chemistry with £1.5 million of funding being split equally between EPSRC and GSK. Strategic partnerships R&D is commissioned through the rigorous peer review process required for Research Council funding.

11. EPSRC also supports a range of collaborative training activities with the sector at both masters and doctoral level. The Sector is a major recipient of Industrial CASE studentships where the studentships are allocated to companies who then chose the academic partner that hosts the CASE student. EPSRC allocated a total of 330 Industrial CASE awards in 2001, of which 59 were associated with the pharmaceuticals sector.

**Figure 1**

EPSRC-SUPPORTED COLLABORATIVE RESEARCH ACTIVITIES WITH PHARMACEUTICAL COMPANIES

**Figure 2**

EPSRC-SUPPORTED PHARMACEUTICAL COLLABORATIONS BY INSTITUTION

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*Figure 1: EPSRC collaborative activity with industry on 1 April 2003 relevant to the pharmaceuticals and biotechnology sectors (The contributions data excludes the £750k contribution made by GSK towards the joint EPSRC/GSK call for proposals in combinatorial chemistry).*

*Figure 2: Academic institutions with major current EPSRC grant funding relevant to the pharmaceuticals and biotechnology sectors (University College London does not include funding provided to the Royal Institution).*
Annex 3

Submission by the Medical Research Council (MRC)

INTRODUCTION

1. The Medical Research Council (MRC) is a national organisation funded mainly by the UK tax-payer. With a total income of £480 million (in 2003–04) the Council promote research and training in all areas of medical and related science. The MRC’s mission is:

- To encourage and support high-quality research with the aim of improving human health.
- To produce skilled researchers and to advance and disseminate knowledge and technology to improve the quality of life and economic competitiveness in the UK.
- To promote dialogue with the public about medical research.

2. Delivery of the mission requires close working with industry, the NHS and Health Departments, charities and consumers among other stakeholders. Many of the issues under consideration by the Committee are central to corporate policy development, business planning and decision making. This submission outlines some of the ways in which MRC works in partnership with industry.

THE MRC RESEARCH PORTFOLIO: WORKING WITH THE PHARMACEUTICAL AND OTHER INDUSTRIES

3. The MRC believes that medical research requires approaches at all levels: molecules, cells and tissues, animal models, whole organs, systems, individuals and populations.

4. The MRC is publicly committed to giving greater priority in future to translational research at the basic/clinical interface. As a result, the Council have readily embraced the need for new approaches to partnership-working in clinical research—including working with the pharmaceutical industry—as outlined in recent reports.1 MRC are playing an integral part in the new UK Clinical Research Collaboration (UKCRC), and have welcomed the setting-up of a new Joint MRC/DH Health Research Delivery Group in order to achieve greater strategic co-ordination of medical research between public sector funders.

5. Industry representatives contribute to MRC policy development and funding decisions at strategic and operational levels, for example through membership of the MRC’s Council, research boards and consultative committees. This facilitates a two-way flow of information and ideas about innovative approaches in research and on commercial realities. In this way the Council are able to develop an understanding of areas where there are common goals and areas in which to work together effectively. Industry representatives do not participate in any MRC decisions relating to the companies for which they work.

6. The MRC believe that the pharmaceutical industry values the high quality of MRC research for its contribution to the knowledge base from which all innovation flows. The MRC’s postgraduate and postdoctoral training programmes also delivers trained manpower to industry as well maintaining standards in the academic sector.

7. MRC’s intramural research units engage in a wide range of collaborative research programmes with pharmaceutical, biotechnology and other companies, as do recipients of MRC grant support in the universities. MRC staff also offer their expertise to companies through consultancy agreements. In general, MRC does not undertake commissioned research which is wholly targeted at industry’s goals, as this is not part of the MRC’s mission. Collaborative research therefore reflects shared or complementary interests, or instances where MRC has particular infrastructure or technology to offer as a resource. Issues such as ownership of intellectual property and publication rights are agreed in advance with a view to ensuring that intellectual property is protected where necessary, mechanisms exist for timely exploitation, and results are published subject only to short delays when patent applications are to be filed. MRC scientists retain the ultimate control over the content and presentation of publications in order to preserve scientific integrity. This is typical of collaborations between the pharmaceutical industry and the academic science base and in general companies in this sector have substantial experience of working with academia and are aware of its particular concerns.

8. The MRC has some dozens of collaborations in place at any one time, ranging from basic science through to identification of drug targets, high throughput screening of potential candidate drugs, and clinical trials. A case worth highlighting is the renewal in 2003 of an existing collaboration between the MRC Protein Phosphorylation Unit, and the University of Dundee’s School of Life Sciences with six of the world’s major pharmaceutical companies—AstraZeneca, Boehringer Ingelheim International GmbH, GlaxoSmithKline, Merck Co, Inc. (USA), Merck KGaA (Germany) and Pfizer. The companies agreed to provide further funding of more than £15 million over five years to investigate two classes of enzymes.

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1 (Bioscience 2015—Improving National Health, Increasing National Wealth—a report to Government by the Report by the Bioscience, Innovation and Growth Team; Strengthening Clinical Science—a report from the Academy of Medical Sciences published in October 2003 and Research for Patient Benefit Working Party—a report from the Department of Health in May 2004).
termed kinases and phosphatases, which have become some of the most important classes of drug target in the pharmaceutical industry. Overall the collaboration will have provided funding in excess of £21.5 million over 10 years and supported the creation of over 20 new scientific posts within the specially created Division of Signal Transduction Therapy. Novel pathways and targets have been dissected and a number of patent applications licensed by MRC to partners within the consortium and more widely.

**MRC CLINICAL TRIALS**

9. MRC funding for clinical trials is approximately £18 million per annum. Around 170 trials are currently in progress covering all aspects of medicine from prevention and diagnosis to drug and primary healthcare treatments for a broad range of health problems. MRC trials have established, for example:

- the role of aspirin and of statins in protecting against heart attack and stroke;
- the use of magnesium sulphate in halving risk of pre-eclampsia in pregnancy; and
- a rise in the cure rate for childhood leukaemia to 80%.

10. The MRC’s role in clinical trials complements that of industry: in general the Council are not concerned with trials aimed directly at licensing new drugs. A recent review\(^2\), confirmed the MRC’s commitment to promote trials in areas that may pose methodological challenges and in which the interventions studied may have an important impact on public health. In future, the MRC wishes to place emphasis on trials of complex interventions such as those aimed at behavioural or lifestyle changes; MRC also undertake trials of non-drug interventions such as surgery or radiotherapy. In the pharmaceutical field, the Council undertake a number of trials which provide an independent comparative assessment of different products, often from different companies, for example in the fields of AIDS or cancer. Companies generally welcome such studies, and frequently provide their products and the necessary trial packaging, free of charge.

11. Within UKCRC, MRC will continue to play a leading role in developing trials methodology, drawing for example on expertise at MRC clinical trials units in Oxford and at University College, London. The MRC’s infrastructure for the conduct of trials will also be made available for use in this collaboration.

12. The MRC is a partner in the European Developing Countries Clinical Trials Partnership (EDCTP), formally representing the UK on the governing body. The aim of this initiative (with EU funding of 200 million Euros over five years) is to accelerate development of effective, affordable and sustainable interventions against poverty-related infectious diseases such as HIV, tuberculosis and malaria. Among other things this includes encouraging the participation of industry and developing partnerships. The focus will be on phase II and III trials of preventive interventions and treatments. Funding for research and capacity development will concentrate on Africa initially, with full involvement of the African nations. The MRC also undertake clinical trials of vaccines and potential treatments for infections and tropical diseases in our own research units in The Gambia and Uganda.

13. MRC helps to set standards of good practice in the conduct of clinical trials and clinical research generally through the publication of a range of guidelines in its clinical trials and ethics series. Recipients of MRC funding are expected to follow these guidelines, which are also publicly available on the web and known to be used by a variety of other organisations including industry.

**MRC TECHNOLOGY (MRCT)**

14. MRC owns the intellectual property (IP) arising in its own research units and institutes. Management of this IP is handled by an affiliate company, MRC Technology (MRCT), whose Chief Executive, Roberto Solari, and others in the company have extensive experience of working in and with the pharmaceutical/biotech industry. Its objectives in fostering the industrial development of MRC inventions are based on the MRC mission statement and are designed to attain—in order of priority—improved healthcare products and services, national economic benefit and a financial return to MRC itself.

15. Over the last four years MRCT has completed over 150 licensing deals and generated £60 million in income. Much of this income derives from the sales of therapeutic antibody products using patented antibody engineering technologies developed by MRC teams in Cambridge. Products on the market include antibody-based treatments for breast cancer, leukaemia, colorectal cancer, infant respiratory disease, asthma, psoriasis, kidney transplant rejection and rheumatoid arthritis. A further 30 products are now in late stage clinical trials.

16. MRC has given particular attention to encouraging the formation of new companies, where appropriate, to exploit new MRC technologies. Two of the largest UK biotechnology companies, Celltech and Cambridge Antibody Technology originated as start-ups based on MRC technologies and 15 other MRC start-up companies have either merged with others prior to listing or have attracted substantial

\(^2\) Clinical trials for tomorrow—An MRC review of randomised control trials 2003.
venture capital or corporate financing as private companies. MRC also created a subsidiary, MVM Ltd, to act as investment managers for funds which have raised over £150 million—all from the private sector—for seed and early stage investment in new companies based on life sciences research.

17. Despite these successful interactions with industry there remain some difficulties to overcome. There are massive costs and high risks involved for the pharma industry in taking potential new drugs through pre-clinical development and clinical trials to product launch. Companies are understandably reluctant to take forward results arising from the science base which, while promising, are as yet at too early a stage for commercial investment. The current depression in the biotechnology investment market, in Europe at least, exacerbates the difficulties. While the problem is particularly acute in those fields where the eventual rewards are relatively limited (e.g., potential treatments for tropical diseases or rare disorders) there are many other instances where initial discoveries require further validation and/or development before they can attract industrial or venture capital interest. MRC has taken a number of initiatives to alleviate this problem.

18. In 2003, following a successful pilot scheme, MRC approved a £4.5 million “Development Gap” fund managed by MRCT to support further investigative research and reduction to practice on initial results with commercial potential that arise in MRC Units and Institutes. The research is project-managed to deliver to commercially relevant targets. Through this mechanism, MRC is able to develop its intellectual property into more robust and commercially attractive opportunities.

19. MRCT has also established an Assay Development Group based at its Mill Hill site which converts MRC molecular targets and bench assays into robust high throughput screens (HTS). MRCT collaborates with MRC scientists to develop the assays and re-supplies the “hit” compounds to the scientists for target validation studies. This means that MRC can offer characterised targets with supporting biology to potential commercial partners.

20. For the future, Council has recently approved development of a full business case for MRCT to establish a new drug discovery capability. The Council noted that the emerging vision—of a medicinal chemistry capability within the public sector which will enhance the value of early stage biology in the drug discovery process—had drawn widespread support in the pharmaceutical industry, among venture capitalists and key global health players including MMV and the World Health Organisation.

REGULATORY ISSUES IN MEDICAL RESEARCH—WORKING IN PARTNERSHIP

21. MRC has welcomed recent opportunities to develop a partnership approach to the handling of a range of regulatory issues in medical research. A widely shared desire to maintain public trust in the governance and practice of medical research, whilst ensuring that research is not impeded by excessive regulation, has helped to develop powerful alliances across the sector on a number of regulatory issues. For example:

— MRC worked closely with the medical charities, the Royal Society and others to brief policymakers on the health implications of stem cell research when the legislative framework was being developed.

— Similar joint briefing has been provided for drafting of human tissue legislation and in relation to the EU clinical trials directive.

PUBLIC ENGAGEMENT

22. MRC has taken the lead in establishing The Coalition for Medical Progress (CMP), an alliance of organisations that share the common aim to ensure the UK continues to lead advances in human and animal medicine. Through CMP, representatives from all sectors involved with biomedical research can work together nationally to explain and illustrate the need for and benefits of research involving animals, and to respond to specific issues of public interest. The majority of the UK’s major pharmaceutical companies are members of CMP.

Annex 4

SUMMARY OF EPSRC PHARMACEUTICAL SECTOR BRIEF 2003

SECTOR ANALYSIS

The pharmaceuticals industry is one of the UK’s strengths. Companies based in the UK maintain a significant presence in all the major markets of the world. Overall, one third of UK-based industry is UK-owned and a further one third is US-owned. The UK industry is very research intense. Key data for the industry is listed below:

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investment in UK R&amp;D (2001)</td>
<td>£3.04 billion</td>
</tr>
<tr>
<td>Sales of UK manufactured pharmaceuticals (2001)</td>
<td>£8.79 billion</td>
</tr>
<tr>
<td>Gross Value Added (GVA) (2002)</td>
<td>£20.4 billion</td>
</tr>
<tr>
<td>Total employment (2001)</td>
<td>69,000</td>
</tr>
</tbody>
</table>
The UK pharmaceuticals market itself is relatively small, with only a 3% share by value of the world market for prescription medicines, compared to nearly 40% for the US, but in terms of overall competitiveness, the UK is only second to the US and well ahead of its main European counterparts. One third of the people employed in the pharmaceuticals industry work in research. In addition, another 250,000 jobs are generated in related industries. Figure 2 illustrates the UK’s significant share of the top prescription medicines.

**Figure 2:**

**SHARE OF THE WORLD’S TOP 25 PRESCRIPTION MEDICINES, 1998**

<table>
<thead>
<tr>
<th>Country</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>63%</td>
</tr>
<tr>
<td>UK</td>
<td>17%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>3%</td>
</tr>
<tr>
<td>Sweden</td>
<td>11%</td>
</tr>
<tr>
<td>Germany</td>
<td>6%</td>
</tr>
</tbody>
</table>

In March 2000, the Pharmaceutical Industry Competitiveness Task Force was established with the following terms of reference:

“To bring together the expertise and experience of the industry leaders in the UK with government policy makers to identify and report to the Prime Minister on the steps that may need to be taken to retain and strengthen the competitiveness of the UK business environment for the innovative pharmaceutical industry.”

Industry takes the view that the Task Force has provided an effective platform for dialogue between the Government and the pharmaceutical industry. A further report has been published updating key performance indicators for the industry. The overall conclusions of this report are that the pharmaceutical industry continues to make an important contribution to the UK economy aided by a strong basic scientific research infrastructure within the UK. With regard to medicines, the regulation process was found to be relatively rapid in the UK (but slower than the US) while uptake of new medicines remained slow in the UK compared to other countries.

Pharmaceuticals are one of the UK’s leading manufacturing sectors, bringing in a trade surplus of £2.9 billion in 2001. The figure below shows the world trade in pharmaceuticals in 2001.

**Figure 3:**

**WORLD TRADE IN PHARMACEUTICALS, 2001**
**INDUSTRY R&D**

Expenditure on research and development by industry within the chemicals and pharmaceuticals sectors and the biotechnology industry is several times larger than the most generous estimates of the relevant public and charitable research spending in these sectors. For example, the pharmaceuticals sector conducts some 73% of UK R&D expenditure in its own field, and around 40% of all industrial R&D expenditure in the UK, spending about £7 million each day.

The UK pharmaceuticals sector and biotechnology industry has also been highlighted by the DTI R&D Scoreboard as having an especially high R&D intensity, 14.6% compared with 13.0% internationally, and 2.2% for UK industry overall. It is second only to the USA’s industry in this respect.

As part of its strategy of engagement with industry, EPSRC visits players across this sector on an ongoing basis to increase its understanding of their businesses and to make industry more aware of the opportunities for active interaction with EPSRC policy and activities. This is in addition to the strong relationships with many companies through community consultation and direct participation by industry in peer review and policy panels, research projects and training.

The top 10 players in the UK pharmaceuticals industry in term of recorded R&D spend are GlaxoSmithKline, AstraZeneca, Pfizer, Shire Pharmaceuticals, Eli Lilly, Merial, Roche, Merck Sharp & Dohme, and Novartis. For global companies it is not always meaningful to disentangle UK from global expenditure, but GlaxoSmithKline is recorded by DTI as the largest investor in R&D in the UK, having a global spend of £2.65 billion in 2001, with AstraZeneca recorded at £1.9 billion. Pfizer is recorded by DTI as the sector’s largest investor specifically in the UK in 2001, spending £373 million.

**INDUSTRY DRIVERS**

*Business drivers:*

Considerable restructuring, including significant mergers and acquisitions, has taken place in recent years within the pharmaceuticals sector. Increasing competition, the cost of clinical trials and a shortage of new drugs reaching launch places companies under continuous pressure to develop new products in shorter timeframes.

*Skills base:*

The provision of appropriately trained people in sufficient numbers is a key driver for the sector, both at masters and postgraduate level. There is a need for a broad knowledge base but there is also a need for trained people with specific expertise. Some knowledge gaps have been reported in analytical chemistry, chemoinformatics and bioinformatics.

*Increasing demand for medicines:*

The ageing and increasingly wealthy population will require new treatments and innovative and more effective medicines. There is also an increased emphasis on maintaining and enhancing lifestyles as well as curing diseases. Along with this, moves towards personalised medicines are also likely to open up new opportunities.

*Intellectual property:*

A number of companies have commented on difficulties in agreeing Intellectual Property Rights (IPR) with some universities. This includes commodity chemicals, fine chemicals and pharmaceuticals companies, who report that demands for unacceptable agreements from universities may be limiting collaboration.

*University-academe collaboration:*

Many companies do not see Industrial CASE as a mechanism for training students but rather as a mechanism for maintaining links with university departments. It is also seen as a good route for getting exploratory research done. Difficulties have been reported by some companies in setting up normal CASE type conversions following the introduction of Doctoral Training Accounts (DTA). In some cases companies chose to fund students directly in research areas of interest to them, thus circumventing the above problems.
**Globalisation:**

The business climate in the UK (legal, regulatory, fiscal and social) will be increasingly important in the ability of the UK to attract new investment. Large international companies increasingly set their sights globally when seeking collaborations, with a preparedness to go overseas rather than compromise on IPR. The same global outlook applies when considering recruitment options. Some strong local and regional relationships do exist between industry and Higher Education Institutes (HEI), particularly for small and medium sized companies.

**Research and technology:**

In many areas of scientific research, the focus is shifting from a wholly experimental approach to a combination of modelling and simulation with some experimental validation. Visualisation, imaging and informatics will change the style of work in the future within the chemicals, pharmaceuticals and biotechnology industries.

**THE SECTOR AND EPSRC**

It is widely recognised that the pharmaceuticals sector is large and diverse, with a history of interaction with EPSRC. Overall, EPSRC funding is divided into two funding streams, research and training. All research proposals received by EPSRC are classified according to the sector(s) that they would underpin, whether or not any industrial collaboration is proposed.

For the purpose of this brief, data has been collated for proposals that underpin the pharmaceuticals and biotechnology sectors. In addition, EPSRC co-funds research projects that are led by other Research Councils that also underpins these sectors although this funding is excluded from to the figures quoted below.

EPSRC interaction with companies in these sectors is not restricted to collaborative funding partnerships. EPSRC receives valuable input from industry in peer review and wider strategic consultations. All EPSRC data given in this brief is based on grants current on 1 April 2003. Interactions extend to, for example, the secondment of EPSRC staff to placements in pharmaceutical companies.

As the current EPSRC grant portfolio is dynamic in nature, this only represents a snapshot of current EPSRC funding at a given point in time. The level of EPSRC funding relevant to the pharmaceuticals and biotechnology sectors is shown by programme area below. The total value of grants relevant to the pharmaceuticals and biotechnology sectors is £175 million.

![Figure 5.3:](image)

EPSRC funding by programme area relevant to the pharmaceuticals & biotechnology sectors (The “Other” category contains various cross programme and cross council activities such as the Basic Technology programme).

The figure below only shows the extent of EPSRC research collaboration relevant to the pharmaceuticals and biotechnology sectors for companies with 5 or more current collaborations. Three companies shown viz. AstraZeneca, GSK and Pfizer appear in the top 10 companies of the DTI pharmaceuticals and biotechnology R&D scoreboard for 2002. A number of the other companies appear in other DTI R&D scoreboards.
Current EPSRC collaborative activity with industry relevant to the pharmaceuticals and biotechnology sectors (An additional contribution of £750,000 was made by GSK towards the joint EPSRC/GSK call for proposals in combinatorial chemistry).

EPSRC currently supports over 700 EPSRC funded grants underpinning the pharmaceuticals and biotechnology sectors distributed cross the UK academic sector. The figure below shows the academic institutions with current EPSRC grant support of £4 million or greater relevant to the pharmaceuticals and biotechnology sectors.

Academic institutions with major current EPSRC grant funding relevant to the pharmaceuticals and biotechnology sectors (University College London does not include funding provided to the Royal Institution)

Collaborative Training Activities

EPSRC is currently consolidated its support for industrial relevant collaborative training into University-based Collaborative Training Accounts (CTAs). CTAs combine several previously separate funding mechanisms and schemes within a single account with the purpose of putting collaborative postgraduate education and training on a more strategic footing. EPSRC supported CTAs will consolidate support for training activities relevant to the chemicals, pharmaceuticals and biotechnology sectors listed below.
Engineering Doctorate (EngD):

The EngD is a four-year postgraduate award. It is a radical alternative to the traditional PhD and was designed to be better suited to the needs of industry. EPSRC allocates 10 studentships per annum to each EngD centre:

— UCL—The Bioprocess Leadership Programme—integration of bioprocess research with the generation of entrepreneurial skills through close linkage with the bioprocess industry.
— Birmingham—Formulation Engineering.
— UMIST—Engineering for Manufacture Process and Production.

Masters Training:

EPSRC sponsors masters-level training, including continuing professional development activities, in a number of areas relevant to the Chemicals, Pharmaceuticals including analytical science, bioinformatics, chemical and biochemical/process engineering (including sustainability, clean technology and catalysis), physical and theoretical chemistry and bio-molecular science.

Industrial CASE:

Through Industrial CASE, a number of studentships are allocated to companies. The companies can then choose the academic partner that hosts the CASE student. EPSRC allocated a total of 330 Industrial CASE awards in 2001, of which 59 were associated with the pharmaceuticals sector.

Collaborative Research Activities

Innovative Manufacturing Research Centres (IMRC):

A key element of EPSRC funded IMRCs are the provision of a focused and strategic approach to the support and organisation of manufacturing research within the UK. The Bioprocessing Centre at UCL is of direct relevance to this sector. The centre has been established through direct partnership with a group of leading companies in the field of biopharmaceutical research and will focus on novel ways of translating exciting discoveries in the life sciences to practical outcomes such as advanced medicines.

Faraday Partnerships:

Faraday partnerships aim to promote improved interactions and networks between the UK science, engineering and technology base and industry, through the involvement of intermediate organisations. The Faraday Partnerships of direct relevance to this sector are CRYSTAL (Green Technology for the Chemical and Allied Industries), Insight (High Throughput Technologies for Product and Process Development) and Pro-Bio (UK Centre of Excellence for Biocatalysis).

Foresight Challenge, Foresight LINK and LINK awards:

A number of projects relevant to the pharmaceuticals sector are supported under these schemes including the Institute of Applied Catalysis (iAc), the Centre for Process Analytics and Control Technology (CPACT), Lab-on-a-Chip and Micrograms to Multikilos.

Strategic Partnerships:

EPSRC has recently engaged in a number of flexible funding partnerships with industry. The EPSRC/GSK Combichem Initiative was one of the first single company and EPSRC joint initiatives. An open call for proposals for research in combinatorial and solid phase chemistry was issued, with £1.5 million of funding being split equally between EPSRC and GSK. Discussions with key companies in the sector are ongoing over the development of further strategic partnerships in a number of areas.

Future Issues

Interface with the Chemistry Leadership Council (CLC):

The CLC was established on the recommendation of the DTI Chemicals Innovation and Growth Team (CIGT). The sector team has been engaged with the CLC and more extensively with its Innovation Task Force (ITF) that was charged by the CLC with the identification of research and innovation priorities. The Sector Team is working closely with the ITF in two main areas of common interest; the chemistry/chemical engineering interface and physical organic chemistry. EPSRC has also engaged with CLC and the ITF over the planned development of national and regional Chemicals Innovation Centres (CIC).
**Intellectual Property Rights (IPR):**

The current EPSRC policy is to assign responsibility for the exploitation of intellectual property (and the returns from it) to universities. Consideration will be given to the “signposting” of model agreements and the provision of training to grantholders, where appropriate. The sector team will continue to gather industry views on the successful establishment of IPR arrangements with universities.

**Industrial CASE:**

An internal review of Industrial CASE is currently taking place. One possible outcome may be an attempt to place some Industrial CASE studentships more strategically through sector-specific targeting. The sector team will continue to scope these ideas in sector discussions.

**People:**

Skill shortages have been reported in some areas such as analytical chemistry, chemo- and bio-informatics. However, there is also a greater emphasis from pharmaceuticals companies on the need for the provision of a sufficient number of suitably trained potential recruits compared to other sectors.

**Structure of the Chemistry PhD:**

There has been some discussion recently on the structure of the chemistry PhD and the provision of appropriate postgraduate training. Concerns have been expressed by some pharmaceutical companies over the lack of breadth of knowledge and industrial awareness of some postgraduate applicants.

**EPSRC Peer Review College:**

The sector team has helped to raise awareness of the recent college exercise amongst chemicals, pharmaceuticals and biotechnology companies. This has contributed to industrial membership of the new college and also greater industrial participation in peer review.

**Strategic Partnerships:**

A key aim for the sector is to try to facilitate a number of “Blue chip” type strategic partnerships with industry, aligned to priority research areas within the Chemistry, Life Sciences Interface and Engineering programmes. Options for partnerships could include a joint call for proposals in key research areas, support for industrial research chairs, consortium proposals involving a range of companies or a major joint funded collaborative programme with a single company.

**Future Discussions:**

Sector visits are planned to Roche, Elli Lilly and Evotec OAI in the pharmaceuticals sector and dialogue will also be maintained with the CIA, Association of the British Pharmaceutical Industry (ABPI) and RSC.

**Current Activity and Future Targets**

The Attached analysis depicts current involvement and future targets for the sector team in interacting with pharmaceutical companies. The graphs are based on the six original objectives of EPSRC sector work and illustrate both differences in the level of current and projected engagement with companies across the sectors and also the relative success of achieving each objective within a given sector.
Memorandum by The Association for Human Pharmacology in the Pharmaceutical Industry (PI 107)

1. AHPPI

The Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI) was founded in 1988. We have 152 members—physicians, nurses, clinical scientists, project managers and various types of support staff—who work for organisations, such as pharmaceutical companies and contract research organisations (CRO), involved in the early development of new medicines. Most of the big pharmaceutical companies and CRO in the UK are represented among the membership.

The purpose of the AHPPI is to provide a forum for continuing education in clinical pharmacology—the discipline that underpins early development of new medicines—and in the regulatory aspects of the early development of new medicines. We hold symposia with invited speakers, twice yearly. Membership of the AHPPI is £15 per year and attendance at symposia is free.

We have links with other organisations involved in developing new medicines, such as the ABPI, Institute of Clinical Research, and Contract Clinical Research Association. Also, we share some of our symposia with the Clinical Section of the British Pharmacological Society, an organisation whose members are mostly from university departments of clinical pharmacology. The AHPPI is run by a committee and provides information to members via a website (www.ahppi.org.uk).

2. Phases of Development of a New Medicine

Medicines research is traditionally separated into four phases, although in practice they often overlap. Phases 1 to 3 are done before a licence to market the new medicine is applied for, and phase 4 is done after a licence has been granted. During phases 1 to 3, the material being tested is called an investigational medicinal product (IMP), whereas after licensing it becomes a medicinal product or simply a medicine. Phases 1 to 3 of a successful IMP can take up to 10 years. Few IMP survive all of the phases. The failure rate is highest in phase 1. The phases of development of a “typical” new medicine in humans are shown below.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number and type of subject</th>
<th>Questions asked</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>100–200 healthy subjects</td>
<td>— Is the IMP safe in humans?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— What does the body do to the IMP? (pharmacokinetics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— What does the IMP do to the body? (pharmacodynamics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Might the IMP work in patients?</td>
</tr>
<tr>
<td>2.</td>
<td>200–500 patients with the target disease</td>
<td>— Is the IMP safe in patients?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Does the IMP seem to work in patients? (efficacy)</td>
</tr>
<tr>
<td>3.</td>
<td>1,500–5,000 patients with the target disease</td>
<td>— Is the IMP really safe in patients?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Does the IMP really work in patients?</td>
</tr>
<tr>
<td>4.</td>
<td>many thousands patients with the target disease</td>
<td>— Just how safe is the new medicine? (pharmacovigilance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— How does the new medicine compare with similar medicines?</td>
</tr>
</tbody>
</table>
Trials of IMP in healthy subjects were excluded from the Medicines Act 1968, simply because healthy subjects derive no therapeutic benefit from an IMP. However, all clinical trials, including ones in healthy subjects, have been regulated since the EU Clinical Trials Directive 2001/20/EC was implemented in the UK on 1 May 2004. The main impact of the Directive is on phase 1 trials in healthy subjects.

3. **Phase 1 Trials in Healthy Subjects**

IMP must not be tested in humans before the necessary pre-clinical studies—the chemistry, pharmacology, toxicology and pharmacy of the IMP—have been completed.

Most IMP can and should be tested first in healthy subjects. But the risk must be minimal. The first trials of an IMP in healthy subjects are usually of single doses of the IMP of increasing size. The next trials are usually trials of repeated doses. The aims of the early trials in healthy subjects are to assess the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of the IMP, and to compare the findings with those in animals. Subsequent trials in healthy subjects may:

- assess the efficacy of an IMP or to define the dose for trials in patients, by measuring biomarkers or using challenge agents against which the IMP is tested;
- compare the bioavailability (how much gets into the bloodstream) or the bioequivalence (if the amount that gets into the bloodstream is not significantly different) of different formulations of an IMP;
- assess the effects of things such as food, gender, age and genetic differences on the activity of an IMP;
- assess the possible interaction of an IMP with marketed medicines; and
- assess the absorption, breakdown and elimination of a radiolabelled IMP.

Some of these trials, such as interaction trials, may be done during any phase of IMP development. Compared with patients, healthy subjects are easier to find, more robust, free of other medicines, more likely to respond uniformly, and better at completing long and complex trials. Trials of IMP in healthy subjects have a good safety record.

4. **UK Phase 1 Trials**

The AHPPI surveyed 29 UK phase 1 units that did trials of IMP for the pharmaceutical industry during 1999 and 2000. The total number of trials per year was just over 600. 82% were done by CRO, 17% by pharmaceutical companies with their own phase 1 units, and 1% by academic departments that provide a service to the pharmaceutical industry. Ethics committees took an average of 14 (range 7 to 28) days from submission of an application to written approval. That response time formed the basis of the target of an average of 14 (maximum 21) days that the MHRA set itself to review an application for a phase 1 trial, after implementation of Directive 2001/20/EC.

Since the AHPPI survey, the academic departments have stopped their service and two of the pharmaceutical companies have closed their phase 1 units. So, probably 90% of commercial phase 1 trials in the UK are now done by CRO. Some of the CRO are based in or are close to NHS hospitals, for safety reasons.

One of the CRO (HMR) surveyed over 300 phase 1 trials that it carried out from 1993 to 2001. About one third of the trials came from UK sponsors, one third from sponsors in other European countries, and one third from countries outside Europe, mainly Japan and the USA. The average income per study in 2002 was £284,000 (range £40,000 to £830,000). If we assume that the data for HMR apply to the 600 phase 1 trials done in the UK each year, the total income is about £170 million per year, two thirds of which are exports. If companies do their phase 1 trials in the UK, they are more likely to do their late phase trials in the UK (“pull-through trials”) as well. Also, phase 1 units use various subcontractors and support services, which need to be taken into account when assessing the overall contribution of phase 1 trials to the UK economy. Although income from phase 1 trials is small in comparison with that from the pharmaceutical industry as a whole, phase 1 trials are a vital part of medicines development.

5. **Comparison of Early and Late Phase Trials**

Clinical development of a new medicine can take 10 years and cost up to £500 million, so time is money. At one time, only academic clinical pharmacology units did phase 1 trials in healthy subjects in the UK. In recent years, CRO have taken over that role because they can provide an efficient, effective and high-quality service that enables companies to plan and execute the early clinical development of their IMP to tight timelines. The ABPI estimates that the UK does over half of the commercial phase 1 trials done in Europe.

The pharmaceutical industry would like but rarely gets such a service for phase 2 and 3 trials in the UK, which are usually done in a hospital setting. Recruitment of patients is often slow. Failure to keep to the protocol can render data unusable. Also, failure to comply with good clinical practice may impair the quality of the data, even if usable. Payments demanded by investigators vary widely for the same trial, and can be
excessive. Academic institutions add overheads, often high, to investigators’ charges. A strong pound sterling makes matters worse for overseas’ companies. For those reasons, companies are increasingly placing their phase 2 and 3 trials outside the UK, in low cost areas such as Eastern Europe, Russia and India.

6. IMPACT OF DIRECTIVE 2001/20/EC ON UK PHASE 1 TRIALS

Feedback from AHPPI members since implementation of the Directive on 1 May 2004 indicates that the MHRA has been keeping to its target of 14 to 21 days to review applications for phase 1 trials, whereas the time for ethics committees to review applications for phase 1 trials has increased. Also, the MHRA and ethics committees are both proving slow to review and approve substantial protocol amendments, which are often essential to during phase 1 trials. That is causing serious difficulties for many CRO. Also, there is uncertainty about the future of many of the ethics committees that are currently allowed to review phase 1 trials in healthy subjects.

The evidence so far suggests that the Directive has reduced the number of phase 1 trials being done in the UK. Some pharmaceutical companies are choosing to do their phase 1 trials in EU countries that have not yet fully implemented the Directive. Pharmaceutical companies from countries, such as the USA and Japan, that are outside the EU are deterred by the extra bureaucracy involved in doing their trials in the EU, and not just the UK.

We intend to repeat our AHPPI survey of UK phase 1 units one year after implementation of the Directive, to get more objective information about its impact.

7. REFERENCES


Boyce M, Warrington S. 312 studies of IMP in healthy subjects.


November 2004

Memorandum by Cancer Research UK (PI 59)

1. BACKGROUND: CANCER RESEARCH UK’S ROLE IN DRUG DEVELOPMENT

1.1 Cancer Research UK3 is the world’s largest independent cancer research organisation, with an annual research spend of over £213 million. Cancer Research UK funds research into all aspects of cancer from exploratory biology to clinical trials of novel and existing drugs as well as population-based studies and prevention research.

1.2 Cancer Research UK recognises the high level of capability and expertise within the pharmaceutical industry, particularly in taking novel diagnostics and drugs to market. Cancer Research UK works with the pharmaceutical industry where such collaborations help us achieve our aims.

1.3 Cancer Research Technology Ltd is the technology transfer arm of Cancer Research UK and is responsible for most direct interactions with industry. Cancer Research Technology’s principal function is to facilitate the development of cancer discoveries which could form the basis of new diagnostics, therapeutics, or enabling technologies. Cancer Research Technology handles all licensing and contractual relationships with pharmaceutical companies arising from research funded by Cancer Research UK. All drugs, diagnostics or research tools licensed to pharmaceutical companies by Cancer Research Technology are issued on the condition that the eventual marketed product is aimed at maximising patient benefit.

1.4 Cancer Research UK is Europe’s major non-commercial funder of research into drug innovation. We support this research through project-based and long term funding. The latter provision underpins our funding of specific clinical trials by supporting areas such as exploratory biology and the development of predictive biomarkers for drug efficacy and toxicity.

1.5 Cancer Research UK supports drug innovation work through two main mechanisms.

1.5.1 Firstly, our in-house Drug Development Office takes new drugs first into man4. The Drug Development Office and key Cancer Research UK clinical centres have taken over 100 drugs into man for the first time. Cancer Research UK has traditionally only taken these drugs to a phase in development where they can be licensed out to the pharmaceutical industry. Because of the cost and regulatory requirements we do not conduct clinical trials aimed at gaining marketing authorisation.

3 Registered charity no 1089464.

1.5.2 Cancer Research UK has stringent procedures to ensure the quality and clinical relevance of our early drug development. Around 30–50% of the drugs that our Drug Development Office takes into man for the first time are provided by biotechnology companies. All proposals to take these drugs into clinical trials are required to have detailed protocols, developed by the investigators in collaboration with our Drug Development Office. These protocols are then subject to international expert peer review and internal review by Cancer Research UK’s New Agents Committee. All trials conducted in the UK are required to be scrutinised by independent Research Ethics Committees. Cancer Research UK requires that all results from trials are published. If the drug being tested has been provided by industry then they will bear the full development cost. In these instances Cancer Research Technology and Cancer Research UK’s Drug Development Office will ensure that appropriate intellectual property rights are negotiated for the charity. In return the company will benefit by having access to considerable intellectual expertise across a wide range of disciplines (eg clinical imaging) during the development process and the clinical trials will be conducted in Cancer Research UK centres.

1.5.3 Our second mechanism for supporting innovative drug research focuses on existing licensed drugs being applied in novel ways, or on different types of cancer from the one in which the drug was originally licensed. To support this, Cancer Research UK and the Medical Research Council have created the Clinical Trials Awards and Advisory Committee to peer-review and fund trials that are then run through the National Cancer Research Network. This body only considers trials for which the primary aim is benefit to patients. All results from these trials are scrutinised by an Independent Data Monitoring Committee, who are the only body to see unblinded data. All results emerging from trials approved by the Clinical Trials Awards and Advisory Committee are published.

1.5.4 Pharmaceutical companies may support the above trials in a number of different ways, from providing free drugs, to fully funding some clinical trials. The key issue for Cancer Research UK, irrespective of whether clinical trials do or do not have any industry support, is that trials are all judged by the same transparent mechanism including extensive international peer-review, to judge the quality of the science and public benefit of the proposed trial. Importantly, Cancer Research UK retains control over the trial and the protocol as well as the data generated to which there is unrestricted access for analysis.

2. QUESTION 1: THE IMPACT OF THE PHARMACEUTICAL INDUSTRY ON DRUG INNOVATION

2.1 Pharmaceutical companies play a key role in bringing innovative cancer drugs and diagnostics to market. However, advances in oncology should not only be considered in the context of individual drugs, but also the use of these drugs in combination with other drugs, surgical techniques or radiotherapy. We appreciate that for commercial or legal reasons it is often difficult for the pharmaceutical industry to make drugs available for clinical trials evaluating combinations of novel treatments. Nevertheless, it is essential that the UK finds a way to overcome this barrier for the best patient outcomes from both commercially and publicly-funded research. The academic sector has a critical role to play in evaluating novel treatment combinations, but may require funding support from Government or the pharmaceutical industry in order to do so.

2.2 The pharmaceutical industry has the capacity to make a huge difference in drug innovation by further investment in novel approaches to early drug development. This could be achieved by greater partnership with not-for-profit research organisations. The future success of the pharmaceutical industry depends on taking new discoveries to the clinic, and we believe a more flexible partnership with the academic community would further enable such innovation. Failure rates in taking cancer drugs to market are high (around 95%), due mainly to difficulties in demonstrating efficacy or for safety reasons. This clearly demonstrates the need for better experimental models, and for proof-of-principle trials to be performed earlier in the development process to prove that the drug will work according to expectation. These are both areas in which academia has particular expertise.

2.3 As failure rates in drug development are so high, and the costs of development so enormous, Government needs to be careful not to further constrain useful drug development with an increasingly stringent and rigid regulatory regime. An example of such constraint is the requirement for primate research for certain types of pre-clinical assessment. If the costs and barriers for drug development continue to increase, fewer new drugs will come to market, thus stifling innovation and, more importantly, potential patient benefit.

2.4 The increasingly high costs of drug development also mean that pharmaceutical companies are less willing to take risks in developing drugs. This is particularly the case when developing drugs for small patient populations, such as some cancers.

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2.5 We welcome the European Commission call that support is needed for further research on rare and orphan disease areas, given their current neglect by the pharmaceutical industry. The majority of clinical research in this area is funded by the non-commercial sector. Cancer Research UK, for example, funds clinical trials conducted by the United Kingdom Children’s Cancer Study Group. There is little incentive for industry to conduct research aimed at small patient populations.

2.6 It is important that studies are carried out which identify which subgroups will benefit from particular therapies. There is currently a lack of pharmaceutical industry funding for these studies, which will, in effect, reduce market size for their products. However in the long term such studies can reduce the drug costs for the NHS by only treating those that will benefit. It is the responsibility of Government, possibly through the academic sector, to ensure that such studies are carried out, and the cost of the resulting diagnostic approaches is met.

3. QUESTION 2: THE IMPACT OF THE PHARMACEUTICAL INDUSTRY ON THE CONDUCT OF MEDICAL RESEARCH

3.1 Cancer Research UK undertakes certain projects in collaboration with pharmaceutical companies. However, there are many areas of our work in which pharmaceutical companies do not have a strategic interest. Examples of these include the development of drugs aimed at cancer in children and orphan conditions, or radiotherapy and preventative research.

3.2 Currently there is no obligation on pharmaceutical companies to publish the results of all trials. Whilst studies have shown that pharmaceutical support does not affect publication of late phase clinical trials, studies comparing all clinical trials have indicated overall that pharmaceutically sponsored trials are less likely to be published. This is of concern as a failure to publish can lead to overestimation of treatment effects, which has the potential to lead to inappropriate treatment decisions. We welcome recent decisions from some pharmaceutical companies (most recently Eli Lilly and GlaxoSmithKline) to publish all research results on the web, and would encourage other companies to follow suit. Ideally these results would be best placed on a comprehensive database for registration of all trials and their results.

3.3 It is important that the pharmaceutical industry is not only focused on specific endpoints in medical trials, but investigates the wider effects of drugs. This information would not only be useful in the drug development process, but also to the wider clinical community when the drug comes to be used in practice or in future research.

3.4 Increasingly research and development conducted on behalf of the pharmaceutical industry is relocating away from the UK to countries presenting larger markets for pharmaceutical products. As long as the UK National Health Service lags behind in adopting new treatments, the pharmaceutical industry will increasingly look elsewhere for future research and development investment. Research and development conducted for the pharmaceutical industry underpins non-commercial medical research in the UK, and the loss of such research activity would present a risk to UK medical research capability as a whole.

4. QUESTION 3: THE IMPACT OF THE PHARMACEUTICAL INDUSTRY ON THE PROVISION OF DRUG INFORMATION AND PROMOTION

4.1 The provision of accurate information to patients, through our CancerHelp UK website and a team of information nurses, is integral to Cancer Research UK’s mission. On occasion, Cancer Research UK does attend briefings on specific drugs by pharmaceutical companies. However before any information is passed on to patients, we take independent advice, and we will not promote the prescribing of any one drug.

4.2 Cancer Research UK supports the current regulations prohibiting direct-to-consumer advertising, and does not believe that they should be relaxed.

4.3 The increased emphasis on the development of lobbying groups by pharmaceutical companies to raise interest in the adoption of drugs or techniques is of concern. This can result in groups or individuals pushing for action in a particular area, without adequate consideration of the relevant evidence base.

4.4 The funding of researchers by pharmaceutical companies to publish papers in journals to promote particular drugs in the absence of any new data should be discouraged.

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6 An orphan disease is a disease for which no treatment has been developed because of its rarity.
7 Commission of the European Communities. A stronger European-based pharmaceutical industry for the benefit of the patient—a call to action. 2003:35.
5. **Question 4: The Impact of the Pharmaceutical Industry on Professional and Patient Education**

5.1 Cancer Research UK provides information on cancer prevention to General Practitioners and other health care professionals.

5.2 Clinicians and researchers are offered a great deal of unsolicited information and invitations from pharmaceutical companies. It is therefore important, in the interests of transparency, that there is a greater emphasis on declaration of interests for all those involved in research, both in the not-for-profit and pharmaceutical industries.

5.3 The European Medicines Agency reports that patients are now actively looking for information on diseases and medicines, and therefore providers of information should take account of this trend. There is a need for clear, objective information for patients. Whilst pharmaceutical companies offer information to patients on treatments, this information will usually be linked to one particular drug or service and may therefore not provide a full picture of all the treatment options available. In this context the work of NHS Information Partners service is welcomed.

6. **Question 5: The Impact of the Pharmaceutical Industry on Regulatory Review of Drug Safety and Efficacy**

6.1 Cancer Research UK is not actively involved in the regulatory review of drug safety and efficacy.


7.1 Cancer Research UK responds to consultations from NICE on the basis of the knowledge of experts in the field and feeds their comments on draft guidance back to NICE on their behalf.

7.2 Pharmaceutical companies have an important role to play in providing information on drugs as they undergo the process by which drugs achieve approval by the National Institute of Clinical Excellence (NICE). During the appraisal of a given drug, Cancer Research UK will therefore on occasion attend briefings by manufacturers, as well as seeking independent advice.

7.3 The World Health Organisation (WHO) review of the NICE Technology Appraisal Process referred specifically to the influence the pharmaceutical companies have in this process. The WHO recommended that NICE address the inconsistency that commercial-in-confidence data will be accepted from pharmaceutical companies, whereas data that are unpublished or in abstract form will not be accepted from other sources.

7.4 In addition, the WHO recommended that NICE should reduce duplication of effort in the assessment phase of technology appraisal development as both manufacturers and the appointed appraisal team produce separate reports to the NICE Appraisal Committee for evaluation. The WHO recommended that the appraisal team produce a single set of analyses incorporating consultation with and input from the manufacturer. All analyses carried out by the pharmaceutical industry should be subject to careful scrutiny.

7.5 There is also some concern over the influence that manufacturers have on the topics considered by NICE for appraisal. Cancer Research UK has asked that more transparent processes be put in place to define the process by which drugs are referred for appraisal or not. We have also asked that a rationale be provided for the process of prioritisation of drugs for appraisal by NICE.

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*Witnesses:* Dr Roberto Solari, Chief Executive Officer, MRC Technology, Medical Research Council, Dr Malcolm Boyce, Chair, Association for Human Pharmacology in the Pharmaceutical Industry, and Mr Harpal Kumar, Chief Operating Officer, Cancer Research UK and Chief Executive Officer, Cancer Research Technology, examined.

**Q469 Chairman:** Welcome to our second set of witnesses this morning. Once again, can I express our thanks for your co-operation with our inquiry. Would you briefly introduce yourselves?  
**Dr Boyce:** I am a physician, a clinical pharmacologist, and I manage a contract research organisation called Hammersmith Medicines Research, which is based at the Central Middlesex Hospital, an NHS hospital. It is a bit unusual for the private sector to be embedded in the public sector. I largely undertake evaluation of potential new medicines for the pharmaceutical industry.  
**Dr Solari:** I am Roberto Solari, Chief Executive of Medical Research Council Technology, the technology transfer arm of the Medical Research Council.
Mr Kumar: I am Harpal Kumar, Chief Operating Officer of Cancer Research UK and Chief Executive of the Cancer Research Technology, which is the technology transfer and development arm of Cancer Research UK.

Q470 Chairman: Can I ask you all to speak up; it is not particularly easy to hear in this room and we want to be sure of what you are saying. The MRC stated that it shares a desire to maintain public trust in the governance and practice of medical research. How do you feel this trust can be best achieved?

Dr Solari: In matters of trust you need, as speakers this morning have said, transparency. People have to feel they know what is going on and have access to the information. They have to build this trust with all stakeholders in industry, and the public.

Q471 Chairman: Do you think that genuine transparency is achievable within a situation where you have this tension in terms of competition and companies obviously wanting to succeed with their products? Is it something we could achieve in the way that you are suggesting you would like?

Dr Solari: You have to look at the drug discovery process and the drug development process, and clinical trials as a very long and complex series of events, which can take anywhere from 15 years from early discovery right through to the product reaching the market. There are periods during that 15-year process where you have to keep things secret in order to protect your advantage over the competition, because this is a business. In the early stages, where you may have discovered a new compound or chemical entity that has some activity, there is still an awful lot of work to do before that early discovery becomes a product. You want to keep that secret, like any business would keep trade secrets to themselves. Coming to a certain point you do make disclosures and file patents, and patents are published. There is a period where just for the functioning of the industry you need to keep certain things secret, but later on in the process when it is appropriate and possible, that information becomes open and transparent. You have to look at the whole process.

Dr Boyce: Can I emphasise something that did not come out clearly in the previous evidence? It is very important to separate the stages of drug development, which can broadly be described as early and late. Early clinical development is essentially part of research, whereas late clinical development once a product begins to emerge tends to be influenced much more by the marketing group. The early group, the research—in my years of experience of working within the industry, as a pharmaceutical physician working within the NHS doing clinical trials, setting them up around the world—the commitment and sense of altruism amongst researchers, whether they are voluntary researchers or in the clinics, is absolutely the same as it is for academia. Indeed, it is probably more transparent because there are those who work—certainly in my experience of trying to liaise with those in academia—they want the money and they want the funding, but they do not necessarily want to recognise the association, so it is a much more insidious relationship. The transparency is there in early drug development. I certainly have no problems whatsoever in recognising that. Occasionally, the industry is less than open about publication of results but we have to remember that the attrition rate is very high in early drug development, some would say as high as 80%, certainly the majority of molecules. Incidentally, I wanted the opportunity to comment on “me too” and your experience in Australia. Our unit works almost exclusively on new molecules. There are abundant new molecules coming through. If you think all the drugs coming through are patent extensions, you should come out and see our unit because that is not our experience. I could give a spirited defence of “me too” products because there is plenty of evidence that, when there are lots of “me too” products, the one that come on early to the market drop out and the ones that are developed as “me too” often are the ones that succeed. To get back to the publication, I have certainly run into difficulties with publishing work when I was based in the industry and in my current practice. I have had problems in recent years persuading companies to publish the work. They do not want to publish it because it is negative. They do not think it merits publishing, or they do not want their competitors to know that they are in a particular area of research. I battle against that. Often they are short sighted. You have to understand the pharmaceutical industry is a large organisation. They do not always have clear policies. You will get a decision from one person and a different one from another. Although the ethos may be towards publication in practice it does not always work out. One has to battle to get publications done but I have always succeeded in doing that and there are ways in which you could make that a bit more transparent. Ethics committees are burdened with lots of unnecessary things but one condition of ethical approval could be that the results are published. That is a gateway and it would be very easy to control all the clinical trials like that. Secondly, the European Clinical Trials Directive requires all clinical trials of investigational medicinal products to be registered, to get a Eudra CT number. That is going to be a marvellous way of monitoring the trials done within Europe and following them up to see how many of them get published. It will be owned by the European Commission and I do not think necessarily by the individual regulatory authorities but I do not know enough about that to comment.

Q472 Dr Naysmith: You said that you tried slightly to justify not publishing negative results. Do you not think that not publishing negative results is dishonest? It is cheating, certainly.

Dr Boyce: Or they are not interesting enough.

Q473 Dr Naysmith: I am distinguishing between publishing an academic journal and a firm saying, “These are negative results.”
Dr Boyce: If it merits publication, it should be published. There are sometimes differences of opinion about whether something merits publication, even amongst academics.

Q474 Dr Naysmith: I am not talking about something meriting publication in the sense of being a scientific paper that lots of people will consult. If you have a drug company doing research and it gets negative results, not to publish them, even if they have to publish them at your expense rather than through a journal, is dishonest.

Dr Boyce: I would not say it is dishonest. It is not sensible. It is not in the interests of medicine in general.

Mr Kumar: You have asked two questions, one about trust and one about transparency. With regard to the question of trust, our own experience in Cancer Research UK where we raise around £350 million every year from the British public is a testimony to the fact that the British public does have trust in medical research carried out in this country. On the general principle of is there trust in medical research, I would say yes. Clearly some of the disclosures or allegations that have been made on various boards, but I do not believe there is a loss of trust in medical research, I would say yes. Clearly some of those disclosures or allegations that have been made over the last several weeks with regard to some of the conflicts of interest amongst pharmaceutical industry might affect that but I think it is unlikely to affect the generality of medical research. It is more about some specific practices. With regard to can we achieve transparency, I would argue that we could achieve sufficient transparency. We, as you know, have argued for a register of all clinical trials so that every clinical trial should be required to be registered centrally; and secondly for publication of all clinical trial results. There are probably ways in which the concerns of the pharmaceutical industry might be mitigated with regard to early phase studies but ultimately all trial results should be published and if that were done I think we would have sufficient transparency.

Q475 Jim Dowd: You said there is general trust in medical research in this country. Is it not the case though that it depends who is carrying it out? I am sure that is true of Cancer Research UK, the British Heart Foundation and others, where they are seen to be a charity or at least not for profit, when they are doing it but when any of the large pharmaceutical companies do it is there not a higher degree of scepticism?

Mr Kumar: The surveys we have seen ask the general question about research as opposed to the question about who is carrying it out. You see percentage numbers around the 70s and 80s in terms of general support for the carrying out of research, so that is the basis upon which I make my statement.

Q476 Dr Naysmith: Do people know it is being carried out by Cancer Research?

Mr Kumar: The surveys I am talking about are just generally about research without saying that we are commissioning the survey.

Q477 Dr Naysmith: Dr Solari, in the written evidence you say that industry representatives contribute to the development of MRC policy and funding decisions at strategic and practical levels. How does this happen? Is there an equal, reciprocal arrangement? In other words, does the MRC attempt to shape drug firms’ research policy or policy in other areas?

Dr Solari: The MRC is governed by a council and there is one industry representative member of council which is a ministerial appointment. It is publicly advertised. That is one person out of about 20. I do not believe there is an undue influence but industry is one of the important partners for the MRC. The MRC has a number of partners. It has the Department of Health; it has universities, other research funders, medical charities and the UK public. What the MRC tries to do is to make sure that on all of its bodies, governance bodies and boards, there are representatives of all of our stakeholders. I think that is one of the great strengths of the MRC, that it is an independent body but that it interacts effectively with all of the bodies with whom it needs to interact. It is part of our remit to have representatives on our council and on our various boards, but I do not believe there is inappropriate influence. Do we influence them? I hope we do. The MRC is one of the greatest supporters of high quality medical research in the world, with 23 Nobel prizes so far awarded to MRC scientists or scientists supported by the MRC. The track record of the MRC is outstanding. I believe we have shaped, biomedical research in a global sense, so yes, I would be surprised if we have not influenced industry.

Q478 Dr Naysmith: Does the Medical Research Council decide that maybe something is needed, a treatment or something, and look around to try and influence the pharmaceutical industry to provide that kind of research that will answer the problem that they are talking about?

Dr Solari: I believe the sorts of clinical trials that the MRC does and supports are different to the clinical trials that the pharmaceutical industry does so we do not do trials on new drugs. You heard about some of them earlier—the Epsom salts for pre-eclampsia; the use of steroids for brain inflammation following head trauma. They were trials supported by the MRC.

Q479 Dr Naysmith: Does the MRC initiate any of these? Do you have anyone looking around and saying, “There is this gap that needs to be filled and nobody is filling it. Can we help?”

Dr Solari: Yes, I believe we do. For example, prophylactic antibiotic treatment of young children with AIDS in Zambia. That was a gap that was seen by the MRC and the MRC supported that trial and showed that there was a real advantage to prophylactic use of co trimoxazole. Yes, I think the MRC does identify those needs. Sometimes they involve a drug that is made by a drug company and so we would ask the drug company to supply that drug for the trial. They are very willing to do that.
The large, prospective use of statins to reduce heart attacks and stroke was such a study. It was done in partnership with a pharmaceutical company but it was to answer a very broad, unmet medical need or question for society.

**Q480 Dr Naysmith:** Do you think there are any adverse effects of this not terribly close but close-ish relationship between the MRC and the drug companies, or some drug companies?

Dr Solari: Potentially. We have to be aware that they are businesses and they are run along business lines. We are here to serve the public good. We have to make sure that our partnership does not stray into areas where they are driving our agenda. We need the pharmaceutical industry and they need us to deliver improved health care. We have checks and balances. We make sure that there is no undue pressure by the pharmaceutical industry on the activities of the MRC but it is potentially a concern and we watch for it very carefully.

Mr Kumar: For Cancer Research UK, I would answer the question in a very similar way to the way that Roberto did. We tend to do two types of clinical trials. We develop new drugs that arise out of the research that Cancer Research UK funds, whether in its own institutes or universities around the country. Sometimes those give rise to new drug possibilities and we will carry out internally the early phase studies on those drugs prior to partnering them with a biotech or a pharmaceutical company.

In those cases, all of our studies are entirely controlled by us with no influence from pharmaceutical companies at all. We also do a number of later phase studies and those span every possible type of study you might think of, from the types of things that Roberto was talking about to does broccoli help you avoid bowel cancer, to new studies on drugs either prior to or post registration. In the cases where we are looking at those types of trials, we will always insist that we control the protocol and the study design. To the extent that a pharmaceutical company is involved at all, it would only be to give a sum of money in the form of an educational grant which would simply be for funding data monitors or the supply of a drug. It would not be to have any control over the trial at all.

Dr Boyce: We contract a lot of trials for the industry but I cannot name a single instance where they have tried to influence the procedures and the results. They might argue about the interpretation but that is not unusual even amongst academics. If there is a breakdown of trust between the pharmaceutical industry and society, that surely must stem from the breakdown of trust about science rather than the industry alone. I do not think the industry has a patent on lack of trust. That largely stems from the lack of grasp of understanding of the general public.

At least that is the way I see it. We can produce evidence that something is not useful but it does not prevent people going on doing it. I wonder how many people in this room took their vitamins this morning. All the evidence is that they are not useful but if you believe published data there will be several people in this room who have taken vitamins. A well informed public is not taking any notice of scientific facts. The trust surely has to start with education rather than the pharmaceutical industry. I think it is a bit unfair to blame the pharmaceutical industry for lack of trust over science.

**Q481 Dr Naysmith:** Sir Richard Sykes was giving the answer to your vitamin thing. There may be a tiny proportion of the population who will benefit but Sir Richard Sykes was saying that very shortly you will be able to identify the relatively small number who want a particular vitamin and make sure they have it. That will be the end of the vitamin industry.

Dr Boyce: That is a lovely concept but I fear that Sir Richard is incorrect.

**Q482 Dr Naysmith:** Have you come across ghost writing of papers?

Dr Boyce: I have in the pharmaceutical industry, yes. Once or twice I have been asked to do it but they have been multicentre studies throughout the world that I have organised and set up.

**Q483 Dr Naysmith:** You must have lots of people who—

Dr Boyce: The problem with academics is, despite the fact that they need publication for their success within academia, they are not always good at writing up the publications and they do not always write well.

**Q484 Dr Naysmith:** Do you write for them?

Dr Boyce: No, I have never done it, but I have known individuals within a pharmaceutical company write up a publication in which the company was involved. Always, the clinicians who do the study are involved and they have a say in interpretation. If they do not like the conclusions, that is because they have not spoken up.

**Q485 Mr Burns:** When they have been ghost written, from your experience, does it say anywhere in the document it has been ghost written?

Dr Boyce: We have to define what you mean by “ghost written”. Many professors put their name on the end of a paper written within their own department and they may have very little input into that study.

**Q486 Dr Naysmith:** In my experience they always say, “The original idea was mine.”

Dr Boyce: Yes. You could argue that the paper has been ghost written for the professor. The difficult bit is getting a blank sheet of paper into a first draft. Lots of people can do that but the honing and shaping requires input from everybody. Providing the clinicians, the sponsors and everybody has two penneyworth, I do not have any strong feelings about who writes the first draft but I do not call that ghost writing. Some people are better motivated than others at writing up papers.

**Q487 Mr Burns:** I recognise that people are very busy but in the non-academic world if a politician, for example, writes his memoirs and they are ghost
written it usually says, “Fred Bloggs with Joe Smith.” People understand that it is not Fred Bloggs who has written from word one to the last word at the end of the book. If there is a professor who is an acknowledged expert in a particular field of research and his name is put on the document, it will be put on the document for one particular purpose, which is it will seek to give credence to the content of that document because that individual has a reputation for expertise in that field. If that individual has done no work on writing the document and it is the work of others, is that not somewhat misleading and very disingenuous?

Dr Boyce: Yes, I agree entirely. There are rules about publication and authorship. In that instance you have just cited, it would be quite wrong of that opinion leader, which is the term people in the industry use for someone that is well known and influences prescribing habits, to allow his name to go onto the paper.

Q488 Dr Taylor: Mr Kumar, I was pleased to hear you say that if Cancer Research UK are taking part in a combined study with industry you control the study and the design. You insist on publication?

Mr Kumar: We do, of every trial we fund.

Q489 Dr Taylor: And the MRC?

Dr Solarri: I believe it is the case for the MRC as well.

Q490 Dr Taylor: I was very intrigued with Dr Boyce’s suggestion that a condition of ethical approval should be that results are published. Is that a feasible condition to put on? Is it practicable?

Dr Boyce: I believe it is, yes. It is also a requirement of the Declaration of Helsinki, the 2000 version, which has not been recognised under the EU Directive but I think it could be. It is in many protocols. It is also a requirement of good clinical practice that there be within the protocol a statement about publication. If I write the protocol, I always put “if the results merit.” Sometimes, despite the fact that they are negative, if you are just doing a single dose rising study to assess tolerability, there is nothing of any scientific value in the study and nobody is really interested in publishing it. It is not hiding it; it just does not merit publication. Maybe when you start to get a randomised trial, which was mentioned by one of the speakers this morning, then obviously I agree it should be published.

Q491 Dr Taylor: That sort of very early study probably would not have ethical approval.

Dr Boyce: It would. Every clinical trial has to have ethical approval.

Q492 Dr Taylor: I thought those were before you got on to the stage of clinical trials.

Dr Boyce: Under the EU Directive, since I May this year, every clinical trial and investigation of a medicinal product, of a potential new medicine, must now have approval of the MHRA and the Research Ethics Committee.

Q493 Dr Taylor: It would seem to me to be a very simple, straightforward recommendation for us.

Dr Boyce: Yes. There should be a statement in every protocol. That is good clinical practice. Several years ago I wrote a publication policy for our own company along those lines. Sometimes the pharmaceutical companies are a bit naughty. We do the work but they go off and publish it. They do not tell us. Sometimes they give us recognition but they do not include us amongst the authors. Under the new rules of authorship, that is probably okay but it is very discourteous to publish something that somebody else has done and not tell them. Usually when we publish there is good collaboration. We discuss the paper. We have different interpretations. We come to an agreement about the wording. In the early stages, it is researched. It is in nobody’s interests to distort the results in early studies. Everybody wants to know: is this a useful medicine? Does it need to go into late development? If not, it needs to be put in the bin and another one tried.

Q494 Dr Naysmith: When I talk about negative results, it is when you do three or four trials and most of them are negative but one shows up as positive. You then suppress the four or five and use the one that shows that your drug is accurate.

Dr Boyce: That is quite wrong.

Q495 Mrs Calton: It seems to me that there is room here for a grey area around the decision not to publish trial results or parts of them. Who makes the decision?

Dr Boyce: For the research that I do, we make it as a group. Often I say, “This is a very interesting result. It adds to the literature. We should publish it.” Nowadays, somebody else writes the first draft. I never allow my name to go on a publication unless I have had a substantial input into it. Until recent years, I always seemed to be the fall guy who wrote the first draft and took it through because I enjoy doing that. There is nothing better than doing a study with a brand new molecule and getting a very interesting result that is going to set the development in process. The decision is usually made amongst the group, as in academia.

Q496 Mrs Calton: Can you tell me who the members of that group would be?

Dr Boyce: It would be the clinical pharmacologist doing the trial and representatives within the pharmaceutical company.

Q497 Mrs Calton: Would they ever say, “We do not think this should go forward”?

Dr Boyce: They may, yes. I have cited examples where it has happened to me, where I have said, “I would like to publish this. It is in the protocol. It says, ‘if the results merit’” which is usually my phrase. Then either the sponsor or us, the investigators, will write the first draft and send it to all the other individuals involved in carrying out the trial to comment in order to hone and polish the final paper. It is a group of people but occasionally when I have initiated that process the pharmaceutical
industry says no. That has happened to me and I have always battled against it. I could give you examples. Once, when I worked in a pharmaceutical company—this is going back 20 years—when I wanted to publish something, I had agreement with academics. They said, “Will we be able to publish this?” I said, “Yes” and I put that in the protocol. It went through a protocol review process so the people in the company had seen it. I was not doing things on my own. When we wanted to publish it, we wrote the first draft and I submitted it to the company for comments. They said, “No, you cannot publish it.” I said, “But you said earlier on I could” and I was threatened with a High Court injunction if I went ahead to do it. Unfortunately the academics backed off, not me. I was in the company, I was left very vulnerable for a period. It was published a year later. A lot of the time it is a storm in a teacup. There is not the need for secrecy in the early clinical development. Once a new molecule goes into studies in humans, it does not go into humans until it is patented and protected. Then you have to produce an information leaflet for the subject. Aunt Mabel would know about it and the man in the street might be a volunteer. Why should it not be published? There seems little point in holding back.

Q498 Mrs Calton: Effectively, from what you are saying, the sponsoring company that clearly has an interest might well block publication?
Dr Boyce: Yes, often for the wrong reasons.

Q499 Mrs Calton: Whatever the reasons, the point is the public and those who are buying the drug subsequently—
Dr Boyce: This may be 10 years away from becoming a product that is sold to the public. The attrition rate is very high.
Mr Kumar: I think there is a relatively simple way of overcoming the greyness that you describe which is if that drug ever does make it to market, regardless of what the reasons were for not publishing when the early phase studies were done, whether it did not merit or commercially in confidence, as and when a drug hits the market all data should be published. That way you overcome any greyness that there might have been through the process.

Q500 Mrs Calton: Earlier you said that Cancer Research UK would always publish the clinical results of the studies.
Mr Kumar: We insist on publication. Sometimes, where we fund academics in universities, given that we do not employ those people it is not possible for us to absolutely force them to do it, if they have other priorities. We can put pressure on them to do it but the terms and conditions are that they must publish.

Q501 Mrs Calton: They must publish all parts of all studies?
Mr Kumar: Everything, yes.
Dr Taylor: By making publication a condition of approval, we remove the grey area and I hope that is a recommendation we will come to.

Q502 Jim Dowd: Has anybody ever resisted that?
Mr Kumar: If they do we do not fund them, but I am not aware of anyone.

Q503 Chairman: Dr Boyce, on the issue of patient involvement, we were interested in Australia to see more patient involvement there in the research and approval process than we have here. I wondered how could the conduct of medical research be improved in terms of patient involvement and consent to the publication of the data obtained from all clinical trials? Have you any thoughts on this?
Dr Boyce: Yes. The problem with the trials that we do is that the subjects are mostly healthy volunteers. By the time we get the results, we have lost contact with the subjects. Many of them do not want to know the results. That may seem strange but they do not. There are requirements within the European Clinical Trial Directive which encourage researchers to give their results to the research subjects. There is already the concept within the legislation—and as you well know the Directive is law—to encourage subjects to have access to research information. In the very early clinical trials, often the results do not mean very much to a healthy subject unless they are interested in the science or the medicine.
Dr Solari: The MRC has an active policy called “Science in Society” which is to enhance the public’s engagement in medical research, in clinical trials and health practice. We are very active and we commit a certain amount of our funds to trying to engage the public in a greater awareness of how medical research is performing.

Q504 Chairman: Have you looked at examples from anywhere else in the world? We went to Australia specifically but I am sure there are other countries who are engaging with patients in a way that maybe we are not sufficiently.
Dr Solari: I would have to check with the office.
Mr Kumar: For all of our late phase trial work, that is carried out as part of a partnership through the NCRN, for all cancer trials. There is a very specific consumer liaison group that is involved in the design of all those studies and the initiation of several of them.

Q505 Mr Bradley: Mr Kumar, you say there is a lack of industry funded research into studies that might identify the specific patient who might benefit from a treatment. Can you explain what the problem is, how it has arisen and how it can be solved?
Mr Kumar: The problem is that the vast majority of drugs will typically benefit only a subset of the population who receive them. Historically, we have not had the technology to be able to distinguish between the patients who would best benefit from a particular treatment. I believe the technology is now there. It is still in its infancy but nevertheless it is there. Within CRUK, for instance, we are now
initiating what we call translational studies on all of our clinical trials to try to determine as much as we can during the course of the trial about the specific subsets of populations that will specifically benefit or not benefit, or who may have adverse reactions or not have adverse reactions. You will see an acceleration of this over the coming years. The problem with respect to pharmaceutical companies is that the corollary of that is that it is a reduction of market size. There is not necessarily the incentive for pharmaceutical companies to do that, although it is not absolutely as black and white as that. Sometimes, if you can absolutely pinpoint the patients who will benefit, you have a greater chance of getting that drug to market. We would advocate a partnership between the NHS, the pharmaceutical industry and organisations like ourselves to carry out these studies because, from the point of view of the Department of Health or the NHS, there will be savings on the drug budget if we target the treatment to the patient who will most benefit.

Q506 Mr Bradley: Presumably you have had discussions on those lines. What sort of reaction have you had to that proposal?

Mr Kumar: The pharmaceutical companies we talk to are increasingly waking up to this as a necessity. I think we are pushing against an open door.

Dr Solari: From my experience, having worked in the pharmaceutical industry for about 12 years, the right drug to the right patient is a concept coming out of improved genomics and molecular biology. We are not there yet. I think it is still a wish and we are still many years away from that. I think the pharmaceutical industry is very aware of this and is investing a great deal of money. The jury is still out though on whether it will fracture markets and decrease their profit margins or whether it will create new opportunities for them. Until these technologies have really matured, I do not think it is clear which way it is going to go.

Dr Boyce: A large proportion of the early clinical research on potential new medicines is molecules from outside the UK. Two thirds of our work comes from companies outside the UK. When I am talking about pharmaceutical companies, I am talking about the global industry. I am not just talking about the UK. The examples I have given are not necessarily in the UK. They may be in America or Japan.

Q507 Dr Naysmith: This is a question again for the Medical Research Council. You have said in your evidence that you need to avoid duplication of research. Personally, I would not avoid duplication. I would certainly want to avoid triplication and quadruplication but sometimes it is good to have checks and at least one other group working. Why do you think this is so important and what can be done to ensure that duplication does not take place?

Dr Solari: Are you referring to early, basic research or to more late stage, clinical type research?

Q508 Dr Naysmith: I think both apply. You would have less control over the early, basic research, I suspect.

Dr Solari: As an academic yourself, you know that we do not read publications that are more than 10 years old generally. As scientists, we often repeat what has gone before without reading the literature. We want to avoid wasting the public’s money repeating studies.

Q509 Dr Naysmith: You do not want to rediscover the stuff that has already been discovered.

Dr Solari: You do not want to rediscover it but it is an important part of the academic process that a piece of research should be able to be replicated in another lab. That adds to the validation that it is correct. That is all part of the publication process. I think that is very important. Sir Iain was making the point earlier that systematic reviews on all the literature are very important for the whole progression of medicines to man and I think the MRC would endorse that observation.

Q510 Dr Taylor: Mr Kumar, trials of combination therapies are particularly important in cancer and other diseases and I think you tell us that sometimes the companies do not make their products available for these combination trials? Is that a problem? Can you give a bit of detail?

Mr Kumar: I do not think I can say that we have lots of evidence that companies do not make their products available for combinations but I think this is again an emerging area in cancer drug development. There is a wide expectation that combination therapies are the way forward. It is for commercial reasons difficult for pharmaceutical companies to test their drugs in combinations with the drugs of their competitors. It is an opportunity; it is a responsibility that organisations like Cancer Research UK see for themselves, to undertake that kind of research and what we would then seek is the cooperation of the pharmaceutical companies in making those drugs available to us to test those combinations.

Dr Solari: In the MRC I do not believe we have had any experience of difficulties. Drug companies are willing to provide their drugs for MRC trials. The breakthrough, for example, in childhood leukaemia has come about because of new combinations of drugs.

Q511 Dr Taylor: We do not need a strong recommendation for that?

Dr Solari: I do not think so, no.

Q512 Mrs Calton: Dr Boyce, does your contract research organisation carry out any studies that you think are for marketing purposes as opposed to understanding how the drug works or how safe it is?
Dr Boyce: No.

Q513 Dr Naysmith: People have suggested to us that it would be a good idea when a drug gets to its pre-market stage that the regulatory checks that have to be carried out on it are carried out by an independent unit that would do clinical trials independently of the industry. Presumably the Medical Research Council could do that sort of thing and if you do not think it is a good idea tell us why not.

Dr Solari: I think the MRC could do it. It has the infrastructure to do it along with the Department of Health. I am sure it does not have the budget.

Q514 Dr Naysmith: Always assuming that the budget will come. I know these promises are not always acted on.

Dr Solari: It is an interesting idea. I would need to think about it a little more rather than giving an off the cuff reply.

Chairman: Write to us because obviously that would be very helpful.

Q515 Siobhain McDonagh: Mr Kumar, you are concerned about the influence that the industry has on the topics chosen by NICE. Why are you concerned and what problems might arise if there was excessive influence?

Mr Kumar: We were concerned that there was a lack of transparency on the topics chosen by us. I do not think we would say that there is an inherent problem but that we do not know if there is a problem. What has happened over the last several months is that my understanding is that NICE now, at least as far as cancer appraisals go, relies on the NCRI, which is a forum of all the major cancer research funders, to determine or at least to take advice on the areas that should be addressed. At least as far as cancer is concerned, I think we have moved forward.

Chairman: Gentlemen, can I thank you for what has been a very valuable session? It has been rather short and somewhat constrained by time but we appreciate the help you have given us. Thank you very much.
Thursday 16 December 2004

Members present:

Mr David Hinchliffe, in the Chair

John Austin
Mrs Patsy Calton
Jim Dowd

Mr Jon Owen Jones
Dr Doug Naysmith
Dr Richard Taylor

Memorandum by Margot James (PI 110)

Industry

I am employed by Ogilvy & Mather (a subsidiary of the WPP Group) as Regional President Europe of Ogilvy Healthworld (OHW). OHW provides advertising, public relations and medical education services to pharmaceutical and other companies in the healthcare field. OHW employs approximately 200 people in the provision of these services in the UK.

In 1986 I co-founded the largest specialist healthcare public relations company in the UK that is now known as The Shire Health Group (SH). I sold SH to WPP in 1999 and SH is now part of OHW.

From 1998 to 2002 I was employed by Parkside NHS Trust as a non-executive director. I was chairman of the Audit Committee and the Clinical Governance Committee. I provided expert advice on the rebranding and marketing of the Royal London Homeopathic Hospital and the re-engineering of the wheelchair service for West London.

From 1997 to 2002 I acted as a mental health manager for St Charles Hospital which involved sitting on lay panels hearing patient appeals against a section under the mental health act.

From 1998 to 2003 I was a member of the “Informed Patient Initiative” task force of the Association of the British Pharmaceutical Industry (ABPI). I was involved in the development of the MHRA Disease Awareness Guidelines issued in 2002.

Scope of Written Evidence

My evidence relates to the impact of the industry on the provision of drug information, promotion and the provision of professional and patient education. In line with the Committee’s terms of reference I have touched upon the influence of the industry on health policies, professional bodies the media and the general public.

1. Public Relations (PR) services are undertaken by our firm on behalf of many leading pharmaceutical companies. It is generally used to communicate news and feature material designed to affect the market for our clients’ products in an appropriate and effective way. We measure success according to the objectives of the campaign. Objectives can vary widely but mostly it is about facilitating an environment that is favourable to one or more of the following ends:

— Creating awareness and better informing healthcare professionals and/or patients and/or members of the public about a particular medicine and/or range of treatment options.
— Creating awareness and better informing healthcare professionals and/or patients and/or members of the public about a particular disease area.
— Improving the detection, diagnosis, treatment and management of people with medical conditions and/or people who are at risk of developing medical conditions the symptoms of which may not yet be apparent or may be silent ie not expressing themselves as feelings of unwellness.
— Generating a positive commercial outcome for our clients.

We are expected to deliver against any objective within the strict regulatory framework that governs the pharmaceutical industry. (For more information see paragraphs 4 and 6 below).

2. Advertising and PR work in different ways. Advertising works by crystallising the product’s features and benefits into a minimum number of key messages that, if well executed, leave an impression on the mind of the target audience that is favourable to the brand. The medium is usually “paid for” space in magazines aimed at healthcare professionals. Brochures are also developed for use by the sales force which go into more detail about the product’s features and benefits than is possible in a one or two page advertisement. The difference between advertising and PR is that advertising is paid for and the content is controlled by the company paying for the advertisement (within strict regulations see paragraph 4) and the media in which it appears. PR on the other hand is not controlled by the company and is not paid for (other than in fees to a PR firm or salaries to PR professionals employed by the company). PR is reliant upon the views of third parties such as patient organisations, professional associations and journalists. PR is capable of delivering
a more complex set of messages about the product/disease area than advertising and because of its dependence on third parties the outcome will be more authoritative but precisely because of that dependence on third parties the outcome will also be beyond the control of the company.

3. In addition to advertising and public relations OHW provides medical education (ME) services. This is the practice of educating clinicians through meetings, articles in journals, congresses, distance learning materials and the web. Previous witnesses to the Health Select Committee have criticised the practice known as “ghost writing”. The rules we follow to preserve the integrity of articles written by our editorial staff on behalf of doctors are as follows: the doctor or researcher discusses the content of the article with the writer and the writer submits draft copy to the doctor for approval. The doctor puts his or her name to the article once he or she is satisfied that it is a fair reflection of the subject and their views. Some doctors do not have the time or the writing skills necessary for publishing their own work and value this service.

4. The communication between pharmaceutical companies and healthcare professionals (whether direct or via a consultancy) is regulated by: the Health and Medicines Act, the EU directive on the advertising of medical products, the MHRA guidelines and the ABPI code of practice. Staff working for OHW (and all agencies to the best of my knowledge) are made aware of the regulations. Training courses are held regularly to encourage one hundred per cent compliance with regulations and the ABPI code of practice.

5. The above mentioned regulations cover promotion and education around particular medicines. Some PR activity is aimed at patients and the public and is focused on education around a disease area rather than a specific product. OHW’s work in this area adheres to the MHRA Disease Awareness Guidelines which requires that information communicated to the public be accurate, up to date, substantial, comprehensive, balanced and accessible with the source identified clearly.

6. Communication with the lay press is governed by Clause 20.2 of the ABPI code of practice and all PR staff understand the importance of adhering to this part of the code in their dealings with journalists. This section of the code reads as follows: “This clause allows for the provision of non-promotional information about prescription medicines to the general public either in response to a direct query from an individual, including inquiries from journalists, or by dissemination of such information via press conferences, press announcements, television and radio reports, public relations activities and the like. It also includes information provided by means of posters distributed for display in surgery waiting rooms etc. Any information so provided must observe the principles set out in this clause, that is it should be factual, balanced and must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.” In general communication with lay journalists is confined to disease awareness, the launch of a new product and the communication of significant product news post-launch eg a major study that has implications for clinical practice.

7. I have experienced the influence of the industry in varying contexts. In general the British medical environment is a conservative and sceptical one as measured by the uptake of new medicines relative to other markets. The decision to prescribe one product or another or no product at all is a complex one that is influenced by many factors including the media (public and professional), word of mouth among doctors and patients, prescribing guidelines issued by hospitals or primary care trusts, the Department of Health, patient groups, individual opinion leaders and the pharmaceutical industry.

8. In my experience the dominant influence over prescribing is Government through initiatives like the National Service Frameworks and/or budgetary constraints. Whilst a mental health manager at St Charles Hospital I observed that few patients were on modern treatment for psychotic conditions. When I asked why this was I was informed that budgetary constraints precluded the wider use of atypical anti-psychotics despite their superior side effect profile and the fact that non-compliance with older therapies created a problem for the hospital, patients and the wider community. There are numerous examples of Government/DOH inspired resistance to newer treatments on grounds of cost which has and still does prevent patient access to superior medicines.

9. During previous hearings members of the Health Select Committee have heard witnesses claim that pharmaceutical companies have too much power in the market place, spend too much on promotion of medicines (such that non-medical interventions are swamped out of the market place) and engage in practices that “over medicalise” the problems of ordinary life. If those allegations were true I believe that many patients who are currently on old treatments which have been superseded by treatments that have fewer side effects and/or are more effective (or are on no treatment at all) would by now be on modern treatment. This is particularly the case in the management of hypertension, schizophrenia and oncology.

10. With regard to non-medical interventions much of the work undertaken by OHW on behalf of clients emphasises the non-medical interventions that can be effective in certain conditions as part of the holistic approach to the disease in question taken in our educational material. If the medicine concerned is a statin then diet will be emphasised as first line therapy in most cases, companies will work with dieticians to provide high quality dietary advice although they have no financial incentive to do so. If the medicine concerned is a treatment for asthma then exercise, in particular swimming and tips on minimising house dust mites will be emphasised. There are numerous other examples. The reasons for the holistic approach are twofold, firstly out of the client’s sense of corporate social responsibility and second because on the PR and educational side of the communication mix companies are working, for the most part, with third party organisations eg patient groups for whom a holistic approach mentioning all treatment options, non medical
and medical alike is a fundamental requirement. Any company wishing to over promote its product at the expense of fair balance and/or proven non-medical interventions will not find a credible third party willing to work with them.

11. It is essential that a plurality of sources of information continue for patients, professionals and the public. Serious health inequalities persist for example: between different postcodes, between younger people and the elderly, between men and women, between the mentally ill and physically ill, between different socio-economic groups, between those who suffer from conditions where government targets abound and those who suffer conditions where there is less scrutiny and publicity. There are many groups committed to ending these inequalities but it will take time. Pharmaceutical companies are more regulated and restricted in what they can communicate than any other stakeholder. It is right that they should be heavily regulated in what they say about diseases and their own medicines but to restrict them further would leave government as the majority voice in healthcare with the under resourced voluntary sector trying against the odds to make it’s voice heard. We should embrace the fact that industry has ‘an interest’ in securing better knowledge about diseases and improved access to treatment and leverage that interest in the battle to overcome health inequalities.

Margot James
9 December 2004

Memorandum from Paling Walters Limited (PI 109)

INTRODUCTION
1. The terms of reference for this inquiry have been stated by the Health Select Committee and this memorandum will only address those issues as they pertain to Paling Walters in the course of its work.

2. Paling Walters (PW) is a London-based advertising agency specialising in the advertising and promotion of medicines and healthcare products. Our immediate parent company is DAS Europe Limited and it, in turn, is owned by Omnicom Inc, which is based in New York.

3. The agency is retained by a number of pharmaceutical and consumer healthcare companies. PW also works with consumer companies on products that have a more diverse health (eg British Airways Travel Clinics, B&L contact lenses and British Meat). The agency works on both a UK and an International basis.

4. The agency was founded in 1980 and currently employs around 40 people.

OUR REMIT
5. The pharmaceutical companies use a number of external suppliers to aid them in their product marketing activities. These broadly fall into three sectors—
   (1) Public Relations
   (2) Medical Education
   (3) Advertising and below-the-line (btl) promotion.
   Many firms are involved in the first two areas; a small number of companies are engaged in all of these activities. PW only operates in the third business sector.

6. The provision of drug information and promotion. It is important to clarify and confirm the sort of work carried out by PW and the range of materials it creates. Our work on prescription medicines is aimed largely at primary and secondary care doctors, with a small percentage of our output aimed at other HCPs (eg pharmacists). Because of our target audience, the types of materials we create are invariably product orientated. This type of work is, of course, not aimed at patients. We have never promoted a prescription medicine to a patient. It is not allowed by law.

7. Almost exclusively these materials are in the form of:
   (a) Press advertisements (paid for space and placed within the medical press)
   (b) Mailings to the medical profession.
   (c) Sales support materials for use by medical representatives face-to-face with GPs, hospital specialists etc, as part of the important process of bringing information to the medical profession. The latter may take the form of brochures containing information such as clinical trial support for a product (in terms of efficacy, side-effect profile etc), dosage information and cost. Other items used by the medical representative, and produced by PW, may include exhibition panels, slide sets, product monographs, dosage information cards and brand reminders. We also produce, from time-to-time, materials for internal use within marketing and sales departments of pharmaceutical companies.

8. Professional and patient education. PW does not produce materials for either doctor or patient education, with one or two notable exceptions, which are outlined below.
9. Where we produce educational materials for doctors, such as A/V presentations and literature, these will invariably be branded and are part of the product’s promotional package.

10. In terms of patient education, we only produce materials for the doctor to pass on to the patient post-diagnosis and after the patient has been given a prescription. These materials are given with the objective of aiding compliance with treatment and to give patients additional advice whilst on the treatment, to help them get the maximum benefit from their medicine and to ensure the treatment is taken safely. It is well accepted by doctors that patients are aided enormously by having written instruction to reinforce what has been told to them about treatment and dosage whilst in the surgery. It is also well documented that a large percentage of treatment courses are incorrectly taken by the patient and such advice is highly valuable.

11. Historically (1999), PW was involved in a campaign with the aim of communicating directly to patients about a medical disease (erectile dysfunction). This was a press campaign for The Men’s Health Forum and The Impotence Association. There was no product association/mention in this work, although it was supported by an educational grant from Pfizer. Despite this and other subsequent campaigns, it is estimated that only 20% of sufferers with ED have sought any medical consultation.

Our Responsibility

12. Whilst pharmaceutical companies are at liberty to promote and sell their products to the medical profession, there are, of course, regulations in place to control this activity. We take a very responsible approach to the advertising and promotional work we produce in support of our clients’ products.

13. Our advertising and promotional materials adhere to the rules laid down by the ABPI Code of Practice and the Health and Medicines Act/Medicines Advertising Act. All product claims made have to be substantiated and reflect the summary of product characteristics.

14. Within this context, it is important that PW copywriters and account managers are familiar with the details of the Code and how it affects their work. As a matter of protocol, all copywriters and account managers at our agency attend ABPI training courses on the Code. Other staff may also attend where there is additional value in them doing so. Staff are also sent on the course again from time to time as a refresher.

15. Our staff working in these areas, along with senior management, have medical, pharmacy or, at the very least, science degree qualifications. Staff in our clients’ marketing and sales departments are similarly qualified.

16. Over and above our responsibility to convey information honestly and clearly, we also have a responsibility to our clients to produce materials that fall within the Code of Practice. Failure to do so results in punitive measures, intensive time investment from ourselves and our clients and damage to our overall relationship. The withdrawal and revision of materials results in a great deal of lost time and lost money from a marketing budget.

17. Breaches of the Code are taken very seriously indeed. There are strict internal legal and medical approval systems in pharmaceutical client companies, to which PW adheres. Promotional materials must not be issued by a company unless the final materials have been certified by two senior officials of the company, one of whom must be a registered medical practitioner. The other is often a pharmacist.

We have never witnessed anything other than a totally ethical attitude from our clients in terms of medical/legal approval.

The complaint procedure exists to ensure that there is an independent review and all breaches of the code are published and in the public domain. Through the ABPI Code, there is a potent mechanism for members to regulate each other. All breaches of the code are published and in the public domain.

The Aim of Our Work

18. Companies such as PW are employed by our clients to aid in the marketing of their products. We are engaged to help establish understanding by the medical profession of a product’s values, its functionality and role in treatment management.

19. As such we have a responsibility to present our clients’ products in the most positive way within its licence, given the data and the product profile. This is part of the necessary process by which clients compete within a commercial environment.

20. Importantly, when we promote products to the medical profession we are talking to a highly educated, intelligent and knowledgeable audience. They will place a product offer into the context of their pharmacological understanding and previous experience. The doctor is the final arbiter of what to prescribe and, indeed, whether to prescribe at all.

21. Whilst doctors need to understand the functional benefits of a product and gain experience of using/
prescribing it, it is still possible to engage them through press advertising. However, advertising is a small component of the overall communication package. Much of the explanation and understanding doctors need to prescribe a product, or to extend its usage, is delivered via the literature, conferences, seminars, peer endorsement and contact with company representatives. This is where the details are discussed and the doctor has the opportunity to ask questions, gain clarification and disagree.

22. Representatives are frequently cited as one of the most important sources of information for doctors about new medicines, new indications, new data etc.

23. So from an advertising point of view the aim of our work is to:
(a) create awareness (eg at launch or in the early stages of a product’s life);
(b) communicate a key message/offer;
(c) be part of the process to encourage trial (the doctor is then in a position to start formulating his own judgement); and
(d) act as a reminder for the product.

COMMENT

24. In the Health Select Committee’s own words, “The pharmaceutical industry contributes substantially to the health of the nation and brings important benefits to the national economy.” Therefore, the value of the industry itself does not seem to be the issue here. It would seem to be in everyone’s interests that it continues to be both profitable and successful.

25. To return to the issue of the inquiry—the influence of the pharmaceutical industry. From the perspective of Paling Walters, a company that has worked with the pharmaceutical industry for almost 25 years, and has been proud to do so, it is our view that the industry does behave ethically in its dealings with the medical profession in the course of marketing its products. In the area of our remit, which is all we are qualified to comment on, checks and controls are in place to make sure that we maintain this ethical standpoint.

Memorandum by Richard Horton (PI 108)

THE PHARMACEUTICAL INDUSTRY AND MEDICAL JOURNALS

*The Lancet* is a weekly general medical journal that publishes clinically oriented research about common diseases. A substantial part of the research that we publish concerns drugs manufactured by the pharmaceutical industry. Most of these research studies—notably, the gold standard means of assessing the efficacy and safety of a product, the randomised clinical trial—are paid for by the makers of the drug. There are many safeguards in place to protect the integrity of this research endeavour, from ethics committees to good clinical practice guidelines to journal peer-review systems. The standards set by the pharmaceutical industry in the conduct of clinical trial research are second to none. However, the extent of the commercial sponsorship of medical research and its intrusion into the academic sphere is one of the gravest threats to the independent evaluation of new medicines—indeed to the notion of an independent science base. Without greater scrutiny of the interaction between private and public sectors, the health of our population will continue to be put at risk by biased, over-interpreted, and misreported research findings. At present, our population is part of a largely unregulated experiment involving poorly investigated new medicines that have been licensed on the basis of insufficient data.

In my own very narrow area of interest—medical publication—I would draw attention to 10 especially damaging practices that distort the evidence base of medicine today.

1. **Manipulation of research findings:** In August, 2004, *The Lancet* published an important and rigorously conducted trial called ACTION, which was designed to investigate the effectiveness of a drug—nifedipine—in patients with heart disease. The results were presented at the European Society of Cardiology in Munich. The authors considered that the drug had “no effect” according to its predetermined criteria for judging effectiveness. The sponsor was Bayer. In the copious marketing material distributed to over 10,000 doctors in Munich, Bayer stressed that ACTION was “proving safety and improving outcomes...adding even more for hypertensive patients.” The marketing claimed “primary endpoints significant in hypertensive patients”, a total distortion of the actual result. Doctors were seriously and deliberately misled. This is not an uncommon practice.

2. **Bias in sponsored studies:** Research has demonstrated clearly that sponsored studies are more likely to produce a positive result for a company than an independent study of their product. The inherent biases in design, conduct, analysis, and reporting of research all reveal this pervasive undermining of scientific excellence. Examples include calcium channel blockers for heart disease and trials of drugs for myeloma.

3. **Undisclosed adverse data:** Research sponsored by industry is sometimes published at an early stage when there is a positive result for a new drug. But longer term follow up may yield an unwanted
negative result. This finding may not be reported even when it is known at the time of publication of the early report. JAMA suffered a particularly egregious example of this deception. In another recent case, a journal was forced to reject a negative article after objections from its marketing department—an outrageous incursion into scientific integrity.

4. Hiding negative data: The classic recent example concerned Paxil (GlaxoSmithKline). The hidden trials showed a pattern suggesting limited efficacy of the drug and risks of potentially fatal adverse effects. The available published evidence indicated a very different story. Under severe reputational threat, GSK was forced to reveal these hidden results—leading to a $2.5 million US legal settlement and an unequivocal FDA warning about the risks of the drug. In response, the International Committee of Medical Journal Editors has called for all trials to be disclosed and registered at an early stage in their development.

5. Supplement publishing: Journal supplements often represent little more than information-laundering operations for industry. A company will sponsor a promotional meeting, pay a pharma communications company to convert the lectures of paid experts into articles, and then seek to publish these papers as a non or lightly peer-reviewed supplement to an established journal. The company will pay the publisher a large sum to secure publication, thereby buying, not earning, the imprint of the journal on its marketing-driven symposium. In one email that The Lancet has seen about a supplement, the sponsor argued that the more the article was peer reviewed the less value the supplement would be to the company—showing clearly the marketing goals rather than the scientific endeavour that lies behind supplement publishing. Multiple research studies confirm the scientific weaknesses of such supplements.

6. Undisclosed conflicts of interest: The escalating problem of industry payments to scientists—stock options, consultancy fees, research grants, staff costs, entertainment, conference fees, hospitality—has been recognised for several years. The International Committee of Medical Journal Editors (which includes the editors of the New England Journal of Medicine, JAMA, and The Lancet), has tried to force such competing interests into the open through tough disclosure requirements. But the continuing privatisation of much of science (science in the service of wealth creation rather than health improvement) threatens to make independent research almost impossible to do.

7. Editorial kick-backs: The Lancet has been offered substantial sums of money in exchange for publishing certain research studies. In all cases, we have declined such offers and these papers have been rejected. The mechanism of this intended exchange is commonly through the explicit promise by the company of a large order of commercial reprints in return for publication of a research paper. The impression left is that if editors reject the paper or try to alter its message, there will be an often major loss of income to the journal.

8. Ghost-writing: It is standard operating procedure for pharmaceutical companies to seed the medical literature with ghostwritten editorials, reviews, and opinion pieces emphasising off-label indications of licensed drugs. These papers are commissioned to a specific marketing-driven brief and are written by non-specialists. A company friendly expert is then paid to have his or her name appear on the article, facilitating publication in a respected journal and thus enhancing the impact of the message.

9. Continuing medical education: Industry is now a major sponsor of medical “education”. As a former editor of the NEJM, Marcia Angell, has argued in her powerful book, The Truth About the Drug Companies, this leap into education is driven more by a desire to lever messages concerning prescribing opportunities than it is about truly educating doctors about the prevention and treatment of disease. She estimates that about 60% of CME in the US is paid for by industry.

10. Failure to align commercial with public interests: Pharmaceutical companies clearly have a legal requirement to earn as much return as they can for shareholders. But their untramelled power in shaping the research priorities of medicine means that national and international gaps in knowledge remain unfilled—eg, concerning the relative efficacy and safety of one product versus another (the damaging dominance of placebo-controlled trials), drugs for neglected diseases, health systems or health services research, and in returning a fair proportion of profit back to the public sector where many of the scientific ideas fuelling drug development have originated.

It is perfectly true to say that industry plays a vital part in developing new medicines to ameliorate suffering and to cure disease. Modern medicine needs a dynamic, innovative, and robust pharmaceutical industry. But it is also the case that the for-profit motive of the pharmaceutical sector clashes with the public-health values of NHS clinical care and independent scientific research. The compromised integrity of medicine’s knowledge base should be a serious concern to politicians and public alike. It is surprising and disappointing that this danger does not seem a serious priority within medicine itself.
Memorandum submitted by Jenny Hope Medical Correspondent Daily Mail (PI 111)

In response to a request for written evidence to the above inquiry, I submit the following observations. They are my personal views, based on my experience as a medical journalist, and do not represent the policy of the Daily Mail.

From a journalist’s point of view it seems useful to consider whether the influence exerted by the pharmaceutical industry is overt, covert, and how this affects news reporting. The business of drug companies can do tremendous public good, drugs save lives and improve the quality of lives, but they are extremely powerful corporations which exist to make profit and recoup research costs. The resulting conflict—making profit out of illness—does not sit easily in the British context of free health provision. Nevertheless, drug promotion is a necessary part of the contract. This takes an all-pervasive form, ranging from sponsorship of medical conferences to the use of PR companies to engage the lay media in telling the public about their products. But it’s an overt influence that becomes part of the background noise of news reporting. Anyone with knowledge of the healthcare industry, of medicine and of the scientific community knows that many vested interests reside among drug companies, device manufacturers, private providers and insurers, researchers, universities and government health spokespeople. Journalists are always looking for vested interests and maintaining an awareness of hidden agenda.

For example, we may assume when a senior doctor stands up on a platform at a drug launch there is a strong likelihood he/she may have been paid a fee to be there. This will be taken into account by journalists but won’t necessarily undermine its news value, negate or distort the coverage of the story. The enormous halls of drug stands at international conferences quite clearly signal the underlying promotional funding for a global industry. Part of the business of these conferences is “selling” stories to newspapers and broadcasters. The conduit is the PR industry. PR companies organise the press conferences, arrange the speakers and provide background material. There is a clear agenda which experienced specialist reporters take into account. The same considerations apply when press releases and company information come into the offices of newspapers and broadcasting organisations. We expect research data to be sourced and referenced, and the format to follow the codes of practice devised by both industries in the pursuit of ethical behaviour. But reporters apply the same journalistic criteria to the information that we would in covering any aspect of news, whether crime, transport, education etc. However, staff reporters working for national news organisations are not the only target for promotional activity. When a story is in the public domain—or being placed with the specific intention of generating publicity—someone will write about it. If it’s me than I know where the information is coming from, the background, and carried out the interviews—there is some quality control. When copy arrives from an agency or individual freelance reporter it’s unlikely to be exclusively supplied. They make a living by supplying stories, often to as many outlets as possible. This also raises the index of awareness about the information provided.

Perhaps the most important issue in assessing influence of the pharmaceutical industry on the NHS is whether it corrupts the data used for an increasingly evidence-based service. Doctors are no longer the prescribing “free agents” they were 10 or 15 years ago. They are subject to NICE guidelines, practice and hospital formularies, prescribing advisers from primary care trusts which are putting increasing restrictions on the decisions they make. The King’s Fund, for example, in a recent report On being A Doctor discussed growing constraints on the clinical freedom of doctors, partly because of the tarnished reputation of the profession in recent years. As a result, one could argue the focus of attention has shifted to the clinical trial and research data used to gain approval of new drugs, not least a marketing licence, and the post-marketing surveillance. Most medical research is funded by drug company money. It is impossible for journalists to assess whether data published in clinical journals or presented at conferences—whatever the source—is corrupt. This can happen in different ways; data omitted, misrepresentation of findings, the skewed nature of the original protocol. On another level, negative or inconclusive results rarely get published and there appears to be no obligation to publish damaging results from trials, even when NHS patients have taken part. A report in The Lancet earlier this year found negative results from trials on antidepressants in children had never been made public. Researchers obtained information about unpublished trials from confidential data held by the Committee on Safety of Medicines when they were compiling NHS prescribing guidelines for doctors. Every request for unpublished data from the pharmaceutical companies involved met with a refusal.

As you know the Royal Society convened a working group to look at how research reaches the lay media partly because, in the words of the chairman Patrick Bateson, the results of scientific research have profound effects on public opinion and policy. Journalists have to rely on ethical committee procedures and peer review underpinning publication in medical journals but even their editors express disquiet about the process. Richard Horton, editor of The Lancet, says in an article published in the New York Review of Books (2004 March 11:7–9) that “Journals have devolved into information-laundering operations for the pharmaceutical industry.” There is some concern about the whole process of peer review used in journals; the potential for bias, the old pals’ act and plain wrongness of interpretation of results. Who does it, what’s their conflict of interest? It may not be obviously pecuniary, it could be a personality clash that’s behind it. It’s a vital part of how specialist journalists assess the credibility of a story but it’s a system creaking under the strain of a myriad of vested interests. Ten years ago Professor Peter Sleight, a leading cardiologist involved in major heart disease trials, coined a memorable description. “Peer review is 50% garbage, 50% malice and 10% good advice” he told a Royal Society of Medicine meeting. “What can you expect if a
reviewer works in the same field and is almost certainly a rival? Many actually steal data and hold up publication while they publish it as their own research.” Just a year later I investigated a research fraud involving a faked trial in the British Journal of Obstetrics and Gynaecology that led to a consultant gynaecologist being struck off for life, the resignation of the journal editor as president of the Royal College, and a shake-up of the editorial board. However, I did not uncover the fraud by unpicking the published research results—I discovered a hospital inquiry was taking place in secret that led to the unravelling of the scandal.

There has been an outcry over the secretive workings of Government regulatory systems here and in the US. The basic premise of the criticisms is that the MHRA and its advisory committees appear to be in the pocket of the drug industry. As a result, it is claimed, members and experts are too close to the drug firms, which in many cases are their ex-employers, investigations into safety are cursory and drug companies are allowed to choose whichever data makes their product look safe. The scandals involving SSRI products and Vioxx are topical examples. Since 1989 the cost of licensing medicines has been covered almost entirely by fees charged to the drug firms which may have fuelled public suspicion. The shake-up of the CSM appears to be designed to address some of these concerns, disallowing interests in the pharmaceutical industry for example, which could be in place next year. But the key point remains that documentation used by the MHRA to approve licensing request is not available to the press. There is no way of checking the documentation at present. The effect of opening up the Freedom of Information Act in January is not yet known. All data should be available for patients/ journalists/ doctors/ interested parties. It is a moot point whether summaries of clinical trials in an online database will be sufficient. The devil is in the detail. The commercial confidentiality caveat has to be overcome. In the current climate, drug companies cannot be allowed to continue to argue against openness on the basis of protecting themselves commercially. All completed trials should be available for independent scrutiny, whether they study licensed or unlicensed uses. However, Europe-wide regulatory processes are taking precedence over national systems in an increasingly global pharma economy. It is unclear whether they will be in step with any changes recommended or demanded in the UK.

How do the Press or public know when things are going wrong? The most obvious signals are drug withdrawals, Government safety warnings and research findings which give journalists the opportunity to raise the alarm and investigate. There is a contribution made to all of these processes by the yellow card system for adverse reporting. Yet it’s well recognised that relatively few prescribers report adverse reactions and low levels of reporting foster the assumption that little is wrong. I took part in consultation carried out by the former deputy CMO Jeremy Metters to explore different alternatives. The conclusion arrived at by journalists (including the Guardian and BBC) is that unexpurgated information from patients has to be accommodated and available for external analysis. Patient reporting is no longer a privilege to be granted to the public but a right. But post-marketing surveillance has to be a more active process than waiting for damage sustained by patients to be reported by them or their doctors. Patterns of problems might emerge more quickly with a more intensive exercise. What surveillance is taking place of any planned surveillance of drugs or devices- are these proposals submitted along with applications for drug approvals? In France a new policy dealing with drugs likely to be used on a large scale was brought in last year. It requires pharmaceutical companies to organise a post-marketing study of the public health impact of a drug, which includes close follow up. According to a letter in the British Medical Journal (BMJ 2004;329:1342) this policy has already resulted in an independent large-scale study of 40,000 patients treated with new or traditional anti-inflammatory drugs. More than 50 such studies have now been agreed, which include in some circumstances a stepwise introduction of a new drug. There may be overlap with NICE assessments but the post-marketing elements may bear closer examination.

The same concerns apply to moves to reclassify medicines from prescription to pharmacy only, which have Government approval (following DoH working party). The system is equally opaque. In the case of the first statin drug to be moved objections were registered by the Consumer’s Association and the Royal College of General Practitioners on safety grounds. Individual doctors also expressed concerns. These were published by my paper as part of a story about the switch. However, there is no automatic access to any submissions on such applications other than those released direct to the Press and no access to documentation detailing the reasons for the decision and opposition. The switch was approved without any proper explanation—despite rejection for a similar request made to the FDA two years ago—and the UK became the first developed country in the world to take this step. Subsequently there has been an explosion of advertising both of cholesterol testing and the drug.

The pharma industry has taken an interest in patient information and patient groups which has resulted in some drug company funding of their activity. However, this should be considered in the context of patients gaining their information on prescription drugs from a product leaflet in which the format and content are strictly controlled by legislation and usually incomprehensible or frightening to the patient. Accusations of disease-mongering are not entirely disinterested. They reveal tensions between prescribing doctors and public health specialists who want population-wide strategies to make a difference, and part of that is managing medical risk factors ranging from osteoporosis to high blood pressure. Guidelines are increasingly being set by professional bodies which define the limits of potential intervention. Raised blood pressure is a serious health threat. I might expect an affected individual to think about it seven times a day—at least until it’s under control. Many people, once they have been told they are at risk, or have been diagnosed with a medical condition, crave more information. They get it from a variety of sources, friends,
newspapers, patient groups, the Internet—there are more than 20,000 health-related Internet sites. Surveys consistently show that newly diagnosed patients are disappointed with the level of information available to them about their condition. MORI research shows the most preferred method of communication of patient information is leaflets from the GP surgery. A recent study found the UK performed worse than other major Commonwealth countries and the US on patients having information about medicines including side effects.

If we accept there is a consensus that people need more information to make choices about their health—even if they are the wrong choices—then disease awareness campaigns can play a useful role. There are an estimated one million undiagnosed diabetics in Britain, and this is a condition which can cause organ damage and premature death. We know companies manufacturing drugs in this area have a commercial interest in promoting awareness, but there is also a public interest that results in energetic activity on the part of patient groups. Donations are made to patient groups by drug companies but in my experience charities tend to ringfence this money for “educational” projects such as leaflets where the funding source is clearly stated, specific drugs not mentioned and an arms-length policy adopted. Harry Cayton, when he was executive director of the Alzheimer’s Society, said it was a caricature to say that patient groups were “fluffy bunnies” at the mercy of the “ravening wolves” of the drug industry. The Society had strict guidelines for its relationship and acceptance of donations, and he acknowledged the need for patient groups to have a good relationship with the industry not least to fill the information gap left by the NHS. Any restrictions or banning of such a relationship which involved the removal of pharma funding would surely have to be replaced by state-funded grants.

One further point about the influence of the industry. Quite apart from the growing significance of PFI in capital investment, we’re looking at an NHS where there will be greater involvement of the public sector in the near future. An estimated 15% of elective surgery on NHS patients will be carried out privately but with NHS funding by 2008—so the profit motive will be more in evidence. It’s not just in acute care that the scene is shifting. US-managed care of chronic conditions has already arrived in pilot form, and there is another NHS pilot scheme being run in a north London PCT which is managed by a wholly owned subsidiary of a major drug company and provides “care management tools”. The PCT states that it does not endorse the use of the company’s drugs or encourage any additional access by drug company reps. The NHS Improvement Plan itself actually makes reference to working with pharmaceutical companies. It states that “pharmaceutical industry involvement in the development and implementation of national service frameworks would benefit both the NHS and industry.” It also calls for “faster and more effective recruitment of patients into clinical trials via the NHS enabling new medicines to be brought on stream more quickly”. We probably need to see a more transparent account of the pros and cons of private involvement in the NHS where profits are being made in the provision of healthcare, and more independent analysis. Whether it’s PFI, acute care or chronic disease management. It’s not just in the regulatory processes that we need more scrutiny, much though these are in need of reform.

Memorandum submitted by Lois Rogers, Medical Editor, Sunday Times (PI 116)

I have offered below, some broad comments on the subject headings being considered by the committee. This is purely to give a sort of shorthand overview of the concerns that I think are felt by the public:

**Drug Innovation**

There is a concern that this may be driven more by profit than need. Lifestyle products with large potential markets, may be looked up more favourably than research for cures for killer diseases. The best-selling drugs in Britain are cholesterol-lowering tablets, stomach ulcer and blood pressure drugs. These conditions could be largely avoided by changes in lifestyle. There is currently a lack of innovation in the pharmaceutical industry. Of 487 new products proposed for licence applications in America since the late 1990s, the Food and Drug Administration ruled that more than three quarters of them were unlikely to represent improvements over drugs already on the market, and the majority of them were merely reformulations of existing products.

**The Conduct of Medical Research**

There is felt to be a suppression of neutral or negative findings, and data is manipulated to present results in the most favourable light. Few people understand the way statistics are presented. Devices such as confidence intervals, used to validate statistical findings, appear to be subject to reinterpretation. There is an impression that epidemiology is used to sustain bogus arguments. For example, research is often presented as impartial when it is not. Sales of a painkiller called Bextra rose by 60% in 2002, following publication of research results in the Journal of the American Dental Association. It later emerged the study had been planted by the manufacturers Pharmacia, and was actually commissioned from an offshoot of an advertising agency. It was also promoting the unlicensed use of Bextra for an additional unapproved condition.
The provision of drug information and promotion

There is a concern that dissemination of information about medicines and the way they are promoted, is open to abuse. There are any number of examples of this, but the promotion of testosterone patches for female sexual arousal disorder, is a case in point. The licence application for the drug was recently rejected by the Food and Drug Administration in America, but its manufacturers Proctor & Gamble, intend to resubmit the proposal. Although they plan at first to market the patches only to post-menopausal women who have had their ovaries removed, large numbers of articles have appeared in the media reporting the general problem of "hypoactive sexual disorder", or low libido, and the potential of testosterone patches to treat it. Questions are now being raised about the long-term risks of dosing women with testosterone—a hormone which can cause raised cholesterol and heart disease—as well as leading to the development of male sexual characteristics.

The promotion of anti-depressant drugs to treat children has been equally questionable. Earlier this year a confidential GlaxoSmithKline (GSK) document from October 1998, was published. It revealed that results from two large clinical trials designed to test the safety of paroxetine, marketed as Seroxat in Britain, were "insufficiently robust" to convince regulators to approve it for use in adolescents. One of the trials did not demonstrate a statistically significant difference from placebo on the "primary efficacy measures", and the other showed no significant difference at all between the drug and the placebo. The confidential GSK document said the results of the first trial would be reported only as showing a "trend in efficacy in favour of Paxil across all indices of depression". The results of the second trial would not be published at all. Doctors admit that much of their post-qualification education and information comes from drug companies. The companies each budget an average of £10,000 for marketing to every doctor in the UK. Marketing is growing in importance possibly because of the lack of any new real "wonder drug" to sell. 44,000 of GSK's workforce of about 101,000 is in sales. The number of people employed by American drug companies in research and development, has increased by 2% since 1995. The number employed in marketing has risen by 59% in the same period.

Professional and patient education

Funding for most disease awareness or treatment campaigns, is provided by pharmaceutical companies with a product to sell. Most medical research is funded by drug companies, which drives the agenda of what are considered important health issues and what sort of research is published in the scientific journals. The British Medical Journal itself is distributed free to doctors in Britain because it is subsidised by the drugs industry. The health issues it highlights are widely reported by the rest of the media, an effect which arguably distorts the public and professional perception of the importance of different conditions, or their prevalence in the population.

Regulatory review of drug safety and efficacy

It is undoubtedly detrimental to the public interest, and to the public's perception of impartiality in the regulatory process, to allow a situation where the very great majority of government advisors have direct financial links to the manufacturers of products they are meant to be evaluating.

This system is under review and is in urgent need of reform.

Product evaluation including assessments of value for money

I am not sufficiently close to the process to comment on this aspect of the select committee's investigation, but I am aware of specific circumstances which have aroused concern—noteably the argument about the approval of the influenza treatment Relenza. This drug was rejected by the National Institute for Clinical Excellence for use in the NHS, but following a public debate about the possibility of GSK relocating its scientific research base outside the UK, the Institute decided Relenza should after all, be purchased on behalf of NHS patients.

For informed members of the public, episodes of this nature arouse suspicion.
Witnesses: Ms Margot James, European President, Ogilvy Healthworld, Mr Mike Paling, Managing Director, Paling Walters, Mr Richard Horton, Editor, the Lancet, Ms Jenny Hope, Medical Correspondent, Daily Mail and Ms Lois Rogers, Medical Editor, Sunday Times, examined.

Q516 Chairman: Good morning. Can I welcome you all to this session of the Committee? Welcome to our witnesses. You must just be able to see us from that distance; we could do with binoculars to see you. It is not the best of rooms to be in I am afraid but I hope you will be able to cope. We are very grateful to you for being willing to come before the Committee this morning. Could I ask you to briefly introduce yourselves to the Committee, starting with you, Ms James?

Ms James: Good morning. My name is Margot James and I am Regional President for Europe for Ogilvy Healthworld, a company which carries out public relations, medical education and advertising services for the pharmaceutical industry. Formerly I have been a non-executive director of an NHS trust and a mental health manager.

Mr Paling: Good morning. My name is Michael Paling. I am Managing Director of Paling Walters. We are an advertising agency specialising in healthcare. Healthcare from our perspective is prescription medicines controlled by doctors, consumer medicines and any product with an interest in health that is consumer product.

Dr Horton: Richard Horton. I edit The Lancet.

Ms Hope: Jenny Hope. I am a medical correspondent with The Daily Mail. I write about health and medical matters for the news section.

Ms Rogers: Lois Rogers from The Sunday Times. I am the medical editor and I cover the whole area of medicine and health related issues.

Q517 Chairman: Thank you very much. Can I begin by asking Dr Horton a question arising from your evidence—and we are grateful for the evidence which was interesting evidence—where you concluded, if I can quote from your last paragraph: “Modern medicine needs a dynamic, innovative, and robust pharmaceutical industry. But it is also the case that the for-profit motive of the pharmaceutical sector clashes with the public health values of NHS clinical care and independent scientific research.” You go on to say: “The compromised integrity of medicine’s knowledge base should be a serious concern to politicians and public alike. It is surprising and disappointing that this danger does not seem a serious priority within medicine itself.” Could you expand on that?

Dr Horton: Perhaps I should start by saying that it goes without saying that we do need a dynamic, innovative industry and it has been a huge success in the last 20 years or so as we have been able to see medicines delivered that have really transformed the practice of medicine. I know you have had examples of that presented to your Committee. Indeed, it is also true to say that there are many common conditions—such as high blood pressure, high cholesterol, asthma, diabetes—that remain chronically under-treated and we need to do better at getting effective medicines to those patients. However, it is also correct to be critical because industry does not just provide an armamentarium of drugs. It also, because of this armamentarium, contributes significantly to the morbidity and mortality of the population. In a study that was done in the late 1990s looking at American data—a study of adverse drug reactions—adverse drug reactions were found to be the fourth commonest cause of death in the United States after heart disease, cancer and stroke. With progress come huge risks which are often underestimated. In addition, the pharmaceutical industry has been enormously successful at inter-digitating itself in the usual process of health care in the UK. It provides people; it provides equipment, services, buildings, facilities and, of course, hospitality. At almost every level of NHS care provision the pharmaceutical industry shapes the agenda and the practice of medicine. The question then is: what is the nature of that shaping, that relationship? It hovers somewhere between symbiotic and parasitic. It is possible perhaps to explore some of that. I guess I feel that the relationship has tilted too much towards the parasitic rather than the symbiotic because of the way we have our regulatory structure for drugs still with MHRA despite the proposals for reform. We are seeing the population taking part in a largely unregulated experiment in the way drugs are provided through the NHS and I think that is something we had not had a serious enough debate about in the public domain.

Q518 Chairman: In an editorial in 2002 you wrote: “How tainted has medicine become?” and you concluded: “heavily and damagingly so”. You qualified medically in 1986, at what stage in your career did you come to this conclusion? Is it something you believed in all the way through or do you feel that something profound has happened during your time since you have qualified that leads you to this pretty strong conclusion?

Dr Horton: This is not something I have thought for a long time at all. It is only since I have worked at The Lancet which is a strange environment to work in. It gives you an insight into many of the practices that we may talk about this morning.

Q519 Chairman: To clarify the point then, your thinking of this has been concentrated by the work you are doing now.

Dr Horton: Exactly.

Q520 Chairman: You talk in your evidence about editorial kick-backs. You have actually had situations where you have been offered substantial sums of money to publish certain research studies. Money from the industry. Tell us about it. Who has offered you money? Be precise because we are interested to know how it works.

Dr Horton: The way it works is that an investigator will give you a call and say they have a paper that they would like to submit to us and ask us if we are interested in it. On the telephone I would ask them to tell me about it. If they describe it I would say we are interested. Then the conversation might go: “It is likely that the company will want to buy several
hundred thousand reprints” and of course several hundred thousand reprints might translate into half a million pounds, a million pounds revenue to the journal. There is an implicit connection between the submission of a paper and the revenue that comes into a journal.

Q521 Chairman: To be clear, it is the reprint where the money is offered.
Dr Horton: Absolutely. Then at various stages after a paper has been submitted there may be interventions by either the authors or the sponsors to try to move the peer review process in a direction that is less critical. I could give you some examples of that if you want me to.

Q522 Chairman: Please do.
Dr Horton: All the examples I will give are very recent, within the last six to 12 months. Over the summer we received a paper on a Cox-2 inhibitor which we fast tracked to publication. In the process of peer review there was a substantial level of criticism against this paper: over-interpretive, reducing the impact of the adverse reactions. So we put these questions to the authors and in the middle of the peer review process as we were trying to get the paper right for publication we received a call from the sponsor of the company saying: “Stop. Pull back. Stop being overly critical because if you carry on like this we are going to pull the paper and if we pull the paper that means no re-print income for the journal.” We then went back to the authors and said, “You need to pull these guys off the journal because if they continue to put pressure on us we do not want your paper”. After a few more days the company backed off; the authors were willing to change the way they had interpreted the paper and report more accurately the data in the paper. That is just one example—and it is not an uncommon example—of how there is this constant continuing conflict (and responsibility of the publishing source to disclose its role in the research: was it responsible for writing the paper? Was it responsible for doing the analysis? Was it responsible for limiting access to data for the authors? We take those kinds of issues point by point in the process of peer review. Prior to 2001 we did not so this whole evolution of quality control is on a very rapid conveyor belt of change.

Q523 Chairman: How do you then determine what you publish? If there are all these influxes how do you come to a decision that you feel it is okay to associate your journal with a particular article?
Dr Horton: We are very lucky because in the last 10 years or so we have been able to set out a series of independent guidelines which have provided some force when we go to negotiate with authors about the quality of their work. We are a member of the International Committee for Medical Journal Editors which has a very detailed list of guidelines about the way research should be reported which we can appeal to. The Committee on Publication Ethics, which is a UK Committee, does exactly the same. It is a forum which has a list of guidance about the reporting of research and it is also a place where we can take difficulties that we have encountered as editors and place that before colleagues to work out a way forward. The third set of guidelines about the reporting of clinical trials again enables us to force authors and sponsors to disclose information about the results of the search. These are not statutory; these are all voluntary codes so I am the first to admit that they are not perfect but they at least allow a benchmark that we can appeal to in order to do our best to improve the quality of reporting.

Q524 Chairman: You have learned some lessons from problems that have occurred. The Andrew Wakefield study is an issue; do you want to say a bit about that?
Dr Horton: The Andrew Wakefield study is not related to the pharmaceutical industry as such but I think the lesson that I took from the paper on MMR was the way a story which has the potential to be enormously controversial can get put in a crucible of publicity with a rather maverick investigator and controlling that message in the public domain becomes almost impossible. The issue that eventually came out this year, as you know, was the conflict of interest issue that he had, although that was related to the Legal Services Commission rather than the pharmaceutical industry.

Q525 Chairman: Which of course you were not aware of at the time.
Dr Horton: At the time of submission we were not aware of it and also the recent information that came out on the Channel 4 Dispatches programme about the patent, we were not aware of that.

Q526 Chairman: Would your guidelines now perhaps be able to take that into account? Would that ensure that you are aware when you publish of any kind of conflict of interest?
Dr Horton: The evolution of the robustness of our own journal’s guidelines has developed very quickly in the last four or five years so that now we are much stricter than we were back in 1998 about disclosure statements; much stricter about insisting on the responsibility of the publishing source to disclose its role in the research: was it responsible for writing the paper? Was it responsible for doing the analysis? Was it responsible for limiting access to data for the authors? We take those kinds of issues point by point in the process of peer review. Prior to 2001 we did not so this whole evolution of quality control is on a very rapid conveyor belt of change.

Q527 Chairman: Going back to the point about the initial question I asked you in terms of the quote in your evidence and about your comments on medicine being tainted and its integrity being compromised, from your knowledge of the time you have been around as a doctor obviously you have just become aware of this particularly in your current role, but do you feel that something significant has changed in recent times that has reinforced the concerns that you have expressed? If so, what has happened?
Dr Horton: I think the competitive environment in which industry works now is ever greater. It is almost an asymptotic relationship. Its progress maybe from the mid-1960s to the mid-1980s was really quite rapid in terms of developing new drugs and then as time has gone on it has become ever
more difficult. Once you have two or three classes of drugs to treat high blood pressure thinking of the next class and the next class and the next class then becomes very hard. The potential gain for research and development investment is diminishing. The pressure then comes—and we have seen that, the numbers of new drugs that have been licensed have gone down with time—and in that almost intolerable pressured competitive environment the emphasis then switches from research more to market. With the marketing focus such as it is the gain that can be got from even 1 or 2% market share, and the great example, of course, is the statin portfolio of drugs and the entry of Crestor for AstraZeneca. Tom McKillop said that this drug is going to be the make or break for AstraZeneca. There was a billion dollars of investment which seems a huge amount of money but when it could be a two, three, four billion dollar a year return it is actually not that huge an investment. That is the kind of environment that has changed. The marketing pressure has been ramped up enormously.

Q528 Chairman: I was interested in what you said because Richard Smith, who used to edit the BMJ is quoted as saying that “marketing and promotional activity has increased inversely to innovative drug production in recent years. Since 1995 research staff numbers have fallen by 2% while marketing staff numbers have increased by 59%.” That, in a sense, ties in with what you have just said.

Dr Horton: And the problem we have at journals is that the great tool for marketing are the papers we publish so that has led to the swathe of ghost-writing, public relations attached to research papers, using the research that we publish as a marketing tool and not as an educational tool. We get caught in that vice.

Q529 Jim Dowd: The main question I want to ask relates directly to what was just mentioned by the chair, but I think I think I missed something. In the case you gave where you came under pressure from the company and went back to the authors, what was the conclusion of that and, if you feel able, could you mention the company?

Dr Horton: It is probably better that I do not mention the company. Do you mind if I do not? The reason being that the negotiations we have with authors are somewhat like doctor/patient relationships; we say that they are confidential. I can give you generic examples but I would prefer not to give it on the record. In that particular instance the authors themselves had come under huge pressure from the sponsor and were very grateful that we were then saying that we would not publish this paper unless they had full disclosure about adverse reactions and considerably toned down the spun message in the research. We were able to be allies with the authors. So often what happens is that the authors are caught between these forces of the sponsors who they need to do the research. Let us be clear, you would not have this research done if it were not for industry. Then industry owns the message as a result and the authors fail to win the argument about how the research gets reported. I give some more examples in my written evidence. In that particular case I think we were able to win although we did publish an editorial to go with that paper that was highly critical of the way the paper had been reported and the way the study had been designed. That is often our only come-back, to run a critical editorial pointing out the weaknesses in the study design.

Q530 Jim Dowd: The pharmaceutical industry generally and individual companies put a great deal of resources into promotional activities, advertising and public relations et cetera which clearly they regard as being in their individual commercial interest. Is the net effect beneficial in promoting public health?

Ms James: I think usually it is beneficial in promoting public health. I think as I said in my evidence most of the programmes that we undertake involving public relations are to meet various objectives: very much to improve awareness of certain conditions and treatment choices, also to improve diagnosis, identification and management of patients with those conditions and also such a way as does provide a commercial return for our clients. Occasionally those goals are difficult to marry but I would say that was the exception rather than the norm. In the vast majority of cases I believe that public health benefits in terms of our reaching the first two of the objectives I outlined in addition to the third. We do not always achieve the third.

Q531 Jim Dowd: Does anybody demur from that point of view?

Dr Horton: I would put a slightly difficult emphasis on it. As we were talking about earlier, I think that the influence of industry on education, for example, one has to conclude if you look at the work that is put out under the mask of education it is largely marketing dressed up as education. One can understand why; that is perfectly reasonable. This is about getting market share. However, let us be clear: this is not education. Again the regulatory environment—despite the ABPI code of practice—is such that while they are fine words they have absolutely no teeth whatsoever.

Ms Rogers: The only other thing I would say is that in general you could reasonably argue that the whole agenda is skewed by the commercial potential of a particular product so we, the media, and in turn the public are influenced in our perception of the relative importance of different diseases by the commercial possibilities of marketing a treatment for it. If there are a lot of people who suffer from something which you can produce a lucrative treatment for, then the perception of that condition will grow. Sorry, I meant the perception of the seriousness of that condition will become more significant.

Q532 Mr Jones: Going back to Dr Horton’s reluctance to reveal the name of the organisation that put him under pressure, you ably describe the difficult position that you are in and your research
publication but the reality is that it is increasingly important as a marketing tool. As well as putting you under all sorts of pressure it also provides with you an opportunity—because you are an enormously important marketing tool—and if you should so choose you have power over that company.

Dr Horton: Yes, that is true.

Q533 Mr Jones: It may be that you are unduly reluctant to use the powers you have in order to solve the problems that you are under.

Dr Horton: I think that is a very fair point and it is an issue that is underestimated in not just The Lancet but across the whole range of journals. There is a bit of a food chain with journals and you have some of the general journals like the BMJ and The Lancet that you hear a lot about but there are thousands of others. These journals are often very good places to drop articles which are clearly promotional on behalf of a particular company. A very good example, to be very specific, is this whole story surrounding SSRIs. I know you have had evidence from David Healy about this but it is probably the best example where the companies have been very clever at seeding the literature with ghost-written editorials and review papers that promote off-label use of these drugs. You can dress up in an academic argument about “would this drug X be quite useful for this condition; why?” and have an interesting debate about that. What it does in the mind of the prescriber is to think “Hah, this patient with this condition, perhaps I will try it”. It is an off-label use and that is how you had two and a half million scripts a couple of years ago for SSRIs in under-18s with no licensed indication for it. I think you are right; I think journals have an enormous responsibility. We are seen as independent; we are seen as a source of evidence and yet we ourselves can be corrupted by this very perverse set of incentives that we are businesses in our own rights, that we are often owned by publishers which have to make a profit.

Q534 Mr Jones: To get back to the point that you have acknowledged that you are maybe sometimes overly reluctant to use the power that you have been given, do you want to reconsider whether you want to tell the Committee the name of the company?

Dr Horton: I would say we do use our powers a great deal.

Q535 Mr Jones: That is all right; I was just giving you a second chance.

Dr Horton: Thank you but I will decline it.

Q536 Mrs Calton: Can we move on to the influence of the industry and articles covered by the press. I am directing my questions now to Ms Hope and to Ms Rogers in particular. Can you give us a general picture of the types of articles you like to write or chose to write and the types of articles to do with health stories and reports that your readership wish to read?

Ms Hope: Health and medicine are very important to our readership. We know that from feedback in the surveys, the letters I get and the phone calls I get. We cover the whole gamut and it can be from new drugs through to hospital closures through to patient problems. Drugs and the drug industry form a small part of all of this. We get a tremendous amount of information coming to the office every day; dozens of potential story idea presenting and competing for attention and space in the paper. Priority is given to the stories that are embargoed for the day because they are the stories that will be going all around your competitors; they are the ones that have to be screened and filtered and we have to assess whether or not we think they are worth running. Certainly they are going to be in our competitors’ papers or considered for publication there. Then you can work through all the other competing attentions such as exclusive stories that you may be working up, government announcements on the day, that kind of thing. New drugs stories are of great interest to us. The whole point is that they are new; they are news; it is innovation; it is discovery; it is possibility of optimism and hope. Something good is coming out of human endeavour. It has all the ingredients. What is there not to like? The point is that that is the news value of the story not the fact that I have been got at by a drug company to run a story about a new drug. It is the fact that here is a story that will interest our readers. Along the way it may be that we are writing a story that actually does not live up to the initial promise of the original announcement or launch or trial data on which it was based. As we know, science is littered with false storms and we cannot know that at the beginning.

Q537 Mrs Calton: Would you like to add anything to that, Ms Rogers?

Ms Rogers: No, because our agenda is vastly different from that of a daily paper anyway and for obvious reasons we just approach it from a completely different point of view. We are not driven by a news agenda, if you like; we are not driven by embargoed stories, press releases or that sort of thing. It is a different way of working.

Q538 Mrs Calton: The answers you have given indicate that you are very much driven by the needs of the newspaper obviously to sell newspapers and nobody can criticise you for that. What role do you think the lay media has in telling the public about new medicines or warning them about problems? Do you have an educational role besides your need to sell newspapers with stories which are news?

Ms Hope: And with stories which readers want to read. That is a critical part of it. We are not going to sell newspapers unless we actually tap into what readers want to read about. I think the thing about the public health element—the educational element—is that it is a subsidiary element of my work. I am completely conscious of the fact that people are reading these stories and may be alarmed, overly optimistic as a result of reading them; they may be my family and friends. I am a responsible journalist and I am conscious of the impact of these
Chairman: When you get this good news story or the bad news story what do you do to check the other side? Last week we had the predication that we are all going to die of bird flu next winter or something; the reason we are going to die of bird flu is because we do not have enough of this great drug that is going to stop us getting bird flu. I do not think it was your paper I read. It was a paper I read. How do you get the balance in there? We all like to read good news. We are all going to live forever, great, it is really nice to know that, but how do you balance it out? What do you do to get the other side of the story, particularly where that other side may not have been analysed sufficiently to get a balanced picture?

Ms Hope: That is a very good point. It is a constant dilemma in journalism about balancing information. If you have a basic story, a basic working hypothesis based on research evidence you are going to want to run this, but you need to ask questions while you are assessing the information and work out if there is someone you want to contact or some people in order to check out problems that you see arising from this data or from the interpretation that the public is going to put upon it. You just have to use your common sense sometimes about how this is going to play with the public and try to contact sources of information you think are going to put some sort of perspective on the story.

Chairman: The worry we have with what is going to put some sort of perspective on the story. You just have to use your common sense sometimes and surrounding the drug and surrounding the vaccine you see arising from this data or from the word. It sums up a whole history of controversy or some people in order to check out problems that "controversial" because it is a newspaper shorthand and work out if there is someone you want to contact questions while you are assessing the information the media.

Chairman: It is very hard because what you are dealing with is one single issue—usually in a story rather than in a debate—and you have about 600 words to put all the points in. You have to include background; you have to include the elements of how many people are affected by this, how seriously they are affected by it and what is currently happening. It does not leave you very much space. You have to try to stand back and see how that story fits into the trajectory of a particular disease or drug. If, for example, there is new push on with diabetes you have to assess whether or not you think it is as a result of a big PR campaign to try to get a particular sort of drug into the market place. As I said in my written evidence, I feel very strongly that journalists are quite used to looking for vested interests, the hidden agenda. That does not mean, if we spot it, that it negates the story or distorts the coverage. We are aware of it in all walks of journalistic life, be it transport, be it politics, whatever. We are used to looking for it; we take it into account. That does not mean we do not run the story.

Chairman: Looking back to what Dr Horton said earlier when the Chairman asked about MMR, I do not know whether it is true of The Daily Mail or The Sunday Times or anybody else here, and I am not expecting you to answer on behalf of the whole media, but take the MMR, certainly the tabloid end of BBC—Radio 5 Live—cannot report MMR without describing it as the controversial MMR. Technically that may be true, but that gives the impression that this is a 51–49 split but the issue on MMR was one rogue—as it is now described—piece of work. Everything else, every other country in the world, every other piece of scientific information said that the MMR vaccine was perfectly safe as it was and there was no link through to irritable bowel or autism or anything else. That is not how the issue continues—continues to this very day—to be reported whenever there is a story around MMR in the media.

Chairman: I would defend the use of the word “controversial” because it is a newspaper shorthand word. It sums up a whole history of controversy surrounding the drug and surrounding the vaccine and surrounding the effect it has had in Britain on immunisation.

Chairman: There was not a whole history; there was one incident.

Chairman: But it has run and run.

Chairman: Yes I know, by you.

Chairman: By a lot of papers. May I also add that whenever papers are asked to run stories about how poor immunisation rates are in large areas of Britain—including London—the MMR vaccine is actually attributed as the reason for this fall; the reason that parents have lost confidence is because they have lost confidence in MMR. Whether we like it or not the vaccine remains controversial.
Q544 Jim Dowd: You do not understand what is cause and what is effect here.
Ms Hope: I think I do. I think the story rumbles on whether or not you think it has been put to rest.
Ms Rogers: Although we are getting off the point, do not forget that there was a huge lobby of parents of allegedly vaccine-damaged children. I suspect a lot of them were not vaccine damaged but statistically some must have been and they are quite a loud lobby group. They pop up all the time. There is an underlying problem of what you do with this minority of kids who are damaged by vaccine because in any vaccine there is a fraction of 1% that will be damaged. They also leapt onto the Wakefield study and that gave it an extra momentum of its own. It was a very unfortunate series of events I think.

Q545 Dr Naysmith: You said about 1%; it is a tiny, tiny fraction.
Ms Rogers: I said a fraction of 1%. I think it is several decimal points.

Q546 Mr Jones: In terms of this study on the pharmaceutical industry the sort of story that needs to be told—whatever tells it—is not the story about the drug that works marvellously (because that is a good story) or the drug that does not work and causes dreadful problems (because that is a good story); one is a good bad story and is a good good story, but in terms of what we are doing we are mostly concerned with the drugs that do not work at all and that is not much of a story, is it? It is particularly not much of a story because people are not paying. If they were paying for the drugs that do not work, that might be a story: you are being ripped off personally.
Ms Rogers: We do report that. We regularly report the fact that the vast majority of drugs work on a fraction of the people they are given to; a minority of the people they are given to. I do not think that that take home message gets through at all. In the same way that we were the paper that demonstrated the MMR thing was a complete con, that message clearly has not got through. It takes a long time to change public opinion and the message from the drugs industry all the time is that here is yet another treatment for cancer which has a response rate of something extraordinary which, when you unravel the statistics, it does not stack up at all. We do report the fact that only one in seven people will actually benefit from this highly toxic drug. We most definitely do, but if you have cancer you want to hear that there is going to be a drug that is going to cure you. You do not want to know that you might not respond to the drug.
Ms Hope: We need a newpoint in order to say that a drug does not work or a class or drug does not work. For example, if you get a report in a journal—I have heard up to now about the journals and the degree of trust we can place in the reports we see—as we did recently about the fact that a blood pressure drug called Atenelol does not work, it just does not have an effect, we run the story. We ran the story but I am not going to be running stories as a matter of course and say that generally speaking drugs do not work because we actually need to have the evidence on which we can base the report.

Q547 Mr Jones: Does Dr Horton or the equivalent of Dr Horton ever phone you up and say, “We have just discovered that this drug does not work at all” or something like that? How do you cover it in your paper?
Ms Hope: That would be undue influence.
Dr Horton: I have never called Jenny.

Q548 Mr Jones: You only get pushed from the commercial side; nobody tells you from the other side?
Ms Rogers: Yes, they do.

Q549 Chairman: Who tells you?
Ms Rogers: It tends to be individuals who I know who have done work.

Q550 Chairman: Not other companies?
Ms Rogers: No, sorry, that is not true. I did get calls about the Vioxx thing from other companies asking why we did not have a look at this. In fact, that is a very good case in point because with Vioxx I had several approaches from competitors saying that we should have a look at this because there was something going on. But unless you have actually got the hard evidence there is not much you can do. You have to say to them, “Unless we have the evidence that it causes heart disease as opposed to you saying what the rumour is, we cannot do anything at all”. These are very litigious companies; you do not take them on lightly.

Q551 Mrs Calton: What are the main sources for drug stories? Out of the articles you have published on medicines what proportion would you say come from drug companies or their representatives and publicity agents and what proportion would come, say, from government sources?
Ms Rogers: For me, neither of those. They would come from individuals I know who are academic researchers. I can say reasonably confidently that I have never in the eleven years I have worked at The Sunday Times written a story about a drug that has come from a drug company.

Q552 Mrs Calton: They have always come from researchers.
Ms Rogers: Yes. Sometimes patients.
Ms Hope: If I could just add to that point, we are very much more embargo driven so a lot of stories would come from journals and conferences where trial data—usually significant results, that is the reason why we are thinking about reporting on them—are embargoed to a certain point in time and that would affect the daily papers. We are six out of seven days and that is where a lot of our stories come from. It may well be that PR companies are drawing your attention to the fact that this is going to happen at a certain point so you can put it in the diary and it becomes a potential story of note.
Q553 Mrs Calton: Going back to Ms Rogers and your response, with all these researchers do you enquire who is funding the research?

Ms Rogers: Yes, absolutely

Q554 Mrs Calton: Does that go into the story?

Ms Rogers: Yes. Obviously it depends on whether it is relevant. Sometimes somebody would ring me up who happens to know something which is absolutely irrelevant to what they are doing at that particular point. You would ask what is their relationship with the company whose products they are attacking and because most academic research is funded by the industry in some shape or form it is inevitable that everybody has had contact in financing from commercial sources.

Q555 Mrs Calton: Does it always come from that side, from people who are attacking another product that they are not involved with or sometimes are there people who are involved with research and are being paid by a company?

Ms Rogers: The Viagra story which we got before everyone else—which is many years ago—I actually was told about by the person who was doing the research. In the course of conversation—we were talking about blood pressure—he said, “We have discovered this fantastic compound which is going to make a huge amount of money”—this is almost how the conversation went—“and it is going to work on erectile dysfunction and the market for that is going to be vast”. The company—it was Pfizer—were not at all pleased that we were running the story because they did not want their competitors to know at that stage. That is how that one came about. It is serendipity a lot of the time.

Q556 Mrs Calton: Do you ever feel you are being used by a drug company in a promotional sense?

Ms Rogers: Yes.

Q557 Mrs Calton: Could you give us some examples?

Ms Rogers: We regularly receive approaches where people are trying to use us principally as a conduit for getting a mention of a particular drug into a story because they know that we are not going to write a story saying that this new drug is about to be launched on Thursday because Sunday papers do not do that. It would be much more try to talk me into mentioning something in a favourable way.

Mr Paling: Could I just make a point here? My company is not involved with the lay press in any way, shape or form. I do think we are hearing some incredibly sweeping statements about some treatments: “drugs work on a fraction of people, the blood pressure treatment atenolol (which is a beta blocker) just does not work.” If that is the case—and atenolol has been genericised for many years but probably available for 25 years—I find it quite remarkable that doctors around the world (hundreds of thousands of doctors) and millions of patients are being treated with a product that does not work when it is actually very easy to measure blood pressure. It does work—I am not saying it is the best treatment and I am not an advocate for it—but I think we have to be a bit careful that we are not making incredibly sweeping statements like that.

Dr Horton: I think it was us who published the paper on this particular drug. You can reduce blood pressure but actually it is not blood pressure you are trying to reduce. What you are trying to do is change the risk that flows from having high blood pressure: the risk of subsequent stroke, heart attacks and so on. It is a question of whether that particular drug is effective at reducing those clinical end points and there is a question about the efficacy of that drug. I think the point that has just been made is a really interesting one about our drug regulations. A drug gets licensed and there it is; it is there for prescription forever more until the company decides to stop making it. That is crazy. Surely what you should have is a regulatory structure for drugs where you have continuous assessment of the evidence and periodic formal reviews of whether that drug should still have its licence. That is something we do not have right now and I do not think it has been suggested in the oral evidence you have heard so far.

Q558 Chairman: We have certainly had the old yellow card system criticised.

Dr Horton: That is nonsense; that is the worst way of doing epidemiology you could possibly think of.

Q559 Dr Naysmith: To be fair, there have been a number of occasions we have suggested to NICE (when we have had them before us) or government ministers that they should look at some of the existing treatment and see whether the work or not. They are over-loaded with work but that would be another possible way.

Dr Horton: Five yearly periodic reviews of every drug on the market looking at what the evidence is for and against would clear our all the dross—and there is a lot of dross—and it would give up-to-date evidence for prescribers about what works and what does not work.

Q560 Mrs Calton: I was actually in the middle of asking two people a specific question, helpful as the exchanges have just been. Can I come now to Ms Hope and remind you of what the question was. Do you ever feel that you are being used by drugs companies as a promotional conduit or as a vehicle? If this happened what would you do?

Ms Hope: I do not feel that I am being used but I feel I am a target for promotional and marketing activity. I think there is a difference. If there is a story there, if there is some news merit, if I think the news values holds up on something I am being offered which is obviously promotional for the company involved then that takes prececence. If there is a benefit—either direct or indirect—to the drug company involved then so be it but I do not feel used and I can weigh up everything that comes in front of me with those news values in mind: should the public know about it? Is it of interest? Would it be wrong if I kept it a secret?
Q561 Mrs Calton: When you are writing drugs stories how often do you rely on opinion leaders—I think Ms Rogers has already addressed this to some extent—or patients suggested to you by a drugs company? Does it ever work that way round? What procedures would you follow to check whether such a story is reliable?

Ms Rogers: That does not happen.

Q562 Mrs Calton: From what you were saying you actually have some very direct relationships with researchers.

Ms Rogers: I have a very good network of people and I know exactly what funding they have had from who because, as I said earlier, everybody has and these are people I know well and whose views I would respect.

Ms Hope: I would concur with Lois that I too have what I hope is a good network of contacts to call upon but the PR industry sets great store by opinion leaders which slightly mystifies me. I just see it as doctors they can call upon to back up what has been said about a drug. It may well be because they are an investigator or because they have many years' experience in the area. That is fine, but you know where they are coming from. If you feel the need—and I usually do, I do not rely on single-source stories—to talk to somebody else then I talk to somebody in my bunch of contacts about where this information comes in the whole stream of information about a drug, where the drug might have its place in the future. I fear that the influence of these opinion leaders is really rather something that has been got up, to be honest with you, by the PR industry.

Ms Rogers: Can I just add to that, even the expression “opinion leader” to me is a deterrent because if I happen to be talking to someone from a drug company and they say, “Have you spoken to so and so about this?” that would immediately tell me that that person in the pocket of that drug company. That would be exactly how I would interpret it so I would be disinclined to talk to them.

Q563 Mrs Calton: Can I ask each of you something which is probably a little unfair but nevertheless I shall ask it: have either of you written up a story and subsequently thought to yourselves, “I really should not have done that because had I had the time or whatever to look into it more fully I would not necessarily have covered this story”? Have you ever regretted putting a story in because it has caused an adverse set of reactions in the public arena?

Ms Rogers: No, but I can say that I would regret seeing things in the media generally that I think are misleading about the value of particular drugs and products.

Ms Hope: My biggest regret is the Pill story and I had no choice about running that. That was a story out there that had to be run and had to be followed up. We assiduously followed it up; we assiduously contacted and talked to people and criticised the original decision and the basis on which it was made but all the caveats were lost in the general furore surrounding it. It had dreadful consequences that you could see unfolding from day one.

Q564 Dr Taylor: I am very interested in your comments about opinion leaders and your active disregard of them and I really want to go to Ms James because a quote from your website is: “The effective development of opinion leaders in all your stakeholder groups is essential for your commercial success.” How do you set about identifying these opinion leaders and how do you use them? We have heard that two important newspapers—if they get any hint that these were opinion leaders that were selected by you—would shy off.

Ms James: I think the evidence was actually slightly different. I think I am right in saying that Jenny checked with other doctors; she did not disregard opinion leaders supplied by companies. If there is a question in your mind then you will go to another doctor as well and I would expect any good journalist to do that. The way we go about identifying opinion leaders, it depends on the condition and how big a pool of expert doctors exist. Obviously if it is heart disease there are a lot of people; if it is a very small, narrow niche in cancer there are not many. There are a lot of variances, but in principle we start off with a conversation with a client and the client already has some doctors that they are working with clearly. A lot of those doctors will be triallists so some of the opinion leaders self-select by participating in trials and leading clinical trials; they will be natural opinion leaders for us to work with. Beyond that we will look at all sorts of databases to identify which doctors have an interest in which fields and we will start targeting a few doctors who have published research in a similar area and are known to have an interest. We might establish some relationships with them. It is a long term process really, over many years.

Q565 Dr Taylor: Can I broaden it out and go back to ghost-writing? I was absolutely horrified to hear Dr Horton say that some—even leading—articles can be ghost-written. In years of practice somebody like me has always regarded BMJ leaders and Lancet leaders as the gold standard. Are you implying that there are some journals that do accept ghost-written leading articles and how do you check to see if something is ghost-written? Or am I wrong in assuming that something that is ghost-written is somehow second-class?

Dr Horton: To start with The Lancet we ask people who write for us whether they have written the article themselves or whether someone else has collaborated. If they have had somebody ghost-write it and they deny that then they will be telling us an active lie if that is the case. I think we have fairly robust—as robust as we possibly could have—procedures for picking that up. However, people do lie and I can give you an example. We received a review earlier this year on a particular subject which had been commissioned. This review was about a particular treatment for a particular neurological disease. As with most things these days it is
submitted on a disc as a Word document. The clever thing about Word documents is that you can go into the properties part of a Word document and see various messages that have been written by the person who has been the author. The author of this paper said, “I’ve written this paper; there was a link with Novatis” and he had had some assistance with the writing of it, but it was his paper and there had been absolutely no substantive input from the company. When we went into the properties field of his Word document it said: ‘Marketing approval required please’ and a little tick box next to it. We were able to go back to the author and say, “Come on, we’ve caught you out here”. The paper was rejected, he went away and we have not heard from him since. I think there are examples of out-and-out lies that come from supposedly independent scientists who are presumably on a substantial retainer fee to get their articles seeded in journals. This is the constant conflict we have in trying to weed these out. It gets worse as you get down the food chain of journals because there the very viability of those journals depends entirely upon the re-print revenue that they get from the editorials, the research articles, reviews and so on. It is critical that if those journals are to survive they are financially successful and then the relationship they have with the sponsoring organisation as an industry becomes much more powerful and influential. There have been examples, for example David Healy’s work where he has shown very clearly in his British Journal of Psychiatry paper—which he gave a summary of in an oral session here—how information is commissioned by industry through third party medical communications companies and then gets seeded in the literature and that information has a systematic bias in favour of a particular drug or issue. That is the thing we are constantly trying to fight against.

Q566 Dr Taylor: Do you think doctors recognise that there is what you call a food chain of these journals and they are sufficiently aware—and I am not asking you to name them but I am sure I know quite a lot of them—of the quality of the ones at the bottom end?
Dr Horton: They are certainly aware of the food chain of journals, but it is the way the articles then get used. If you get what is essentially a promotional piece of work written up and it looks beautiful in print and it is all fantastically typeset and that gets given to a doctor, whether it is in The Lancet or the journal of whatever it might be down the food chain then it looks credible. It has the imprint of the journal and the publisher attached to it. There is an authenticity given to what are often completely spurious views not owned by the author him- or herself.

Q567 Chairman: As a non-medic, how aware would the average doctor be of the quality within this food chain of what he or she was reading?
Dr Horton: I would believe—maybe I am naïve—that most doctors would be aware of the fact that the BMJ and The Lancet are somewhere hopefully near the top and then you would have leading speciality journals in the middle and then there is a whole bunch of third and fourth rate promotional journal that sit somewhere at the bottom. I would hope they would understand that, particularly those in the general practice community. They will not necessarily have the academic background and critical appraisal strengths to be able to discern which are strong and which are weaker articles.

Q568 Chairman: So key prescribers could be fed a load of rubbish by these at the lower end.
Dr Horton: They are, daily. That is what drug representatives are there to do, to feed them rubbish; that is their job.

Q569 Dr Taylor: Going on from that, Ms James in your submission you give us some of the rules you follow to preserve the integrity of articles written by your editorial staff on behalf of doctors, one of them is that some doctors do not have the time or the writing skills necessary for publishing their own work and value this service. I do not want to argue about the writing skills because we are all notoriously bad at writing, but I do argue with the sponsoring organisations as an industry becomes more powerful and influential. That is the thing we are constantly trying to fight against.

Q570 Dr Taylor: I would not argue with that. We certainly never had time to do the yellow cards.
Ms James: That is very important, too.

Q571 Dr Taylor: But if you have done a bit of work you are desperate to get it out.
Ms James: I accept your point but I think the service really came about partly because of people’s desperation to get this work published. It is not just the doctors who are keen it is the companies as well.

Q572 Dr Taylor: Mr Paling and Ms James, how do you actually build up relationships with journalists?
Mr Paling: We do not build relationships with journalists; we do not have contact with journalists. The only time we have material that is appearing in a newspaper or a magazine is paid-for advertising space so that is through a very different channel. My company does not even plan and buy that either but we are really filling the space; that is all, and that is paid for and it is branded.
Q573 **Chairman**: Would it not help you sometimes to have contact with journalists?

**Mr Paling**: I cannot honestly say that I have had contact with a journalist in my life apart from a friend who was a sports writer with The Mirror.

**Ms James**: I think in days gone by the word “relationship” might have been more applicable because there was more time to get to know people, take people out for lunch and so on. These days I think the relationship is much more business-like. If we think we have a story we will assess the likely extent have you been obstructed by pharmaceutical companies in trying to gather information about stories you want to write? Can you give us some examples of where you have been obstructed in trying to obtain the truth?

**Ms Rogers**: I will give you a recent example. I did something a few weeks ago about testosterone patches because I thought it was a very interesting example of the way something had been promoted. They are produced by Proctor and Gamble; they are patches because I thought it was a very interesting example of the way something had been promoted. They are produced by Proctor and Gamble; they are initially trying to get licence approval for their use in post-menopausal women who have had their ovaries removed but they have managed to seed across the whole of the media a huge number of articles about testosterone patches will be the answer to Viagra for women. There has been quite a lot of data that has emerged suggesting that testosterone does not actually work very well and, not only that, it has never been tested properly as a drug but it might have extremely unpleasant side effects in the formation of male characteristics et cetera. The food and drug administration in America turned down about two or three weeks ago the licence application for this product. I tried to ring Proctor and Gamble and they were very, very difficult. I put in any number of calls to Proctor and Gamble but I kept being put through to answering machines with messages left from last September. Eventually I rang their offices in America and got a call back at about eight o’clock on a Friday night, a day after I had attempted to get a response to the question: what was their reaction to the suggestion that testosterone patches were potentially harmful? The reason they take so long to come back to you is because they hope that if they do not you might lose interest in pursuing the idea and not write it.

**Q574 Dr Taylor**: Going on to promotional campaigns—by which we mean really advertising campaigns—do you target patients? Do you target nurses? Do you target doctors? Where do you target your campaign?

**Ms James**: I am sure Mike will want to come in here because I know that is his area of expertise and we do advertising as well. Advertising is 80% aimed at doctors, increasingly aimed at nurses and to a very limited extent aimed at consumers. There has probably been about five to ten disease areas where the company has decided that it wants to use advertising to reach patients and consumers.

**Q575 Dr Taylor**: What about over the counter drugs?

**Ms James**: That is predominantly aimed at consumers, yes.

**Mr Paling**: We work across a number of audiences, as you say. When it is over the counter medicines we are largely aiming at the end user or sometimes at the pharmacist who has a role in advising a customer or a patient. In terms of prescription work we do, the vast majority—90% of it—would be aimed directly at the doctor who maybe in a specialist sector or more likely to be a general practitioner. The only time we would do anything which was not branded would be when it was a disease awareness campaign. We have been involved in one of those which I mentioned in my submission.

**Q576 Dr Taylor**: The contract to run this campaign comes from the maker of the drug presumably.

**Mr Paling**: We would agree with the company concerned depending on the nature of the product who we would be aiming our advertising at, yes, and they would have a budget although we do not actually buy space as I said so we would not be controlling that budget.

**Q577 Dr Taylor**: Would you have any control over the content of the advertisement, for example?

**Mr Paling**: We would develop the content of the advertisement in agreement with the client. We would jointly develop a brief. Our role is really to put that into a communication form and have that medically and legally approved through the normal system, which I am sure you will get onto.

**Q578 John Austin**: I have a question for our two journalists. You talked about the way you are fed information to try to produce stories, but to what extent have you been obstructed by pharmaceutical companies in trying to gather information about a patient. In terms of prescription work we do, the vast majority—90% of it—would be aimed directly at the doctor who maybe in a specialist sector or more likely to be a general practitioner. The only time we would do anything which was not branded would be when it was a disease awareness campaign. We have been involved in one of those which I mentioned in my submission.

**Q579 John Austin**: In one sense that is them obstructing you by not giving you information.

**Ms Rogers**: That is the normal way they would do it.

**Q580 John Austin**: Do you have examples of where they might have been giving misleading information? For example, on the testosterone patches you said in your evidence that there is also an increased risk of raised cholesterol and heart disease as well which presumably the company—Proctor and Gamble—manufacturing it are aware of. Have they at any time attempted to suppress that information?

**Ms Rogers**: I cannot recall having asked the direct question when I eventually got through to someone who was put up as the company spokesman; they were too junior to deal with that sort of question anyway so I never went down that track particularly.
There have certainly been other occasions at regular intervals where people ring you up and tell you things. As a journalist you do not want to miss anything so if somebody tells me something that sounds phenomenal and plausible then you have to check it out. If it turns out to be completely and utterly untrue then I would make the time to ring back the source and tell them that they have wasted however much of time and also make it clear that any subsequent approach would not be looked on favourably. It is a give and take relationship. If people are helpful and truthful you build up a relationship with them where you respect them. If they say you are wasting your time on this, whatever you have been told is actually not quite how it is, then you know not to pursue it.

**Q581 John Austin:** You have the luxury of not being a daily driven by embargos and having the time to investigate. I wonder if Ms Hope has a similar experience.

**Ms Hope:** I am sorry to disappoint you; I cannot think of any specific examples of active obstruction. As Lois says, it is more the case that they might not get back to you or they might be economical with their answers and that could be because you have asked the wrong question. That happens even when I ask some government departments; I might not get the right answer because I have not asked the right question. I just want to add to the testosterone patches story because we published a story saying that testosterone patches offered some relief to symptoms in eligible women based on a paper given at the American Society for Reproductive Medicine. I think it was in October. I was there and saw the paper being given, looked at it, went to the press conference where they presented the details again. I asked about side effects, side effects were included in our story. They had a company spokesman there, very upbeat and, as is to form, I included one quote from him saying, “I hope to get marketing approval” but I did not feel I was a particular target of the marketing campaign but obviously, as Lois suggests, they are getting papers together, presenting them at conferences, putting them into journals and then they become a potential news story.

**Q582 Chairman:** You went to the States for that.

**Ms Hope:** Yes.

**Q583 Chairman:** Your paper paid for that presumably.

**Ms Hope:** Yes.

**Q584 John Austin:** Since the other question I was going to ask has already been asked, I want to go back to something that Dr Horton said earlier about the food chain. I am not sure whether you are prepared to name names as to those publications which are lower down the list, but reference was made earlier to general practitioners and general practitioners, by their very nature, are generalists. The Lancet publishes very specialised and specialist articles which perhaps general practitioners might not have the time to study in detail. What they do get weekly is a whole range of magazines, presumably sponsored by advertisements and the pharmaceutical industry which gives them easily readable information or mis-information. Would you say that the presence of those magazines was overall helpful or a malign influence?

**Dr Horton:** Definitely a malign influence.

**Q585 John Austin:** Would you name the magazines?

**Dr Horton:** There are many magazines that get given out to general practitioners and it would almost be invidious to name one because it would put a focus on one rather than another but you are right, I can probably count on the fingers of one hand the number of general practitioners who read The Lancet in the UK; you are quite right, nobody is going to read The Lancet, it is not written for them.

**Q586 John Austin:** That is not a criticism.

**Dr Horton:** No, it is just that that is not who we are; that is not what we do. So you have theses intermediaries and the intermediaries may be through a promotional campaign or advertising, a drug representative visiting where the work that is published in general is completely distorted—I have examples if you want me to go into that—so that the general practitioner would see the results of a study and be completely misled as to the efficacy and safety of a particular drug. Or what happens is that with these controlled circulation free newspapers that will come to doctors the reporting of the studies there or the presentation of those studies at meetings again often is filtered through company PR systems. To take an example, if you have a big meeting—a research conference—where work is presented many of the journalists who will be attending—I am not talking about Lois or Jenny here, but journalists on these sorts of free newspapers—will have had their travel and hospitality paid for by industry.

**Q587 Chairman:** Which is why I asked that question, obviously.

**Dr Horton:** Exactly. They will go with the express purpose of covering the conference but particularly to cover the conference about the products made by the company which is paying for their travel. It may not be the company that has taken them; it may be a PR company working on behalf of the pharmaceutical company involved. They will go, they will go to the satellite symposium, they will write up the story and that will then get published in their newspaper. That is what the general practitioner will read. Again, there is no identification that the travel was paid for by the company, no identification that this journalist was there for just 24 hours to go to the sponsored satellite symposium, no indication that the way that study has been reported is misleading. The quality control here is appalling.

**Q588 John Austin:** Does this also lead to unnecessary prescribing?
**Dr Horton:** I think you have examples of that. You have examples—whether it is SSRIs. Vioxx or other drugs—where you can see that the prescribing rate has gone up hugely and then you have a public health disaster. Ken Woods, Chief Executive of MHRA, said only the other day—I think last week—that there had been over-prescription of SSRIs. Yes, the way drugs are marketed and the way that information gets seeded in the pseudo literature as well as advertising material has enormous impact on prescribing habits.

**Q589 John Austin:** Could I raise one which has not had a great deal of publicity and is costing the NHS an enormous amount of money at the money, and that is the prescription of proton pump inhibitors—PPIs—when there are much cheaper remedies which are applicable to most people who might turn up at their general practitioner’s surgery. Has that been influenced by marketing campaigns by the pharmaceutical industry?

**Dr Horton:** Yes, and the classic case example that we talk about a lot is the way AstraZeneca very successfully took omeprazole to Nexium which had a little bit of fiddling with its formulation but was essentially the same drug, got marketing approval for what was a new branded drug—supposedly—and kept the patent life for that supposedly new drug when in fact it had no competitive advantage on now what was a generic medicine. Yes, there are very good examples.

**Q590 John Austin:** Does Mr Paling share your concerns?

**Mr Paling:** When you were talking about the issue of PPIs—proton pump inhibitors—unless I am wrong I thought that NICE had recently deliberated on the treatment of oesophageal reflux and said that these were the treatments to use. They did put the caveat in that it should be the cheapest and I do not think that is a negative issue at all; I think that is important. I think that proton pump inhibitors have made a tremendous difference.

**Q591 John Austin:** In that specialist area?

**Mr Paling:** In the treatment of all the conditions that they are involved in. Their big impact has been on ulcers, first of all the H2 days of Zantac and so on and these treatments have literally wiped out the need for surgery for the treatment of ulcers. I think they have value; I am not arguing the case for them one way or the other but I think they have value and I think we have to be careful not to make too many sweeping statements as I said before because I think there are drugs which have brought tremendous benefit over the last years where appropriately used and used in the right patients and used in the right way. I do not want to swing the pendulum too far the other way. I do take issue with something that Dr Horton said when he said that drug representatives are there to feed doctors rubbish. I do not know whether he means the information they are giving them or that the products are rubbish, but given that journals—including *The Lancet*—carry advertising for pharmaceutical products, I do not know whether that is vetted by *The Lancet* before the adverts are allowed to appear, but advertising is an important function of all of these publications. I would also say that when we are talking about what general practitioners read whether this is right or wrong the bulk of the readership to my knowledge seems to be in news-based publications not pseudo-scientific or scientific publications. They are not reporting on clinical trial results; they are giving doctors other information whether it is political or news or whatever. That is where the bulk of the advertising goes in my experience.

**Q592 Dr Naysmith:** I want to explore the area of voluntary regulation that all of you are under in terms of putting out the information that you put out and so on. I am going to start by asking Mr Paling a question. The kinds of bottom end of the market that Dr Horton was talking about in terms of journals are often described as “the comics” by GPs and I think quite a few of them understand that they may not be fully scientific. What I wanted to ask Mr Paling was, you say you adhere to the ABPI code of practice and guidelines and that you are satisfied with the existing standards relating to the quality of drug promotion. Why do you think there is such concern about the practices of companies such as yours? Why do you think that people do not have a particularly high opinion of the work that companies like yours are performing?

**Mr Paling:** Just one comment first of all about the journals, in terms of comics they are news based publications, as I say. I think the ones that we have both got in our minds are actually the highest readership amongst general practitioners so it would suggest that it is their choice.

**Dr Naysmith:** They are given free or they are sent through the post freely.

**Q593 Chairman:** If nobody else will name names, will you name names? We are in the dark you see.

**Mr Paling:** Almost all of the publications are free.

**Q594 Dr Naysmith:** There are so many of them that if you name one or two or three then you are sort of picking them out. Things like the GP and *Hospital Practice* and things like that.

**Mr Paling:** In terms of how materials are regulated for prescription products through the ABPI code of practice—which is what we adhere to and obviously our clients adhere to—the process there is a self-regulating one and you are quite right to point that out. When we are talking about pharmaceutical products it is a vast amount of knowledge base, it is not like regulating advertising in FMCG consumer sector where you may be looking at other things but you are not looking at the same amount of data and I think it is important that a large part of the self-regulation goes on at the company where the highly responsible people—one of whom has to be a doctor—have to regulate all the output. We have worked with client companies on that basis for many years now and I think it is the most stringent and incredibly accurate place to verify the output of the material. The code of practice is very clear; the
products can only promote within their licence and their summary of product characteristics. The checks and balances I think are very tight and I think if a company does breach the code—and I am not saying there are not breaches; there are breaches, I think about a hundred a year and about 70% of those are upheld (the ABPI would be able to give you that data)—that is taken very, very seriously. It causes all sorts of problems within companies, not least of which from a commercial point of view is loss of time while advertising is removed, the cost of replacing it, which we obviously feel; it has an impact on us as well. I do not think it is taken at all lightly; it is a very detailed stringent system.

Q595 Dr Naysmith: Do you have any worries about the length of time the advertising complaints procedure takes from the time of a complaint being put in before there is an adjudication?

Mr Paling: I cannot give you an accurate answer on that I am afraid. I would imagine it is a matter of weeks.

Q596 Dr Naysmith: It can take longer than that; sometime six months. That is a disincentive. Why can they not adjudicate much more quickly than that?

Mr Paling: I would have thought they would be able to adjudicate much more quickly than that. As I said, there is not a vast amount of complaints so there are not a thousand complaints sitting waiting. I would imagine that is something you would have to take up with the ABPI. I think if there is a complaint, particularly if it is going to be upheld, it should be adjudicated and sorted out very quickly.

Q597 Dr Naysmith: If one of your adverts was found to be misleading would you be penalised in any way or would this cause any problems for you?

Mr Paling: For our company directly?

Q598 Dr Naysmith: Yes.

Mr Paling: We have had a misleading advertisement through the ABPI and it created a great deal of difficulty between ourselves and the company concerned. Both of us had to be carefully audited and monitored to see how that process had occurred. It is important. Our relationship with our clients is a very important one and we do not want issues like that to get in the way, plus the fact that we do not want to be breaking the code full stop.

Q599 Dr Naysmith: Have you ever withdrawn from negotiations with a drug company because you felt that a campaign they were asking you to undertake might be unethical or misleading?

Mr Paling: No, never.

Q600 Dr Naysmith: Have you ever come across the need to argue or discuss that with a client, or you just accept it?

Mr Paling: Not at all, no. The ultimate responsibility for a campaign rests with the doctor inside the companies and I think they could not be more careful, stringent and totally honest with what they are doing in my experience and in the work we do, which is advertising and sales promotion, as you know.

Q601 Dr Naysmith: Ms James, do you have anything you want to add to what Mr Paling has said?

Ms James: I would like to reiterate the seriousness with which the code of practice is taken by our clients and by ourselves. I was amazed to hear Dr Horton say earlier that it has no teeth, it is just words because that really is not the case. I have also noticed that over the time I have been in the business—over 15 years—that the seriousness in which it is taken has significantly increased. When I started in the business the code was a bit over there and although it was taken seriously the top directors would pay lip-service to how important it was and the product managers would just turn a blind other eye. Now that is most certainly not the case. Even the product managers now go in fear of breaching it.

Q602 Dr Naysmith: Why do you think that has happened?

Ms James: I think it is partly a societal trend overall in business. I think the whole trend of corporate social responsibility is having an effect and that effect is being felt within pharmaceutical companies just as in any other industry. That would be my first comment. I think also the regulatory situation is becoming tighter around the world and companies that start to get a bad reputation for breaching ethical guidelines are probably going to feel the heat from the regulators.

Q603 Dr Naysmith: Dr Horton, you were talking to the Chairman earlier on and you were talking about the rules that The Lancet has for conflicts of interest for authors and editors and reviewers. In general terms do you think your rules are effective? You told us about one example where you discovered that you were being deliberately misled about a paper, but do you think in general that they are effective and you can be sure that you are not publishing anything that you would not really want to be publishing?

Dr Horton: As you rightly point out, the system is voluntary; it depends upon trust; it depends upon good faith between ourselves and the authors who work with us. Clearly there is room for great exploitation in that relationship. I think that over the last four or five years we have made our procedures much more robust. We have changed the conflict of interest disclosure now so that you actually have to actively lie if you are going to deny that you have had a conflict if you have in fact had a conflict. We insist that we have a description of the role of the funding source in the research: did they take part in the design, the conduct, the analysis, the writing up and submission of the paper. We did not used to do that. We insist on the naming of all contributors to the paper including those who might have been ghost authors of the paper. I think within the voluntary nature of this we have done all that we can do. We have tried—that is the editors of journals—have tried to strengthen this and so the Committee on Publication Ethics that was created in
1997 was created largely out of a failure amongst us to persuade those in medicine at the General Medical Council and some of the other colleges and organisations that run medical research that we need to actually go a step further and to create what we call the Council for Research Integrity. This is a body that is a place where complaints about the way research was done and reported could be taken to that had legal teeth. If you look in some European countries—particularly the Scandinavian countries—they have statutory bodies where these kinds of issues can be referred where there has been a breach of practice and sanctions can be made against individuals, against sponsors and against universities that have taken part in these malpractices. We have been singularly unsuccessful—our failure—to persuade anybody that we need such a body. There is great scepticism within the science community because they feel this would be another layer of bureaucracy and regulation and that is the last thing science needs. However, from where I sit we desperately need it because we do not have the teeth that we need to enforce these voluntary regulations.

Q604 Dr Naysmith: Do you think that similar voluntary regulations apply to other journals of the standard of The Lancet?

Dr Horton: When the code was introduced about 1997 it was the BMJ, The Lancet and one or two other journals that came together to create this and we tried to draw in many other journals in the last five or six years to make them part of this process. Again, it only goes a small step of the way; this is really just a scratch on the surface.

Q605 Dr Naysmith: The point you made just now was a very good one. The last thing science needs is more bureaucracy and more regulation. Where do you feel the balance lies now, having laid out the case for it and then pointed out why it is not going to happen or is very slow to happen? What would you like to see happen?

Dr Horton: What we do not see is an office of research integrity like they have in the US, a huge superstructure of bureaucracy looking over science and interfering in the conduct of research. We do want something very light. There are models—and I would look to Norway, Sweden and the Netherlands as very good models—of lightweight oversight but which have some sort of legal statutory teeth. I think there are models that we can draw on and that is what I would go for.

Q606 Dr Naysmith: Turning to Ms Hope and Ms Rogers, are there any kind of voluntary regulations that apply to The Daily Mail and The Sunday Times?

Ms Hope: Speaking for myself I feel I have personal ethics that I abide by in reporting. I have been a reporter for a very long time and I am a trained reporter, but because I knew this question was coming up when I rang yesterday I specifically went and looked at the code of practice for the National Union of Journalists (of which I am a member) and I was delighted to see, for example, point eight: “A journalist shall not accept bribes nor shall he/she allow other inducements to influence performance of his/her professional duties” which I feel is just taken as read by journalists, let alone those who are members of the NUJ. Certainly in this context, talking about the pharmaceutical industry, I feel it is important to highlight and I can confirm that I have never personally felt that I have been unethically lobbied or offered a bribe or inducement to run a story or not run a story. I have to say that I cannot imagine a drug company or a PR company would have the temerity or the stupidity to approach me with that kind of offer.

Q607 Dr Naysmith: You have never had such an offer?

Ms Hope: No.

Q608 Dr Naysmith: Travel or gifts or hospitality of that sort? Nothing like that?

Ms Hope: Do you think that going out to dinner with somebody is an inducement? I do not.

Q609 Dr Naysmith: I think many MPs would have difficulty answering that question.

Ms Hope: It is likely to go both ways. I take doctors out and I get taken out by doctors or occasionally by PR companies. For example, I had an offer to go to a dinner last month which I leapt at because sometimes PR companies run supper attached to a kind of educational programme—about an hour’s worth of press briefing—and it was on heart disease and the Government’s heart tsar was speaking. It is not often you get the chance to spend 20 minutes listening to him talking about heart disease and then questioning him. I leapt at it and so did other journalists on national papers and broadcasting organisations. I was also going to make the point about advertising that we should not lend ourselves to the suppression of truth because of advertising considerations. For example, I think I am correct in saying that ours is the only national newspaper that has actually written stories about the potential detrimental consequences of putting statins over the counter, of re-classifying them for pharmacy use. We were a paper that ran stories about how the Royal College of General Practitioners and the Consumer’s Association had produced evidence that they were against this on safety grounds and other grounds. We ran stories about this on at least two occasions. It did no good whatsoever; it just went through on the nod as far as I can see. That is another opaque system that I feel you should address because we do not get to see the information on which these decisions have been made. It appears to me that new classification is now a big deal for the health service. It has all sorts of unforeseen consequences that may come from it. The point I am making is that we now run enormous full-page ads for statins that you can buy from your pharmacy. If I had given it one single minute’s worth of thought and thought whether this would affect our future advertising if we wrote stories which actually ended
Ms Hope: No, I have better things to do with my time.

Ms Rogers: Yes, I do but I do think that the issue of hospitality is one that should be looked at not just a propos of journalists but MPs even because the drugs industry does spend an enormous amount on it. As Jenny just said, there are often occasions when there are government advisors or people you cannot normally get to because the Department of Health is very protective about its advisors. All journalists have to go through the press office in a way which is peculiar to the Department of Health; other government departments are less protective. If you want to speak to an advisor in an informal way often you might have to go to an event which is sponsored by a pharmaceutical company which they are also attending. I think you could argue that that is problematic, that the influence of the industry is so all-pervasive and tight.

Ms Rogers: If you go big conferences around the world—the heart disease and cancer conferences in particular—I have often found myself the only person who is not in the thrall of one or other drug company. There will be all the leading specialists from around the world at these functions and every minute of their time is timetabled by whichever drug company has sponsored them to go so you can hardly get to talk to them because they are going straight from the session on whatever to the drinks party to the white water rafting event the next day or whatever. It is like that. There are all these jolly activities that are bolted on to their whole stay in whichever resort it happens to be; they not necessarily resorts but they tend to ferry them out to nice places around wherever the city is. Every minute of the time they are there can be absolutely timetabled so you hardly get to talk to them.

Ms Hope: To pick up on a point that Lois was saying about access to people via the Department of Health, I can only concur that it is incredibly difficult. You just cannot get to speak to people there; you cannot get any sort of meaningful dialogue going from anybody involved in the drug regulatory system, for example. I am going to see Ken Woods next week and this is quite frankly an earth shattering occasion; I have never had access to the MHRA before. The only other time I have come into contact with the system, as I said in my written evidence, was when I was invited by Jeremy Metters—along with some other journalists—to comment on the yellow card system. A fat lot of good that did, quite frankly. The point is that there is some movement because the MHRA for example, is appointing its own press office, but it all comes back to the point that we have hardly touched on which is the regulatory system: how little access journalists have to the information being discussed there and how we are in an impossible position when it comes to looking at whether or not data has been corrupted by lack of evidence being put forward or it being distorted because we—and anybody else who asks to look at the data—just cannot get to it.

Ms Rogers: That is a very good point.

Q616 Mr Jones: We have heard what you have said about your reluctance to accept hospitality from organisations. We have three professions represented here—doctors, journalists and politicians—and there seems to be an inverse relationship in terms of public trust. Doctors come
right up there; the only people below politicians in public trust are journalists but we appear to be the other way round in the way in which we accept hospitality. From the evidence we have had doctors seem to accept hospitality at the drop of a hat.

Ms James: Can I make a point on behalf of the advertising and PR profession which you did not mention.

Q617 Mr Jones: I assumed everyone understood you were below journalists.

Ms James: I like and respect Lois very much but she must have been to different conferences than the ones we run. The code of practice that we abide by now precludes any excessive entertaining of the sort of white water rafting, glossy resort hotels and all of that. I would concede that those kinds of activities were more common place in the past but now we have very strict rules that we abide by: no spouses are paid for; no accommodation is booked in four and five star hotels; no accommodation is booked in any kind of spa or resort type of hotel. The guidelines for entertaining costs are: lunch, no more than £30 a head; dinner, up to a limit of £70 a head. These are very strictly supervised by our clients. I appreciate I am saying something which is in direct contravention to what you have heard, but that is our experience and we are one of the biggest companies laying on these kinds of conference and events. I am quite happy to send you after this meeting typical examples of conference programmes so that you can see for yourselves.

Q618 Jim Dowd: I am sure that is true from your end of the operation but we get too many reports from the way that companies operate themselves for them all to be simply disregarded and I think there is a difference there. If you could send us an outline of the programme it would be very helpful. I want to move on now to direct to consumer advertising particularly of prescription drugs, drugs that can only be obtained through a general practitioner. Certainly we had evidence—very alarming evidence—of how this works in New Zealand and it is also prevalent in other parts of the world. Is it your view that this is opening up information to the lay person and to the man and woman in the street in the face of professional jealousy, the gatekeepers wanting to keep all the information to themselves and this is actually a liberating feature for ordinary citizens, or is this going to lead to disease mongering, over-subscription, to increased prices and to a perversion of the prescription market.

Ms James: Are you suggesting that that is going to happen in the UK?

Q619 Jim Dowd: I am trying to assess what the effect might be if it were to; it does in the US and there is similar pressure on the EU to accept it. I do not want to argue about it; I just want to know what your assessment of it is.

Ms James: I will give you my assessment of it; it is an individual point of view and the pharmaceutical industry in the most part is actually now against bringing in this form of advertising into the UK. They might have had a more open mind about it a few years ago. I sat on the ABPI’s informed patient initiative task force which looked at this issue for four years. There is no appetite among pharmaceutical companies for bringing that kind of advertising to the UK. My own opinion of it is that largely I think it has had a positive health effect in the US. The most recent FDA research was actually published last month and it showed that by and large the public (they interviewed doctors and patients) felt that it did prompt them to seek information. Most of the information that it prompted them to seek was actually about side effects and risks rather than benefits—which questions the competence of the advertisers, possibly—by quite a large margin. On the benefit: risk ratio 60% of the public felt that the advertising did not provide enough information about risk which might explain why they sought the information independently. However, 44% did say also that it did not provide enough information about benefits. In terms of the doctors’ viewpoints, slightly under half—41%—said it was beneficial and only 18% said it caused problems. I think that the main benefits really are that people get more informed about diseases and both professionals and patients are able to enter into a more productive dialogue as a result of the DTC advertising in the States. I think it has also had a positive effect on prescribing. I know that the branded advertising that AstraZeneca did for tamoxifen over there led to doctors getting up to speed on the benefits of that drug as well as patients asking about it.

Mr Paling: I think something else that came out of that research was that the FDA concluded that it had had no noticeable increased effect on prescribing. I know that is very difficult to judge because there is no control on that, but I think that was the biggest worry, that it was having an increased effect. Whether, in the long run, even in the United States, this will be seen as a good way forward I personally doubt. I am certain that we will not have it in the UK and that was definitely not the intention of the ABPI.

Q620 Jim Dowd: If it is being contended that the US experience is beneficial to the patient why should British patients not benefit similarly? Why is the industry against it? Given the fact that the people who are advertising in the USA and New Zealand are the self-same drug companies who would be advertising here, why do they think it is a good thing there and they will take part in it and something they would not want to see here?

Ms James: I think there are two possible reasons for that. One reason is that they do not see that it is possible for it to happen here. We have a very difficult healthcare system in Britain compared to the US. Some of the disease areas which people have become much more conversant with as a result of DTC advertising and some of the under-treatment that existed in those categories has been removed or certainly improved so that where patients were not getting decent treatment for high cholesterol or schizophrenia, for example, they now are because they are informed. I think that the companies feel
that would obviously have a cost implication because statins are more expensive than doing nothing; atypical anti-psychotics are more expensive than the dreadful old therapy which causes awful side effects. I think the companies accept that there is an issue in this market with what I have just described. The second reason I think that some companies—not all perhaps—are reluctant is because it is costing an awful lot of money in the United States. The cost of consumer advertising is much more costly than representative and professional advertising and I think quite a few of our clients do not want it here.

**Q621 Jim Dowd:** That has also impacted on driving up prices to the consumer in the US.

**Ms James:** There is no evidence of that at all.

**Q622 Jim Dowd:** Where do all these costs go? Do they just disappear into the ether?

**Ms James:** If a patient was not on medication that he/she needed before and thanks to the advertising and the dialogue with the doctors they now are, that is obviously an add-on cost. That does not mean that the price of the treatment has increased.

**Q623 Jim Dowd:** Presumably someone has to pay that somewhere.

**Ms James:** In the States it is a different system. It is based on insurance and co-payment. Obviously the patient is bearing more of a brunt of that cost than the patient is here where most people are on free prescriptions.

**Q624 Jim Dowd:** Is this not at heart just an attempt by the pharmaceutical companies to recruit the patients into their promotional campaigns by increasing pressure on prescribers?

**Ms James:** I think from all the transcripts I have read from your debates I think what I detect is an inability to see that an action can have two consequences. It can improve public health and be to the public good and it can also provide a return to the shareholders of the pharmaceutical companies. The example of patients being better treated in the States is an example of just that point.

**Q625 Jim Dowd:** Is that a general point on the work of this Committee?

**Ms James:** No, just some of the transcripts I have read I have felt there was a reluctance to accept that an action can be to the good and be also profitable.

**Q626 Jim Dowd:** The premise of this whole inquiry is that the pharmaceutical industry in this country at least are a genuine legitimate business. We do not dispute that for a moment; they have shareholders and they have the right to make money. Certainly one of the cases from the New Zealand experience was a completely manufactured condition that nobody was complaining about before: bladder incontinence. They alleged it was incontinence; they said, “Are you going to the lavatory too many times a day? If so, you need this drug.”

**Ms James:** Are you suggesting that does not exist?

**Chairman:** Of course incontinence exists; I think we need to clarify this.

**Q627 Jim Dowd:** What I am saying is that they introduced this problem by direct marketing to patients telling them to go to their general practitioners and demand this drug and even giving them a free sample. They showed the rate of consumption of this drug; the rates of consumption went up enormously. The effect it had on the condition was zero. People had not even asked their general practitioner about this being a problem before and it was done entirely to inveigle the patient into the position of marketing on behalf of the drug company. That is the great danger.

**Mr Paling:** Often patients do not go to a doctor if they do not think there is a treatment available. Erectile dysfunction would be a very good example of that. To me the bigger issue is that if you take a country like the UK, and the way we treat and compare it to the United States—even to other European countries like France—there is serious under-treating of very, very important conditions (diabetes would be one very good example) because we do not have such a level of contact between the patient and the doctor. Our treatment is therefore not so early; it is not so aggressive in terms of the disease and I think that whoever creates it or whoever does it there is an important need for further information. I am not talking about branded pharmaceuticals, but we need to get more information to the patient to understand conditions (a) that they might have them and (b) that they should seek medical advice. Then the doctor can decide if they have to have treatment. The numbers suggest that there are 300,000 diabetics in this country at large who have never seen a doctor and never been treated. That, to me, is a really worrying concern.

**Q628 Jim Dowd:** There are many things that are very worrying; what is also worrying is if you try to tell somebody that they are ill without them knowing it because you have a treatment for them.

**Mr Paling:** If they go to the doctor the doctor will tell them they are well.

**Q629 Jim Dowd:** Are these people who were not presenting with this condition before.

**Ms James:** I do know about that condition in terms of this country—I do not know about the New Zealand example that you have quote. And a great many people over the age of 40 do suffer from incontinence and I know one of the pharmaceutical companies did undertake research about four years ago of a population of women over the age of 40 and also general practitioners and they found that a large number of women—I cannot remember the exact numbers—did have this problem, it really did bother them and they were too embarrassed to consult their doctor about it. When the company did the research with the general practitioners they found that 90% of general practitioners were too embarrassed to
mention the problem as well. So this is the role for the pharmaceutical company, to bring these things out into the open and give patients hope.

Q630 Chairman: No-one would deny what you have just said as being a problem. Women with childbirth implications obviously understand that. What was a concern in New Zealand—we have not explained it fully because it was quite detailed—was the way in which a problem had been created that did not really exist. It was implying that if you went to the loo so many times a day then that was abnormal when, in view of people objectively, most medics would say it was not abnormal. What Jim was saying was that an apparent abnormality had been created in the interests of a particular company when a problem did not really exist. That was the difficulty.

Ms James: I suppose you are saying that it was exaggerated.

Q631 Mr Jones: If there is a problem and it is medically treatable and that sells X amount of drugs, if you widen the market out so that you include in the range of abnormality a large part of what would then be the normal population you would increase the market for the drug.

Ms James: This is a very bad strategy commercially because all you do is you get a lot of people in, you treat them, they go away, their lives are unchanged and your drug gets a bad name. Most of our clients would not want to do that for that very reason.

Jim Dowd: The point was that they can behave in this fashion because DTCA is available. That is when they said, “Go to your GP and get a free sample” and they used DTCA precisely to generate this. Anyway, I have gone far enough on this point.

Q632 Dr Taylor: Can I just go back to Ms Hope for a moment. I am afraid it highlights a paper that I do not read for which I apologise, but do you say that statins are being advertised with whole page advertisements?

Ms Hope: Yes. This is now appropriate because one statin has been granted approval to go from prescription only to pharmacy and it is just a start, really, of a whole lot of things that are going to be rolled out.

Q633 Dr Taylor: Are these sorts of advertisements appearing widely in other newspapers as well?

Ms Hope: Yes, it is consumer press that we can now run these. There have been some surveys carried out—which I am sure you are aware of—since this happened in July showing that some pharmacists are giving inappropriate advice and also highlighting a conflict of interest between pharmacies offering cholesterol testing with a statin next to it. I think there are real concerns about this and we do not really know what led to this decision to free up the market because we do not have access to the decision-making information that was in font of the authority but against the advice of, for example, the RCGP, but it also coincided—as you will be aware—with the extension of the patent (if you like, in quotes) on the statin concerned from six months to a year when this particular statin cannot be challenged in the market place. A cynic like me might think that this is a very interesting development that you can now move your statin which is out of patent in the prescription market into pharmacy only medicine and get a year’s worth of protection.

Q634 Dr Taylor: I think we are aware of that and are looking into it. Can I just go back to Dr Horton? Advertising revenue: does that depend from any companies on the publication of articles or are they completely separate? If you refuse to publish something do they then withdraw some advertising revenue?

Dr Horton: I do not know of any instance of that, but what I do know is where journals have published critical editorials of a particular company or industry and an advertising has been withdrawn from those journals which has precipitated a crisis within the publication where the editors have got sacked or there has had to be some whole scale change in the way the journal is organised. For those journals that depend upon advertising revenue very much advertisers are key constituents for that journal and they wield enormous power in shaping the agenda of that journal. The example I am thinking about is the Annals of Internal Medicine which published a few years ago an article very critical of industry and advertisers just withdrew their advertising whole scale and two very well respected editors were sacked.

Q635 Dr Taylor: Do you actually vet the advertisements?

Dr Horton: Yes, we do. I think we are very lucky here because the advertising that gets submitted to The Lancet goes through the commercial department of The Lancet and then it comes to the editorial department and we apply criteria to adverts as much as one can in the same way that you look at research articles. Actuality, The Lancet does not have a massively high circulation so we do not publish huge numbers of adverts; it is not such a difficulty for us.

Q636 Dr Taylor: Going back to Ms James, your website produces evidence that campaigns actually work. I think the quote is that your work can “independently increase sales”. What is the evidence behind that? What is the evidence that promotional campaigns work?

Ms James: It is difficult to demonstrate a direct link with sales and we do not do so very often. The reason it is difficult is because there is so much going on in any particular market that to pinpoint your own activity and pull it out and demonstrate that patients have had better treatment because of what you have done is difficult. There was a campaign we ran last year for increasing the uptake of flu vaccination and I think that we did demonstrate an increase; certainly over 200,000 who were not planning to take up the vaccination took it up as a result of a huge publicity campaign that we ran. There was not too much else going on in the market so we were able to demonstrate that that was a success that was
driven by our campaign. For the most part, the way we evaluate and monitor our programmes is more to do with benchmarking awareness levels: has our campaign increased the awareness of a particular problem or a range of solutions or have doctors become more aware?

Q637 Dr Taylor: How would you assess that they have become more aware?
Ms James: We sometimes undertake benchmarking before a campaign starts so that we might research medical awareness and views of a particular area of medicine or treatment or a message that we want to get across and then after a series of activities we would undertake the research a second time and we would monitor the difference. Again it is difficult because you are not the only player in the communications mix.

Q638 Dr Taylor: What is the response rate to questionnaires from general practitioners about those sorts of activities?
Ms James: You obviously have to provide a financial incentive and as long as that is appropriate to the time that it takes you can usually get quite a substantial response, probably a good 20% if it is appropriately remunerated.

Q639 Dr Taylor: Ms Rogers, in your memorandum to us you say, "The British Medical Journal itself is distributed free to doctors in Britain because it is subsidised by the drugs industry." I remember paying a whacking subscription to the BMA which included the BMJ so it is not quite true to say that it is distributed free, is it?
Ms Rogers: I do not know whether the subscription that you pay to the BMA would cover the production costs of the BMJ. I do not think it does.

Q640 Dr Taylor: It is a lot more than you have to pay for The Lancet.
Ms Rogers: Yes I know, but you are belonging to the BMA and you are supporting the editors of the BMA principally rather than the journal, I think, which is a fairly enormous operation employing a large number of people with regional offices.

Q641 Mrs Calton: Can we move on to contact with patient groups and professionals? Ms James, the Shire Health Policy Unit is involved in—and I quote—"health policy intelligence gathering and lobbying". Could you explain what this lobbying involves? Is this an important part of the work of medical communications companies?
Ms James: Lobbying is a very small part of our business. The example that first leaps to mind is a campaign that we undertook in the late 1990s on behalf of a drug called Taxol which was a new treatment at the time—or relatively new—for cancer. It was not funded by the majority of health authorities at the time so we brought our expertise at a local level to deploy a series of meetings around the country in the areas where we knew women were being denied the treatment of Taxol and we would get together a local oncologist, some interested general practitioners and a member of a patient group (I cannot recall which one it was, it was probably BACKUP but I could not be sure about that now). We would then have a meeting and invite the local press to attend a press briefing at the end of it. We would write up the outcome of the meeting and use that in a series of one-to-one meetings with key decision makers with the then local health authorities. That campaign was combined with a lobbying campaign here in Parliament as well. There was a lot of activity trying to make MPs aware of the benefits of better treatment for breast cancer and how this was being denied at the time. That is a typical example of a quite all-embracing lobbying campaign. For the most part our relations with patient groups I would not describe that as lobbying: I would describe that as a meeting of minds about a particular condition, what the patients’ needs are. The patient groups are obviously expert and I think they will help companies put across very appropriate and very balanced messages about a particular disease. We will help them with a lot of research and communication skills and so forth. The moment that relationship gets out of kilter it is a disaster; you cannot try to influence the patient groups to think a certain way about a condition. Any patient group worth its salt—and I am talking about quite small ones as well, not just the big ones—will not wear that.

Q642 Mrs Calton: Could we just explore this a little further? I am aware as an MP that I frequently have people coming to my surgery who are my constituents who are, nevertheless, asking questions about specific drugs or whatever. As part of your lobbying package, if you like, of all of the different things, would you encourage members of patient groups to go and see their MP to raise this issue; to raise a particular issue about a particular drug that you were working on?
Ms James: Very rarely. I would not say that it did not happen, but it is certainly not commonplace. I suppose our motivation really is to inform patients such that if they have questions in mind they visit their doctor rather than their MP. There are conditions, I suppose, when it is funding related that I could imagine companies would do that, but I do not myself have personal experience of it.

Q643 Mrs Calton: Could I go back to the original question which I asked about the health policy intelligence gathering. The Shire Health Policy Unit states that it is involved in health policy intelligence gathering. Could you tell us a bit more about that?
Ms James: Yes, it is straightforward monitoring of public health policies so, for instance, when the national service frameworks came out we would make sure that we were very much in touch with the advisors to the Government on those implementation task forces. Where vacuum policies are concerned we would make sure that we are in touch with advisors so that we know where Government priority is going to be and that way we can advise our clients. If any of our clients have an interest in helping the Government reach its targets.
then we would bring that kind of information to our client’s attention and work with them to see how best to capitalise on the opportunities.

Q644 Mrs Calton: How would you go about gathering the health policy intelligence? How does that work?

Ms James: An awful lot of it, to be honest, is available on the internet. The Department has a good website that issues names. A number of these doctors are known to us anyway. We would make contact with them; we would discuss the way things were going, what sort of priorities were going to come out. It is not in any sense to manipulate the agenda, it is more to find out what is going on so that if our clients, for instance on the elderly side, have anything that would be really beneficial in helping the Government attain those targets then obviously there will be a pay off for the company as well. It is a case of getting intelligence and using it appropriately.

Q645 Mrs Calton: Mr Paling, would you say it is fair to say that the core of your business involves promoting clients’ brands by stimulating demand through authoritative third parties such as patient organisations or leading healthcare professionals?

Mr Paling: We do not work with patient organisations and have never done except with one exception which was on some disease awareness work which I mentioned in my submission for erectile dysfunction. The bulk of the work we do—which is paid-for advertising or sales promotion—is very clearly branded and it is a branded message that we have developed as part of the process of deciding how to present and offer the product to the doctor which would primarily be a general practitioner in most instances.

Q646 Mrs Calton: So you would not say that you are involved in stimulating demand.

Mr Paling: Advertising and promotion is there to do a number of things. It is there to raise awareness first of all of a drug, particularly if it is a new drug or raise awareness of an issue that might be a new indication or a new piece of information for instance. In that sense we are part of the process of taking the information on the products we work on to the doctor. That could result in him changing his practice from one treatment to another. If it were a treatment that he was not particularly aware of it could start him using that treatment in isolation. The way that all advertising works—the advertising to doctors and the advertising to the general public—has many similarities. The difference is in tone and approach.

Q647 Mrs Calton: What about yourself, Ms James? Would you say that you stimulate demand via the vehicles of patient organisations or leading healthcare professionals?

Ms James: I think what we want to achieve is improved management of the conditions that our client has an interest in. I think, whether it is a happy coincidence or what—I do not know—that 90% of our clients I would say have products which are really going to improve opportunities for patients. We seek to inform opinion leaders and get their views as well. Sometimes clients are over-ambitious with their products and the intelligence we gather from opinion leaders reveals something of a gap between the clients’ aspirations and what the opinion leaders feel is an appropriate goal and at that point we will go back to the client and say, “Look, doctors are thinking that this treatment has a place, but it is not perhaps the sort of place in the sun that you were hoping for”.

Q648 Mrs Calton: Would you say your work involves any form of relationship that the public might conceive as improper?

Ms James: No, I really do not. I think in any commercial relationship in the healthcare business there is always a potential for something improper, but I think that the checks and balances work in such a way as to preclude that from being a possibility.

Q649 Mrs Calton: Do you believe that drug promotion through disease awareness campaigns is a good thing? Are there any aspects of this type of campaign that concern you or that you think might have negative effects? Could I start with you, Ms James, and then move on to others?

Ms James: I think for the most part they are a very good thing, yes. I think without them patients would be in the dark on so many conditions. I have the benefit of quite a lot of hindsight now and I can remember the introduction of statins for the treatment of cholesterol in this country. They were introduced in 1989 and for the first five years of their life the BMJ led a vociferous campaign to undermine them, claiming that cholesterol was not a risk factor for heart disease at all and that drug companies were manipulating and stimulating demand for something that people did not need. Looking back it was quite scandalous. This is not the only example; I do not have time to give you all the examples. A lot of people did die unnecessarily from that mis-information but many more would have done. I think we really do need the pharmaceutical industry appropriately regulated to bring out some of these things with a kind of “not invented here” syndrome that attacks them at every turn. It is the same thing in schizophrenia, in cancer. These public awareness campaigns are a vital source of good
public health. They do need to be properly regulated and I accept sometimes the case you outlined from Australia sounds most unfortunate and I am sure they do exist, but in a very small minority of cases.

Q650 Mrs Calton: Does anyone else want to add to that or put a different point of view?
Mr Paling: I do not think anybody would disagree that we need to increase the level of public awareness on general health issues in this country. It is the view of the public—it is certainly the view of the Government—and I think that is very important. Like Margot, I think the industry can have a large part to play in that partly because to do it would cost money and that perhaps is part of the reason more has not been done before. I think if it is harnessed in the right way there are rules and checks and regulations and they should be adhered to. I think it is very important that we are able to communicate with the public. I would rather—particularly in a condition where somebody has diabetes or whatever—that 10 patients went to the doctor who did not need treatment than one missed it who did and subsequently could be in a far more serious situation because they had not received treatment. Having said that, with our limited experience I think it is quite surprising how hard it is through disease awareness to actually get patients to go to doctors. Maybe that is a British thing; maybe it is the condition that we worked in (which was basically middle aged or older men who do not like going to the doctors) but it is not simple to do that. It is a hard task; it takes a lot of time and money.

Q651 Mrs Calton: Dr Horton?
Dr Horton: I think if you are looking at disease awareness campaigns amongst doctors, let us be real: this is about selling drugs. We had a paper submitted to us about a disease awareness issue. It was submitted to one of The Lancet’s speciality journals, Lancet Neurology and in the process of peer review of that paper the company was trying to negotiate a reprint sale and the e-mail from one of the communications companies that the pharmaceutical sponsor had hired read: “As I am sure you can appreciate the more reviewing that is done on the papers” (that is the papers that were submitted to The Lancet) “the less value the ultimate publication will have to Sheering as the information on Sheering’s products becomes more and more dilute.” So let us have a reality check on the purpose of disease awareness campaigns. This is about sales; it is not about disease awareness.

Ms Hope: I recognise that disease awareness campaigns will at least indirectly benefit drug companies. I probably think on balance they are worth while because of the information gap in this country between the way that people get information about drugs from newspapers and doctors and the fact that it is very hard in the middle when you are diagnosed with something to actually get more information easily. It is a fine line with disease awareness campaigns because you cannot advertise prescription medicines directly to the public in this country and this is a way, if you like, of— in quotes—getting round it. You could argue the same with celebrity endorsements that are carried out of a disease whereby somebody who has got a disease talk about it because they want to raise awareness which is all well and good, but they may well be being paid to raise that awareness so I take that into account when I am actually looking at something that is being offered like that, but I think on balance people would like to read about a famous person who has a disease.

Ms Rogers: I would say it is highly arguable whether they have any benefit at all. It is an almost daily irritant. A PR person rings me to tell me about a disease awareness campaign and I think where disease awareness campaigns end and disease mongering begin is a very indistinct line and I think that in general if people are ill they know they are ill and they go to the doctor. Disease awareness is basically selling more drugs to people who do not necessarily have anything wrong with them.

Mr Paling: I think there are many illnesses where a patient certainly would not know they were ill unless something was pointed out and therefore they went to the doctor. At the end of the day the doctor is in a position to decide, surely, if a patient needs treatment. If it is not a sick person the doctor is not going to give out a drug anyway.

Q652 Dr Taylor: We have heard a great deal about the length of time it takes for a drug to be developed. At what stage does a company like yours get involved with the process, with the planning of publicity?
Mr Paling: Over the years that I have been involved with the pharmaceutical industry I think it is fair to say that that time period has shortened quite dramatically. Twenty-years ago it probably would have been a year or 18 months and all sorts of development was being done relating to the product. Right now I would say it is more likely to be five or six months.

Q653 Dr Taylor: Five or six months from what stage?
Mr Paling: Five or six months from the point where an advertising agency would be appointed by a pharmaceutical company to a point where a product might be launched.

Q654 Dr Taylor: So five or six months before the launch.
Mr Paling: Yes, that would be more normal time now; six months probably.

Q655 Dr Taylor: I think we are all extremely keen to make this report fair. Something that Ms James said implied that reading through the transcripts before it has been heavily loaded against the industry. This is because we have not really had much evidence from the industry yet. Mr Paling, right at the end of your written evidence you say you have been proud to work with the pharmaceutical industry and in your opinion it does behave ethically in its dealings with the medical profession. Yet we have these tremendous criticisms coming. Would any of you like to summarise the criticisms that we have heard in a very few words?
Mr Paling: I think part of the reason I feel like that about the pharmaceutical industry—and I have been in or around it now for 35 years—is the incredible difference that the industry has brought about because of its medications. I do not think anybody would deny
that and I know that this Committee does not deny it in literature and information I saw at the beginning of this inquiry. I think what is unfortunate is that starting from that base the industry does not have the best possible reputation it could have of any industry in the country. I do not think by any means the reputation is dire and there is a piece of research that MORI brought out last year which showed the reputation of the industry was much better than most people who have been in front of you in the last few months would feel. I think there needs to be a more open attitude. I think there has to be more transparency in certain areas and the way that we present ourselves to the doctor I feel is ethical and open. I feel that in the areas we work in—and I am sure Margot would say the same thing—everybody is tightly governed by a code; that code is part of how we behave as well, we are part of that process. Everybody knows the code; everybody is trained to the code and I think it is rigorously applied and is stringent and strong.

Q656 Dr Taylor: Could I ask each of you for one sentence of the main criticism? Is that fair?
Ms Rogers: I would respond to that by saying that I think the Government could help to improve the reputation of the industry by assisting the likes of us—Jenny and myself—with information when we ask for it. It recently took me 10 days to get information on adverse drug reactions on a particular group of products; that is 10 days of daily telephone calls. This is on a database and they obviously are withholding it from the press. That is not the first time it has happened. If you ask about adverse reactions to drugs it is sort of deeply confidential, sensitive information and the impression that you are automatically given is that somehow the Department of Health is assisting the manufacturers in withholding information. It is not conducive to us thinking that everything is all right in the pharmaceutical industry.
Ms Hope: I would completely agree with that and say that the whole point of going to the Department of Health is because we are concerned about drug safety not because we are going there to get a puff or a drug. We still find it hard to get information.
Dr Horton: In one sentence it is hard, but I would say that the practice of medicine and the delivery of healthcare have become overly dependent upon the pharmaceutical industry to the point where the integrity and validity of medicine and science is being compromised and risks being compromised further.
Ms James: Are you asking me to summarise any criticisms?
Dr Taylor: If you have one, your main one in one sentence. If you do not have one and are full of support, great.

Q657 Chairman: Can I ask a final question which might help you? In a sense Richard Horton referred to his views on this some time ago where when we try to strike a balance between the commercial imperatives and the public health good it is a tricky area and this is at the heart of this inquiry which I am sure you all understand. Richard Horton was talking about some kind lightweight oversight with legal statutory tests. I do know whether you have any thoughts on this as to what might be that key conclusion as to where this tension could be resolved and some of the issues we have picked up today addressed in a way in which the public can have some confidence.
Ms James: I think that the tension between the public good and the commercial interests have to be resolved in the regulatory process. From what I have read there is a need for a greater transparency of the regulatory process. There have been various recommendations to you of a way of tightening up the process of clinical trial publication so that absolutely every trial embarked upon has the potential for publication. Most are published and a lot of the time they are not published because they are not deemed of interest for quite genuine reasons. Where there is any scope for a trial that does not give the desired outcome to be suppressed that shocked me; it had not been in my consciousness before. If there is any potential in the system for that to occur then that should be regulated out.
Mr Paling: I would agree with that entirely. That was the point I was making about transparency before. I think through this process I have also learned a few things and that is one that I was not aware of. I think that is important and I think there are firm moves within a number of companies—we heard that from Sir Richard Sykes—that should happen; I am sure that will happen and I think that is a very good thing.
Ms Hope: We need to know how decisions are arrived at as to whether a drug gets licensed or not and why and what the evidence was upon which that was based.

Q658 Chairman: Transparency is crucial.
Ms Hope: Yes, exactly. Then you can market these things because we know that they do work.
Ms Rogers: I would concur with almost everything that everybody else has said. I think that the regulatory process needs to be far more transparent.
Chairman: Can I place on the record the Committee’s thanks to all of you for an excellent session and for your written evidence which has been most useful. We are very grateful to you for coming along today to take part in this inquiry. Before we conclude, can I just say that after this meeting we are losing the most important member of our Committee, Anna Browning, who is our Committee Secretary. I would like to place on record the Committee’s thanks to you for your work over many years. You are a very key figure in our Committee’s work and we appreciate everything that you have done. We wish you well in your retirement because you retire at Christmas. We thank you for all your work. Can I also wish everyone the compliments of the season; this is the last meeting before Christmas. Thank you very much everyone.
Thursday 13 January 2005

Members present:

Mr David Hinchliif in the Chair

John Austin
Mr Keith Bradley
Mr Simon Burns
Mr Jon Owen Jones

Siobhain McDonagh
Dr Doug Naysmith
Dr Richard Taylor

Memorandum by GlaxoSmithKline (PI 51)

Executive Summary

GlaxoSmithKline (GSK), along with the rest of the pharmaceutical industry, makes a very strong contribution to the health and wealth of the UK. The company does this in a number of ways:

— GSK has its headquarters in the UK where it employs over 21,000 people.
— GSK believes that the UK has to remain competitive in the global marketplace in order to attract and retain investment by the pharmaceutical industry.
— GSK invests around £2.8 billion in research and development (R&D) each year with over £1 billion directly in the UK. GSK is the largest investor in R&D in the UK. At the cost of almost £4 million, GSK is supporting 375 PhD. studentships—more than any other company in the UK.
— GSK’s total expenditure on global community programmes is the largest of any UK company. In 2003, such expenditure amounted to £338 million and £11 million in the UK.
— GSK has pioneered significant innovation in medicines development with many “first in class” therapies that have revolutionised patient care in diseases such as asthma, diabetes and HIV/AIDS.
— Animal extremism is one of the biggest problems facing the research-based industry. The Government needs to act to control this threat through legislative action and effective enforcement.
— GSK provides high quality medical information to support health care professionals. The company handled over 30,000 telephone calls in 2003 both in and out of office hours.
— In providing information to health professionals, patients and the public, GSK strives to meet the highest ethical standards and adheres to the ABPI Code of Practice and all other relevant professional codes.
— GSK actively supports the personal development of health care professionals, assisting health care professionals to achieve major objectives in their educational plans.
— In June 2004 the company announced the creation of the GSK Clinical Trial Register, an electronic database to enable dissemination over the Internet of information about GSK-sponsored clinical trials.
— The pharmaceutical industry operates within one of the most complex and regulated frameworks of any industry. Good communication and high quality scientific assessment between regulators and companies is essential to ensure the regulatory system is efficient and effective, ensuring maximum benefit to patients whilst minimising risk.
— GSK actively supports the letter and spirit of the law to monitor the use of a medicine and its benefit/risk balance throughout its lifetime and proactively updates and communicates product labeling as new information is assessed.
— GSK strongly endorses the goals of NICE in promoting faster more equitable access to modern treatments, the need to address post-code prescribing and the promotion of the longer-term interest of the NHS in the development of innovative new treatments.
— Pharmaceutical innovation is a crucial factor in improving the quality of life. It impacts positively upon health status, overall health expenditures and on the global economy. Innovation should therefore be seen as a key part of sustainable health policy. In turn, sustainable health policy should be part of an integrated and sustainable economic and industrial policy.
1. **Introduction to GlaxoSmithKline**

1.1 GSK is one of the world’s leading research-based pharmaceutical and health care companies. The company’s mission is to improve the quality of human life by enabling people to do more, feel better and live longer. GSK develops and manufactures prescription medicines, vaccines, over-the-counter medicines and oral care and nutritional health care products.

1.2 GSK has an estimated 7% of the world’s pharmaceutical market. The company has its headquarters in the UK, where it also has a further 23 sites at which it employs over 21,000 people.

1.3 GSK invests around £2.8 billion in R&D each year. The UK benefits from more than £1 billion of this expenditure. GSK’s global R&D organisation employs almost 15,000 people in more than 22 sites. In the UK, GSK R&D employs 6,000 people, 40% of the total R&D employment. Three of top six R&D investors in the UK were pharmaceuticals companies, with GSK the single largest UK investor.1 Against this backdrop the UK represents only 3.3% of the global pharmaceutical market.

1.4 GSK contributes significantly in bringing new medicines to patients. GSK is a world leader in the discovery of innovative new medicines in respiratory disease, antibiotics, HIV/AIDS, metabolic and neurological disease. These fully complement the priorities of the NHS.

1.5 Vaccines are crucial for maintaining public health and are one of the safest, most cost effective and efficient ways to prevent sickness and death from infectious disease. GSK researches, develops and supplies paediatric, adult and travel vaccines, supplying the NHS with 20 vaccines that provide protection against 17 diseases. (see appendix 1)

1.6 In 2003, GSK spent £338 million supporting global community programmes, including product donation and charitable contributions. This total expenditure was greater than that of any other British company and included major contributions of £500,000 to establish a children’s hospital in Wales, establishing a £1 million specialist unit for the elderly at Ashludie Hospital, in Dundee and £1 million over four years in support of Phase II of the new Darwin Centre at the Natural History Museum in London.

1.7 GSK is currently the only company conducting research into the prevention and treatment of each of the three priority areas identified by World Health Organisation (WHO)—HIV-AIDS, tuberculosis and malaria. In addition, GSK offers anti-retrovirals and anti-malarials for HIV and malaria, at not-for-profit prices, to 63 of the world’s poorest countries.

1.8 GSK has contributed to the Association of the British Pharmaceutical Industry (ABPI) written submission to the Health Select Committee inquiry and submits the following additional comments.

2. **Drug Innovation**

*The Development of a New Medicine*

2.1 The pharmaceutical industry contributes the majority of health care-related R&D in the UK, which is more than all other health care research organisations combined. Developing a medicine takes 10 to 12 years, costs over £500 million ($897 million)2 and is an increasingly costly, difficult and risky process. R&D productivity is one of the biggest challenges facing the industry today; only three in 10 medicines launched generate sufficient sales to repay their R&D investment. To develop a medicine, a number of sequential activities take place, as represented in the diagram below. This process is described in more detail at www.gsk.com.

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1 DTI R&D Scorecard 2002–03.
— Phase III—studies in a large population to generate safety and efficacy data for licence application.
— NDA—New Drug Application—filing all data to regulatory bodies. (Marketing Authorisation Application—MAA in Europe).

At each stage in this process, there is a significant rate of compounds failing to progress to the next stage.

The Environment for R&D Investment in the UK and Europe

2.2 Pharmaceutical innovation can be a key element for European and UK economic growth and competitiveness on the global market. However, European cost -containment practices deny patients access to needed, cutting-edge medicines. Price controls also hurt European economies by decreasing medical innovation—transferring jobs, research, infrastructure, investment and technology from Europe to the US.

2.3 From leading the way in R&D, the European industry has increasingly lost ground to the US; today more medicine development takes place in the US, which provides an environment in which it is possible to conduct research in well-equipped sites, with skilled well-qualified staff and appropriate levels of regulation. There are now many emerging countries, such as India and China, that offer a highly skilled workforce able to operate at lower cost; companies are beginning to invest in R&D in these countries in addition to traditional manufacturing investments. If the UK is to retain R&D investment it will need to remain competitive in this global marketplace.

2.4 Despite the considerable challenges and costs relating to the R&D process, the UK still has a thriving domestic pharmaceutical industry. The UK is a leading location for medicines research and compares favourably with other countries, in particular with those in mainland Europe. GSK remains the largest investor in R&D in the UK. A major contributor to the company’s success in the UK, and a key factor in its continued investment, is the quality of graduates and postgraduates and the high standard of basic research carried out in the many universities with which GSK collaborates. A thriving commercial environment for innovative medicines is also a prerequisite for attracting and maintaining investment.

GSK’s Contribution to R&D in the UK

2.5 GSK has pioneered significant innovation in medicines development. It is responsible for many “first in class” therapies that have revolutionised patient care and provided significant benefits by targeting novel receptors and pathways.

2.6 These include the first H2 antagonists (Tagamet® (cimetidine) and Zantac® (ranitidine)) for patients with peptic ulcers; inhaled steroids (Becotide® (beclomethasone dipropionate)) and inhaled short acting bronchodilators (Ventolin® (salbutamol)) for patients with asthma; one of the earliest PPAR agonists (Avandia® (rosiglitazone)) for patients with diabetes; the first 5HT1 agonist (Imigran® (sumatriptan)) for patients with migraine; two 5HT3 antagonists (Zofran® (ondansetron) and Kytril® (granisetron)) for patients experiencing nausea and vomiting as a result of cancer therapy, and the first nucleoside analogues (Retrovir® (zidovudine)—AZT) for patients with HIV.

2.7 Almost 15,000 people work in GSK’s global R&D organisation. GSK has 22 R&D facilities in eight countries worldwide. In 2003 GSK invested almost £2.8 billion in R&D; £1 billion of this was spent in the UK.

2.8 GSK employs around 21,000 staff in the UK, of whom 6,000 work in R&D. GSK has R&D sites in Harlow, Stevenage, Greenford, Ware, Tonbridge, Beckenham, Welwyn, Cambridge and Dartford.

2.9 In a bid to increase innovation at every stage of the drug discovery and development process, GSK has re-engineered its R&D organisation to meet the new challenges and opportunities the company faces. In particular, it has created a number of Centres of Excellence for Drug Discovery, small innovative working groups focused on specific therapeutic categories. Three of the seven centres of excellence are based in the UK.

2.10 GSK is committed to forming partnerships with academic institutions. The company funds research for hundreds of masters-level, doctoral and fellowship students each year. GSK funds more academic research in the UK than any other company. In 2003, GSK provided funding of more than £14 million to support UK academic based pre-clinical collaborative/Contract Research agreements. In addition, GSK is also supporting 375 PhD studentships—more than any other company—at a cost of almost £4 million. In a typical year GSK funded scientists and physicians will publish more than 1,400 journal articles and meeting abstracts.

2.11 In a unique relationship set up with Imperial College to develop new medicines, GSK has provided several million pounds to support a programme which shares risks and rewards to get molecules through to “Proof of Concept” in man. In addition to funding, GSK is providing Imperial with access to its chemicals and innovative platform technologies in certain areas.

2.12 High levels of innovation take place at the boundaries of disciplines; GSK currently provides two £500,000 endowments each year for Fellows working at the clinical/pre-clinical interface. The GSK Clinical Fellowship scheme aims to provide an entry into the academic career pathway for such able young clinical scientists, at a time when entry points are difficult to find.
2.13 Experimental medicine, the interface between laboratory-based research and research using human subjects is playing an increasingly important role due to the development of new technologies such as non-invasive imaging, pharmacogenetics and the use of surrogates and biomarkers. GSK recently announced a unique research collaboration with Imperial College to build an imaging centre at the Hammersmith Hospital. With insufficient imaging capacity in the UK, this facility will allow researchers to understand better how drugs work in human subjects; this will be of particular relevance for cancer as well as neurological diseases such as multiple sclerosis, Parkinson’s disease and Alzheimer’s disease.

2.14 GSK has an active programme that seeks to encourage children to study science and to pursue science as a career. For example, more than 150 staff volunteer their time to schools as “Science and Engineering Ambassadors” in support of this government-sponsored programme. GSK also supports INSPIRE, the Innovative Scheme for Post-docs in Research and Education, a partnership between GSK, DfES, Imperial College and the Specialist Schools Trust.

**GSK’s Investment in Tomorrow’s Medicines**

2.15 In the past four years, GSK has more than doubled the number of candidate medicines entering Phase I and II clinical trials; this demonstrates the high productivity of its early phase research. At the beginning of 2004 GSK had 148 projects in clinical development, 83 of which were New Chemical Entities, 20 were vaccines and 45 were product line extensions. GSK will be actively working towards filing for regulatory approval for many new products over the next few years as illustrated in the following chart:

<table>
<thead>
<tr>
<th>Year</th>
<th>CV &amp; Metabolic</th>
<th>Infectious Diseases</th>
<th>Oncology</th>
<th>Neurosciences</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>vulvar herpes simplex</td>
<td>HIV/AIDS (AIDS)</td>
<td>bladder cancer</td>
<td>localized</td>
<td>skin infections</td>
</tr>
<tr>
<td>2004</td>
<td>neuropathic pain</td>
<td>meningitis</td>
<td>pemphigus vulgaris</td>
<td>gastrointestinal</td>
<td>bowel cancer</td>
</tr>
<tr>
<td>2005</td>
<td>post-operative pain</td>
<td>irritable bowel syndrome</td>
<td>head and neck cancer</td>
<td>cardiovascular</td>
<td>ovarian cancer</td>
</tr>
<tr>
<td>2006</td>
<td>diabetes</td>
<td>allergic rhinitis</td>
<td>melanoma</td>
<td>musculoskeletal</td>
<td>breast cancer</td>
</tr>
<tr>
<td>2007</td>
<td>COPD mortality</td>
<td>dyspepsia</td>
<td>lung cancer</td>
<td>musculoskeletal</td>
<td>allergic rhinitis</td>
</tr>
<tr>
<td>2008</td>
<td>COPD</td>
<td>cardiovascular</td>
<td>ovarian cancer</td>
<td>muscle cancer</td>
<td>skin infections</td>
</tr>
</tbody>
</table>

— MIGU—Musculoskeletal/Inflammation/Gastrointestinal/Urology.

**Addressing the Issue of “Me-toos”**

2.16 The term “me-too” is pejoratively used to refer to a medicine that has a similar mode of action to one that is already available. It ignores the nature of drug development, which is highly unpredictable. There is no guarantee that the first drug to market will be the best. Some new medicines will be revolutionary breakthroughs; others will deliver incremental benefits over existing treatments. Medicines with similar modes of action can have significant differences in terms of their efficacy, metabolism, tolerability and side-effects as well as duration and magnitude of therapeutic effect. The availability of different medicines for the same condition allows physicians to tailor therapies appropriately to meet individual patients’ needs. It also provides therapeutic alternatives if the drug of first choice fails in any given patient.

2.17 The range of products available within each therapeutic class plays a key role in generating competition between different medicines, also acting as an incentive for continuous improvement in the product profile. Indeed, it does not make commercial sense for pharmaceutical companies to flood markets with identical drugs. A company’s focus in R&D is to address unmet medical needs; this may be through the development of a medicine with a novel mechanism of action or through the development of a medicine that offers genuine clinical advantages over existing medicines that work through a similar mode of action.
The Critical Role of Animals in Research

2.18 GSK’s huge investment in modern R&D technologies has transformed the way the company works, and this includes the use of animals. Over the past 10 years GSK has doubled its R&D activity, but its use of animals has remained stable. The company is actively engaged in research to develop and validate experimental methods that can provide more and better alternatives to the use of animals in research. However, at present there can be no new medicines or vaccines without using some animals for research and development. Animals are used where no alternative is available and GSK aims to exceed industry standards in the care and welfare of the animals. All animals are well cared for by qualified, trained staff.

2.19 GSK is committed to implementing the three Rs—Reducing the number of animals used for research, Replacement by non-animals methods whenever possible and Refinement of the techniques used to eliminate or reduce suffering and improve animal welfare. In addition, GSK has added a fourth R—Respect to ensure that appropriate care is taken in the conduct of all its animal studies. This approach is both ethical and makes good financial sense: animal testing is not a cheap option.

2.20 GSK has recently established with AstraZeneca and Pfizer—working with the British Pharmacological Society, a fund of £4 million to support animal-based in-vivo research in UK universities. Having established this fund, GSK will work with other funders of research including funding councils and medical charities to co-fund a number of in-vivo capacity-building initiatives.

R&D for Diseases of the Developing World

2.21 GSK is currently the only company conducting research into the prevention and treatment of all three priority areas identified by WHO—HIV-AIDS, tuberculosis and malaria. In addition, GSK offers its anti-retroviral and anti-malarial agents for HIV and malaria, at not-for-profit prices, to 63 of the world’s poorest countries. GSK is committed to doing more in this area.

2.22 There is some comment about lack of industry R&D for diseases of the developing world. The key issue is one of market failure; in many developing nations poverty means that no market exists for drugs that tackle the diseases that afflict these countries and therefore there is little commercial incentive to invest in them. This issue has been recognised and is being addressed through a variety of public/private partnerships (PPPs) such as the development and launch in late 2003 of LAPDAP® (chlorproguanil/dapsone) a new anti-malarial for sub-Saharan Africa. The initiative brought together GSK drug development researchers with scientists in Africa and two leading UK medical schools. GSK, the WHO and DfID jointly funded the development project. Further information is available at: http://www.gsk.com/about/developing_world.htm.

Recommendations

2.23 It is increasingly recognised that to help improve the productivity of the pharmaceutical industry in the UK and Europe, attention needs to be paid to identifying and removing some of the barriers to innovation, where this can be achieved without harming patient welfare. Some of those barriers include the following:

The need to generate increasing amounts of data before and after the approval of a new medicine

2.24 Regulatory authorities are more demanding and increasingly risk-averse—translating into expanded data requirements. The need to generate increasing amounts of data both before and after regulatory approval of a new medicine is a global issue and is a major driver of drug development costs.

2.25 Solutions could include improved dialogue with regulators early on in drug development. Consideration should be given to near-binding negotiated agreements on the requirements for licensing approval, with commitments for further monitoring and/or studies post registration where appropriate. If the nature of a phase III programme for a medicine is agreed in advance with the regulators and this is completed as planned with positive results, approval should be anticipated without a post-hoc shift in the requirements.

Increased acceptance by regulatory authorities of biomarkers and surrogate clinical end-points

2.26 Industry is increasingly using a range of innovative technologies in the search for new medicines. These include novel scanning methods to evaluate disease progression, for example in Alzheimer’s disease. These technologies have led to the development of new markers of human disease (receptors, proteins, enzymes); such biomarkers are increasingly used to inform development decisions by industry and have the potential to speed the availability of medicines to patients if they can also be used for regulatory decision making. There is a continuum from “biomarker” (used as a development tool) to “surrogate end-point” (sufficiently widely accepted to be used as the clinical basis of approval). Historically, only a few biomarkers
have gained acceptability as surrogate end-points (e.g., blood pressure or cholesterol levels in cardiovascular medicine). GSK recommends increasing approvals on surrogate endpoints, especially in areas of unmet medical need, as this would allow earlier access to new therapies.

The difficulty of conducting clinical research

2.27 Pharmaceutical research is increasingly focused on developing treatments for chronic and degenerative diseases. Clinical research for such conditions is generally more costly as more complex patient care and monitoring is required; longer periods are needed for effects to be observed while ever larger trial sizes are needed to establish efficacy. In addition, there is a lack of skilled clinical scientists in the UK and infrastructure in the public sector is frequently inadequate.

2.28 GSK recruits just 2% of its global clinical trial subjects in the UK—this figure has been declining due to the slow start up times and high costs for trials in the UK. The company would like to do more clinical trials in the UK.

2.29 GSK acknowledges the Government’s allocation of more funding to NHS R&D in the Budget, and welcomes the establishment of the UK Clinical Research Collaboration (UKCRC). However, as a major contributor to clinical research in the UK, the company would like to see industry play an active role in the development of the clinical research networks. The proposal to review both skills and training issues and the current regulatory burden affecting clinical research in the UK are welcome.

Slow uptake of new medicines and lack of recognition of the value of incremental innovation

2.30 One of the greatest barriers to innovation in the UK is the slow uptake of new medicines, which also denies access to needed medicines to patients. Research (PICTF indicator 16) shows clearly that uptake of new medicines in the UK is about one quarter of that in the average of comparator countries one year after launch. Even five years after launch, median UK consumption per person is still some way below the international average. This means that UK patients get less access to life saving or life-enhancing new drugs. Those UK patients who do get access to these medicines tend to get them later than they would in the US or mainland Europe. The Government-commissioned Wanless Report (Securing Our Future Health April 2002) illustrated how slow uptake of new health technology could lead to poorer population health and higher health care expenditure.

The need to control animal “rights” extremists and to ensure there is a balance between good regulation and a competitive environment for animal research

2.31 Animal extremism is one of the biggest problems facing the research-based industry. GSK welcomes the Home Office/DTI paper “Animal Welfare—Human Rights: Protecting people from animal rights extremists”. The Government needs act to control this threat through legislative action and effective enforcement.

2.32 Obtaining authorisation to do animal research is more difficult in the UK than in any other comparable country. GSK endorses the guiding principles of the UK’s Animals (Scientific Procedures) Act. However, the company believes firmly that many of the layers of complexity and detail progressively added to the systems of operating the Act add nothing to animal welfare and may even detract from it. The company believes that an extensive review is needed into the operation of licensing procedures for animal research in the UK to improve the competitiveness of those doing the research and to improve animal welfare.

3. Objectives of Medical Research

Objectives of Research

3.1 Research aims to develop medicines that are safe and effective in providing benefit to patients both in treating and preventing disease. GSK recognises that all medicines have unwanted effects and it is only the balance of the therapeutic benefits, in the context of the seriousness of the disease being treated, and any unwanted effects in patients that justify the use of any medicine.

3.2 Novel therapies aim to provide incremental benefits over existing therapies in safety, tolerability and efficacy or a combination of all three. By improving the risk benefit ratio of medicines, better medicines can be taken by patients and are more likely to be taken correctly if they are tolerated well. This allows the full therapeutic benefit to be realised for the patient. An example of this is the development of less frequent dosing regimens that aid compliance, such as Bonviva® (ibandronate) for postmenopausal osteoporosis. Current bisphosphonates have daily or weekly dosing and require the patient to undergo an overnight fast and to sit or stand upright for 30 minutes following administration of each dose. The once-monthly dosing regime of Bonviva® (ibandronate) will greatly improve convenience to the patient, which should enhance compliance with medication and ensure that patients receive optimal therapeutic benefit.
Overview of Drug Development—Safety

3.3 The proportion of clinical studies undertaken in the UK is declining. However, of all the clinical studies conducted by industry and academia, industry conducts the vast majority.

3.4 The pharmaceutical industry is a clear leader in quality, research integrity and external scrutiny, and works closely with various regulatory authorities worldwide in study and programme design. The results of clinical studies are judged by the regulatory authorities in their consideration of applications for marketing authorisations.

3.5 Safety is paramount in these considerations. GSK has departments with the specific aim of monitoring and acting upon safety signals in order to protect study participants and populations. Where newly emerging data become apparent and raise concerns, appropriate action can be rapidly implemented. GSK has in place trained staff able to communicate rapidly and widely with investigators; it has cancelled programmes and withdrawn products based on such information. This accounts for much of the high attrition rate seen in modern pharmaceutical development. Given that unwanted effects may occur very rarely, it is not always possible to identify these before a medicine is first licensed.

3.6 Although thousands of patients are included in pre-licensing studies, sometimes unwanted effects occur much more rarely. For this reason, continued safety monitoring and Phase IV clinical trials are performed, to follow up and learn more about the profile of medicines. As an example, GSK is spending more than £200 million on Phase IV studies of Avandia to examine further its profile and to generate diabetes progression and cardiovascular outcome data in patients with diabetes. Data generated from Phase IV studies are always submitted to regulatory authorities, in line with Safety Assessment of Marketed Medicines (SAMM) guidelines. These data may result in updates to the product information.

3.7 GSK supports academic medicine to enhance its ability to conduct research in the UK by supporting a research infrastructure to benefit both academic and industry studies. This is supported by ongoing work arising from the Prime Minister’s Pharmaceutical Industry Competitiveness Task Force (PICTF), an ongoing collaboration between NHS R&D, industry, ABPI and other interested parties such as the MHRA. GSK is an active participant and supporter of PICTF. GSK also welcomes the outcome of the DTI/BioIndustry Association’s Biosciences Innovation Growth Team (BIGT) initiative and the work on the UK clinical research base being taken forward by its Biosciences Leadership Council (BLC).

3.8 GSK was encouraged by the recent announcements in the Government’s “Science and Innovation Investment Framework 2004–2014” concerning the future of clinical research. GSK strongly supports the Government’s science and technology strategy to restore the pre-eminence of UK research capability and looks forward to working closely with the recently established UK Clinical Research Collaboration (UK CRC) and the MRC/DoH Health Research Delivery Group.

Regulation/Governance—Clinical Trials

3.9 Clinical trials undertaken in developed countries are managed in a highly regulated environment to high standards. These are enshrined in law with the implementation of the European Clinical Trials Directive. Even when GSK undertakes studies in countries outside of those whose health authorities have agreed to these high standards, the company maintains the same uniform standard across its development programmes. Many regulatory agencies provide input to clinical development programmes and will receive ongoing safety updates according to these internationally agreed procedures. Authorities such as the MHRA will inspect studies and the processes followed against internal company processes and to check adherence to national standards, many of which are now legally enforceable.

3.10 Once a study is completed, all data are analysed according to the previously agreed analysis plan. After analysis, a report is distributed to participating investigators and to the ethics committee and regulatory authorities, as is required by law. Subsequently, the data is communicated more publicly, either through publication or presentation at medical congresses, and frequently by both. Unfortunately when the main study hypothesis is not proven, or no difference between treatments in the study is seen, medical journals are often reticent to publish studies, despite the submission of manuscripts. As a result there is an inherent barrier to the distribution of data from “negative” studies. In 2003 GSK produced approximately 1,400 publications based on its preclinical and clinical research.

3.11 GSK has announced the creation an electronic database to enable dissemination over the Internet of information about GSK-sponsored clinical trials. The GSK Clinical Trial Register will provide summaries of trial protocols and corresponding results for GSK-sponsored trials of marketed medicines. In addition, the register will provide references to publications that have appeared in the medical literature. The register will be accessible to physicians and the public. GSK will continue to communicate clinical data in journals, at scientific meetings, and in letters to health care professionals.

Recommendations

3.12 GSK recommends that the committee addresses proposals that support the recent Research for Patient Benefit Working Party report to enhance the competitiveness of the UK in undertaking clinical research. Key factors that will enhance this are to improve the UK infrastructure to facilitate the conduct of research.
3.13 Consideration should be given to provision of an NHS IT strategy to facilitate the identification of patients who may be willing and eligible to participate in studies.

3.14 It has been noted that the application of NHS Trust overhead fees and approval times varies widely across the UK. GSK urges the committee to provide some recommendations to standardise charges and review times to enable UK clinical research to regain its competitiveness.

4. **Provision of Drug Information and Promotion**

*Marketing and Sales Practices*

4.1 GSK markets most of its products, both in the UK and globally, through sales representatives who meet regularly with doctors and pharmacists. New GSK representatives are trained by GSK on the medicines they promote, the diseases the medicines are designed to treat and appropriate marketing practices. The training provides a thorough understanding of their obligations and responsibilities under our marketing codes.

4.2 GSK is committed to marketing that is ethical, responsible, and patient-centred. The company has a global policy governing its marketing activities that applies to all employees, suppliers, contractors and agents. GSK’s policy requires that all marketing and promotional activities are based on valid scientific evidence, and comply with applicable laws and regulations. The company complies with relevant industry codes of practice, such as the International Federation of Pharmaceutical Manufacturers Association’s (IFPMA) Code of Pharmaceutical Marketing Practices, the Pharmaceutical Research and Manufacturers of America (PhRMA) Code on Interactions with Healthcare Professionals and the ABPI Code of Practice.

4.3 Additional information about GSK’s global marketing practices can be found in the company’s Corporate Responsibility report and on the company website: [www.gsk.com](http://www.gsk.com)

*Compliance with the ABPI Code of Practice*

4.4 As stated above, in the execution of all of its activities, GSK vigorously supports the principles of self-regulation embodied in the ABPI Code of Practice. GSK places great emphasis on the importance of the Code of Practice in the training of all of GSK staff and in their day to day management.

4.5 GSK takes sanctions of the Code of Practice seriously and believes this method of regulation is effective, and quick in its conclusions. Breaches of the Code result in a review and corrective action by the company; when individuals are at fault disciplinary action is taken.

4.6 In 2003, GSK implemented a European Promotional Code of Practice, to ensure that all staff are subject to similar high standards to those in the UK. This GSK European Code is extensively based on the ABPI Code.

4.7 The requirements of the Medicines Act 1968 (as amended) relating to the promotion of medicines to health professionals and the public are fully reflected in the Code of Practice. The Act provides criminal sanctions for breaches of the law and the MHRA has used its enforcement powers under the Act in serious cases. The possibility of criminal sanctions significantly encourages support for and compliance with the voluntary code. The voluntary code is wider in scope than the statute and is better able to address the majority of breaches, which are usually minor questions of interpretation, in a proportionate manner.

4.8 In addition to the Code of Practice, GSK also ensures that its activities are aligned to other professional codes of conduct, such as the General Medical Council’s (GMC) “Duties of a Doctor”.

4.9 With regard to over-the-counter medicines, GSK complies with the Proprietary Association of GB Code on Medicines Advertising and the Committee on Advertising Practice British Code on Advertising, Sales Promotion and Direct Marketing.

*Information for Health Care Professionals*

*Pharmacists, Suppliers and Providers of Medicines*

4.10 GSK provides high quality medical information support to pharmacists, both during and out of working hours, for emergency enquiries. In 2003, GSK handled around 12,000 medical enquiries from pharmacists. This service is much valued by pharmacists as it helps them to deal with many issues in medicines management, ranging from complex pharmacology to enquiries about appropriate dosages. A joint survey organised through the UK Medicines Information Pharmacist Group found that on one working day 59% of NHS Medicines Information Centres contacted a pharmaceutical company for advice. 70% of these calls were for information relating to the management of existing or future patients, and in 47% of cases industry was the only source of the information.

4.11 In addition to support around issues and queries, GSK works with pharmacists through the GSK “+ Plus” scheme, to help pharmacists develop medicines management skills and develop expertise in chronic disease management. This partnership has recently worked well through jointly producing patient materials and training 40 pharmacists from across the UK. This scheme has helped pharmacists develop skills in asthma diagnosis and management, to identify patients with inadequately controlled asthma.
Specialist nurses

4.12 The GSK Medical Information department responded to around 9,000 medical queries from nurses in 2003. Rapid access to scientific information is greatly valued by busy nurses, who often do not have the time or the research resources to find quickly the information they need for day to day practice. Queries cover a broad range of topics, from complex pharmacological information regarding drug interactions to information about vaccine storage.

Clinicians

4.13 GSK provides in and out-of-hours medical information support dealing with around 8,000 queries from doctors in 2003. GSK also deals with reports of adverse events related to the use of medicines and follows these up via its pharmacovigilance department, which works closely with the MHRA and abides by all relevant legislative and regulatory requirements.

Patients, Consumers, the General Public and Representative Bodies

Patients and Consumers

4.14 GSK provides non-promotional information for patients in a number of different ways. For many patients, patient information leaflets are the major source of information about their medicines. GSK patient information leaflets are worded to be accurate, compliant with regulations, to be of use and benefit to the user of the medicine and written in language that is easy to understand. On occasions, GSK has consulted with the organisations, for example Consumption and The Plain English Campaign, and patient groups, over the wording of such leaflets. All patient information leaflets are approved by the MHRA in line with the legislation.

4.15 In addition GSK has a patient enquiry line, which last year dealt with around 1,000 medicine-related queries from patients.

5. Professional and Patient Education

5.1 GSK supports clinicians in their personal education according to ABPI guidelines.

5.2 GSK supports junior doctors in training for general practice and for specialist roles. This is achieved through informal sponsorship of courses and meetings and through formal support through a variety of schemes. GSK’s “SPARROW” programme supports Specialist Registrars in metabolic and respiratory medicine. The programme runs with the support of clinical tutors who select applicants presenting research at major international academic meetings and organise educational objectives and follow up meetings. Last year GSK supported 150 specialist registrars in this way, allowing these physicians in training to present their research and have the chance to interact with fellow specialists from around the world.

5.3 GSK also supports consultants in their attendance at independent international symposia, last year helping 180 consultants to attend such meetings in the field of respiratory and metabolic medicine. GSK also supported approximately 150 consultants to attend symposia in other disease areas such as neurology, urology and HIV medicine.

5.4 GSK places great emphasis on providing high quality educational support for specialist and practice nurses, many of whom have little access to training funding. In 2003 GSK funded diplomas in respiratory disease management for 235 nurses at independent academic training institutions. For diabetes management GSK funded 199 diplomas, 490 advanced study days and 290 other study courses, again all at independent academic institutions.

5.5 GSK has engaged in partnerships with independent patient groups, charities, government agencies and other pharmaceutical companies in developing and launching disease awareness and health promotion campaigns. An example of this was the “out of the water closet” campaign: a project to increase men’s awareness about prostate health. This project was developed with the Men’s Health Forum, the CEDC, the NHS Health Development agency, The Prostate Cancer charity, The Orchid cancer appeal and Yamanouchi Pharmaceuticals.

5.6 GSK has also directly accessible non-promotional web based information to help patients increase understanding of their disease. One such example is the Action Asthma website www.actionasthma.co.uk, which is aimed at educating adults and children with asthma as well as their families.

6. Regulatory Review of Drug Safety and Efficacy

Regulatory Framework

6.1 The pharmaceutical industry, medical community, patients and government all have a common interest in ensuring that the regulatory system in the UK is transparent, efficient, and robust and bases its decisions on a high standard of scientific evidence. Government has a particularly important role to play in ensuring that new regulation is well formulated, targeted and responds to a real need. The aim should be to regulate effectively and efficiently—unnecessary over-regulation is a disadvantage to both industry and patients. The regulatory system should provide timely access for patients to effective medicines, while ensuring patient safety, and stimulating research into new treatments or technologies. GSK is committed
to bringing innovative medicines and technologies to patients and clinicians and the GSK research agenda is driven by unmet medical need. Industry and regulatory agencies must work together to ensure maximum benefit to patients whilst minimising risk.

Communication between Industry and Regulatory Authorities throughout the Lifecycle of a Medicine

6.2 There are clearly defined legislative requirements, which necessitate communication, dialogue and the submission of data from industry to the MHRA at various stages in the life-cycle of a medicine. In addition, early and continuous dialogue between companies and regulatory agencies is essential to facilitate the understanding and introduction of new technologies as well as the development of appropriate regulation. This is particularly critical when there is a need to adapt regulatory requirements eg pharmacogenetics. In light of the recent formation of the MHRA, there are areas where closer collaboration between the medicines and devices sector is particularly important.

6.3 A high quality scientific assessment is facilitated by objective scientific dialogue between regulatory authorities and companies. Such regular dialogue is in the public health interest to ensure that effective and safe new medicines, and information pertaining to them, reach the patient as quickly as possible. It is essential that this integral part of the regulatory framework is continued throughout the various regulatory processes, including pharmacovigilance.

6.4 It takes 10 to 12 years to develop a new medicine and various issues of a technical or scientific nature might arise during this process where written guidance is not available. It is important to ensure that the right development programme is carried out to enable registration of safe and effective new medicines in the most efficient way and avoid unnecessary clinical trials or delays in getting new medicines to patients.

6.5 During the regulatory review of a new medicine, or a change to an existing medicine, there is an ongoing dialogue between the applicant company and the MHRA. The applicant company explains the data, provides clarifications and answers questions based on the scientific evidence provided. Through such dialogue, the MHRA is able to make decisions on the safety, quality and efficacy of the medicine based on the totality of the evidence available and the proposed usage. GSK takes a proactive approach to updating information on all of its medicines. This is demonstrated by the fact that the vast majority of licence changes are identified and driven by GSK. It is important that for safety related changes, the MHRA review process does not delay the timely update of medicine information in this respect.

6.6 Good communication channels between the MHRA and the company is also essential when the MHRA requires information from companies, often at very short notice eg general safety reviews such as those relating to review of all medicines to minimise the risk of transmission of Transmissible Spongiform Encephalopathies or for particular classes of medicines.

6.7 A more specific example of where it is important that industry and the MHRA work together is the optimal provision of clear and effective information to patients about their medicines. GSK welcomes the Government’s initiative to focus on this with the set up of the Committee on Safety of Medicines working group on patient information leaflets.

Recommendations

6.8 Where possible there should be increased collaboration between industry and the MHRA, particularly where, for example, patients’ interests could be damaged without an effective, data driven and co-ordinated approach including communication eg issues related to the media.

6.9 GSK strongly supports the ongoing development of the MHRA as a leading agency in the European regulatory agency “network”. This will require additional high quality staff resources to achieve this and to accommodate the current agency workload. Companies now have the possibility to select any one of the 25 Member States to lead the assessment of their medicines. Companies select European regulatory agencies that not only provide high scientific excellence, but also consider customer service and efficient performance.

6.10 GSK supports the continued representation of industry on relevant advisory bodies of the MHRA. This link is essential to provide input relating to the practical implications of medicines regulation policy and feedback on the Agency’s performance from one of its major stakeholders.

6.11 GSK supports a robust and transparent regulatory procedure, but recommends that the Health Select Committee does not only consider MHRA transparency towards the public, as improvements can also be identified in relation to industry. Transparency and effective communication between the company and the MHRA during the assessment process promotes better understanding of issues, and ultimately results in more efficient resolution. GSK supports any measures to ensure that the MHRA is independent of all external influencers including any proposal to review the financing of the MHRA if this would help dispel any perception of undue external influence.
7. **Product Evaluation, Including Assessments of Value for Money**

7.1 GSK contributed to four NICE appraisals in 2003. GSK contributes actively and openly to all NICE scoping debates, bringing disease area, pharmacological and health outcomes expertise.

7.2 GSK strongly endorses the goals of NICE in promoting faster more equitable access to improved treatments, the need to address postcode prescribing and the promotion of the longer-term interest of the NHS in the development of innovative new treatments. GSK has been disappointed to date by the lack of progress in delivering these goals. Although negative guidance can block the uptake of new medicines, there is only limited evidence of any impact of positive guidance on prescribing. GSK therefore welcomes the steps the Government is taking, including the appointment of a Director of Implementation at the Institute, to improve this situation.

7.3 To date GSK has participated in seven initial appraisals and two reviews of guidance in a professional and constructive manner, as outlined in NICE’s guidance to manufacturers. Particularly at the early stage of a medicine’s lifecycle it is likely that much of the evidence of the new medicine will be unpublished, at least in full, and considerable expertise on the profile of the medicine will rest with the manufacturer. GSK therefore believes that the manufacturer’s submission plays a vital role in informing the discussions of the appraisal committee, however, the company recognises the need for this evidence to be subject to appropriate external scrutiny.

7.4 As required by the process, GSK submits all relevant data to NICE and also provides a listing of any evidence that GSK considers not to be relevant to the scope of the review and why. This evidence is then also available on request. GSK has also tried to limit the data submitted to the Institute in confidence, as GSK understands the importance of transparency of decision-making. GSK fully endorses the recent guidelines agreed between the Institute and the ABPI on the limitation of confidential information in industry submissions, and will be implementing these in future reviews for which GSK are stakeholders.

**APPENDIX 1**

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Memorandum by AstraZeneca (PI 33)

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Summary of Key Points

— AstraZeneca is a responsible and ethical company that works to improve the health and the quality of life of patients.

— Great progress has been made in combating disease. Technology developed over the past 15 years will further improve our ability to continue to discover truly life-enhancing innovative medicines.

— Improvements in existing drug therapy by improving tolerability and efficacy are equally important.

— Discovering innovative medicines is expensive and risky. It requires government to create a stable and competitive environment that values science and innovation.

— World-class medical research requires a renewed, strong physical and procedural infrastructure in the UK.

— AstraZeneca’s commitment and investment in medical research benefits the UK in many ways: economic, improved health, improved medical research infrastructure.

— All medical research is conducted according to stringent international and national laws, regulations and guidelines.

— AstraZeneca operates a 24 hour medical information service about our medicines.

— The provision of non promotional information would support other high quality information services and counter misleading information.

— The ABPI self-regulatory code of marketing practice provides wider control than statutory processes.

— AstraZeneca has in place an effective approval system for promotional material and activities and works hard to ensure all aspects of its activity fully comply with the code.

— Before any Sales Representative can have contact with a health care professional he must have passed an examination of the PMCPA and demonstrated thorough understanding of the medicine he wishes to discuss.

— AstraZeneca supports local education programmes to assist in the implementation of National Service Frameworks.

— AstraZeneca openly sponsors patient bodies in order to improve access to good lay information and help patients take greater responsibility for their health.

— Interaction with Sales Representatives enables healthcare professionals to gain access to the latest information and ensures their continuing professional education.

— Hosting clinical trials benefits the NHS by developing the skills of the clinicians, enabling learning of key legislation and protocol development.

— The UK Government provides through the MHRA a solid and objective regulatory system promoting the needs and benefits of the British patients. This system further operates within an effective and comprehensive European and international framework that is constantly being updated and revised to reflect new medicinal progress and scientific advances.

— As a leading regulatory Agency in Europe it is, however, very important that the MHRA fully supports and co-ordinates their work with the European regulatory process, rather than duplicating assessments being undertaken on behalf of Europe by European Committees or the designated Reference Member State or Rapporteur Agency. There is some evidence of such duplication and this is not in the interest of an efficient regulatory process.

— AstraZeneca works constructively with the HTA bodies in England, Scotland and Wales in a transparent way and in accordance with an agreed framework.

— AstraZeneca contributes to both the appraisals and clinical guideline programmes by submitting evidence and critically reviewing drafts documents.
Further improvements in NICE process are, however, still required. These include the addressing of NICE blight and providing clarity about the relationship between health technology appraisals and clinical guidelines including clarity on how the decisions to review and update existing HTA guidance within the context of a clinical guideline are made, and. In addition NICE should work with respective bodies to address issues of implementation, the consistency and quality of HTA groups and finally the duplication of effort between NICE, SMC and AWMSG.

AstraZeneca welcomes the inquiry announced by the Health Select Committee into the role of the pharmaceutical industry and its influence on health policies, health outcomes and future health priorities and needs and is pleased to submit written evidence.

1. **INTRODUCTION**

*The industry and its influence*

1.1 There are very few, if any, industries that are as regulated as heavily as the pharmaceutical industry. Government or their agencies regulate all activities of pharmaceutical companies ranging from the discovery of a compound in the laboratory to the authorisation to market a medicine.

1.2 Regulation is complex, time consuming and expensive. It is not only right but also appropriate that companies like AstraZeneca are able to discuss with government and their agencies issues relating to their medicines. On average it takes about 12 years and £500 million to bring a medicine from the laboratory to the patient. No other organisation will know more about the medicine than the one that discovered it.

1.3 Ensuring patients’ safety while at the same time allowing rapid access to the most modern treatments is crucial.

1.4 Equally important, is balancing the needs of the pharmaceutical industry for a stable business environment which recognises and rewards innovation, with the requirement to provide cost-effective medicines as one part of a sustainable and responsive healthcare framework. Those governments that are successful in finding the right balance are often equally successful in improving standards of health (which in turn drives wealth creation) and sponsoring a successful pharmaceutical industry.

*History*

1.5 AstraZeneca has a long and proud history of investing in the United Kingdom and developing innovative medicines to treat illness ranging from cancer and cardiovascular disease to infection.

1.6 Our discovery of medicines began during the war with the development of Paludrine, an anti-malarial and Xylocaine, a local anaesthetic. This tradition has carried on into the 21st century. Most recently we have developed two groundbreaking treatments, IRESSA for non-small cell lung cancer and EXANTA, an oral direct thrombin inhibitor, the first alternative to warfarin in 50 years.

*AstraZeneca and the United Kingdom*

1.7 Within the United Kingdom, AstraZeneca has eight principal sites and employs over 10,800 people. We have two Research and Development centres of excellence in Alderley Park, Cheshire and Loughborough, Leicestershire, two major manufacturing sites in Macclesfield, Cheshire and Avlon near Bristol, UK sales, marketing headquarters in Luton and corporate headquarters in London.

1.8 The United Kingdom represents just 3% of AstraZeneca’s total sales. Yet it remains an important location for its manufacturing, research and development. Nearly a third of all its Research and Development is conducted in the United Kingdom. Between 1999 and 2006 AstraZeneca’s investment will approach £1 billion resulting in over 550 new jobs. Nevertheless as a multi national company with many sites across the globe competing for new investments, the UK’s sites must continually demonstrate their efficiency and value for money.

*Competitiveness of the industry*

1.9 The government and its citizens need a successful pharmaceutical industry in the United Kingdom. A successful pharmaceutical industry benefits not only the economy in terms of the high quality employment it offers and the positive contribution it makes to the balance of payments, but also to the health of the nation. A healthy nation correlates favourably with high economic performance.

1.10 Just as the National Health Service (NHS) needs a strong and successful pharmaceutical industry to enable it to treat and cure the millions of patients it sees every day so the pharmaceutical industry needs the government to create a competitive environment that encourages and rewards innovation in the United Kingdom.


2. **Drug Innovation**

**Leading in Innovation**

2.1 While healthy people may value innovation in terms of a smaller, faster laptop, those who are sick only care about getting well again. For these people, the pharmaceutical industry has demonstrated its innovation in delivering a succession of new medicines over the last 50 years, which have saved lives and increased quality of life.

2.2 There have been many significant new medicines in the last 50 years. Many of these improvements are the result of completely new therapies; others are the results of incremental advances with the latter often not as valued as much as it should be.

2.3 The industry has in fact worked diligently on both fronts. All involved in drug discovery want to deliver big breakthroughs where possible, but they also recognise that the safety and efficacy of existing drugs often needs improvement. In AstraZeneca, we have been able to deliver on both radically new drugs and also on valued improvements to existing drug classes. Our pipeline is delivering a high proportion of drugs, which are being considered as breakthroughs. About three-quarters of AstraZeneca’s R&D expenditure is targeted towards diseases identified by the UK government as priority areas: cancer, coronary heart disease, mental health, diabetes and diseases of the elderly.

**Drug Discovery is Changing**

2.4 It should be realised that, in discovering new drugs, the industry is very dependent on the state of mankind’s knowledge of how the human body works and of what goes wrong in disease. Drugs launched in the last few years today were discovered with a much more limited science base than the ones that are being discovered today and will be launched in the 2010s. Also the drugs that dominate the market today reflect the drug hunting approaches of the past—for example mimicking the body’s natural hormones, exploiting the activity of natural products from plants and following up side-effects noticed in clinic practice. This has inevitably limited the industry’s ability to find breakthrough drugs. It has also limited the disease areas that were addressed, leaving many diseases with little or no effective treatment.

2.5 Fortunately, things are set to improve. In the last 10–15 years there have been several significant improvements in our ability to discover innovative new drugs. These are starting to impact on new drug launches with the impact continuing to increase over the coming 10–15 years.

2.6 Firstly, in the nineties, there were several improvements to the way that the industry discovers drugs. For example, new molecular biology techniques enabled us to work with purified human protein targets, rather than with crude extracts of less relevant animal proteins. High throughput screening emerged as a significant way of finding compounds with drug activity. Our ability to design drugs at a computer has improved with increased computer power and new approaches to determining the 3D shape of protein targets. In addition, a whole “drug discovery technology” industry emerged, offering a huge range of new techniques and approaches for making R&D more efficient and effective. AstraZeneca has invested considerably in these new approaches. For example, we have a leading position in protein structure determination and have augmented our capability for structure-based drug discovery with collaborations with a leading British Biotech company in the field, Astex.

2.7 Secondly, in the last 10–15 years, there has been an acceleration in our ability to understand disease mechanisms at a molecular level. This has been fuelled by, for example:

- Massive investment in the biological sciences, particularly by the NIH in the USA.
- The completion of the Human Genome Project.
- Investment in the Biotech sector.
- The emergence of powerful new tools such as microarrays, protein mass spectrometry, imaging and bioinformatics.

**A New Wave of Drug Discovery**

2.8 The net effect of these investments is that many diseases are now starting to be understood much better at the molecular level. This includes some of the more difficult diseases where society is looking for big improvements, eg cancer, Alzheimer’s, schizophrenia and the chronic inflammatory conditions such as rheumatoid arthritis. With these new techniques and the ever-improved understanding of disease, the industry is well placed to make good progress against these and other diseases.

2.9 While the impact of these investments lies mainly in the future, we are beginning to see the fruits today. For example, in AstraZeneca, we have been able to build on the explosion of knowledge of the molecular basis for cancer in the discovery of our innovative cancer drug “IRESSA”®, described as the biggest advance ever in the treatment of lung cancer. This shows that investment in basic science together with innovative drug hunting can lead to paradigm shifts in treatment. But, to emphasise, it is a partnership: success that is still highly dependent on the broad progress in biomedical science outside the industry.
Improving on Existing Drug Therapies

2.10 We should not underestimate the importance of improving on existing drugs. For example, AstraZeneca’s new anti-coagulant, Exanta®, is a huge improvement on the standard therapy, warfarin: it is faster, much safer and does not require anticoagulation monitoring. The significant health economic benefits will allow the NHS to direct the funds saved elsewhere.

2.11 Furthermore, it has always been well known that people differ considerably in their response to a given drug, either due to their genetic make-up, or due to subtle differences in the type of disease they have. This can lead to ineffective prescribing and non-compliance by the patient. Our understanding and ability to address this issue is improving fast. In AstraZeneca, we have invested considerably in the new field of “pharmacogenetics”, with the aim that our medicines should be effective and safe for all patients.

Enabling Innovation

2.12 In summary, the level of innovation in the pharmaceutical industry has always been high, and is set to get even higher. In the coming few decades, we should see the fruits of the science and technology investments of the past. AstraZeneca’s pipeline is already showing this. But pharmaceutical R&D is inherently risky, and tackling the diseases that are hard to cure is always going to be more risky than those we know more about. The cost of innovation is high and rising. The latest estimates put the cost of developing each drug at £500 million. For this enterprise to continue to deliver value for society well into the future there is a need for governments to provide stability for the industry—in terms of recognising and rewarding innovation supply of talent, funding biomedical science, maintaining IP rights, defending necessary animal experimentation, and encouraging the Biotech sector. Governments therefore have a key role to play in creating the climate in which innovation can thrive and deliver value to society.

3. The Conduct of Medical Research

The Value of Medical Research in the United Kingdom

3.1 There is no doubt that new medicines can bring about significant improvements in patient health. High quality medical research is essential for the discovery and development of such life enhancing new medicines and medicines that will deliver improved patient health. AstraZeneca invests heavily in medical research for these reasons and needs a commercial return on its investments. The United Kingdom has, to date, provided an excellent environment in which to conduct medical research, and AstraZeneca has a significant commitment to Medical Research the UK. Even though the UK represents only 3% of our total market, more than 10% of the patients involved in our clinical trials live in the UK. At our R & D sites in Alderley Park, Cheshire and Loughborough, Leicestershire and in our marketing company, in Luton we have over 1,000 people devoted to the design, conduct, analysis and interpretation of medical research. Each year we work with more than seven hundred clinical investigational centres in the UK conducting more than one hundred clinical studies—many of them multinational collaborations. Our track record of important medical research in the UK is second to none and has resulted in many key medicines, such as treatments for cancer (Nolvadex, Zoladex, Casodex, Arimidex and Faslodex), cardiovascular disease (Inderal, Tenormin, Zestril, CRESTOR), anaesthesia (Diprivan) and psychiatry (Seroquel). Most recently, medical research in the UK led to the discovery of IRESSA—the first of a new generation of well tolerated medicines for lung cancer now licensed in many countries including the US but not yet licensed in the UK.

The Conduct of Medical Research

3.2 Patient care is of paramount importance to AstraZeneca. We fully support the regulation and stringent control of medical research. We conduct all our medical research according to international and national laws, regulations and guidelines as established by UK Government, and other bodies such as the European Medicines Agency and the US FDA. We welcome opportunities for positive interactions to develop regulations and guidelines whilst recognising the need for complete independence of the regulatory bodies; for example, AstraZeneca has contributed to defining best practice in the ethical conduct of pharmacogenetics studies and we have collaborated with the Department of Health (DoH) to develop a model clinical trials agreement.

3.3 All AstraZeneca and investigational site staff involved in the conduct of our clinical trials receive extensive training in Good Clinical Practice (GCP); this training better equips the site for future work, whether industry sponsored or academic.

3.4 AstraZeneca is committed to providing healthcare professionals and patients with relevant information that enables them to make the best treatment decisions. AstraZeneca has put in place a mandatory Publication Policy that outlines the company’s principles with regard to external communication of scientific and medical information. Specifically this policy describes the company’s aim to publish the results of AstraZeneca-sponsored clinical trials; our commitment to maintain high standards of medical and

scientific integrity by presenting research results in an accurate, objective, and balanced fashion; and states that selective publication that would misrepresent the medical profile of an AstraZeneca product is not acceptable. Compliance with this policy is formally monitored.

3.5 Our ethical principles are publicly documented and rigorously implemented.4

Wider Benefits of AstraZeneca’s Contributions to Medical Research in the UK

3.6 In addition to directly benefiting patients, we believe that our contributions to Medical Research in the UK bring wider benefits by raising the overall quality of medical research science in this country not only in terms of the science of therapeutics but also the development and application of novel technologies (particularly genomics, proteomics and imaging). Via direct collaboration or by providing grants we support a significant number of non-drug related medical research efforts. Collaborations include efforts to understand better the pathophysiology of various diseases and the development “biomarkers” to aid selection of dose and to better target therapies to patients (the right drug at the right dose for the right patient). We are also sponsoring medical science aimed at reducing the frequency and severity of drug induced side-effects, improving statistical analysis techniques and speeding the collection and evaluation of clinical data from patients—particularly side-effect data.

The Future

3.7 AstraZeneca looks forward to further successful Medical Research in the UK. We welcome the science and innovation investment framework 2004–14,5 however, we do believe that the UK needs a renewed and deepened pool of talented medical researchers. The health service priority of service provision has resulted in fewer people with time available for medical research, and postgraduate medical training has placed less emphasis on developing relevant skills (Strengthening Clinical Research, Academy of Medical Sciences Report, October 2003).

3.8 AstraZeneca has, with other pharmaceuticals companies, provided training fellowships in clinical pharmacology; we have also independently sponsored clinical training fellowships, studentships and courses. However, the training provision for physicians and non-physician medical researchers in the UK remains inadequate to provide sufficient individuals who are able to collaborate with the industry either by direct participation in clinical studies or by review, understanding and practical implementation of the results of research.

3.9 Similarly, the UK needs to develop a strong physical and procedural infrastructure to deliver world-class medical research. The recent Pharmaceutical Industry Competitiveness Task Force (PICTF) Report—Performance Indicators (2003) notes the gap between US and UK government expenditure in medical and biological sciences expressed as a proportion of GDP. AstraZeneca has seen the benefits of the development of the National Cancer Research Network and NTRAC initiatives and has established clinical and translational collaborations with these organisations. AstraZeneca strongly supports the recent initiatives to establish the UK Clinical Research Collaboration and the NHS research networks for Alzheimer’s disease, Stroke, Diabetes, Mental Health and Children’s medicines. These initiatives should serve as a foundation for a renewed, positive medical research environment but will require significant financial investment beyond that already announced and eventual extension into other important disease areas.

4. Provision of Drug Information and Promotion

Importance of Information and promotional activities

4.1 The appropriate and safe use of medicines depends on information about the medicine provided to health professionals, patients and carers. A medicine used inappropriately is potentially dangerous and a medicine not taken at all is a waste of taxpayers money. Pharmaceutical companies, such as AstraZeneca, are able to provide very high quality information about medicines and on health topics in general. Unlike many other providers of information our communications are tightly controlled by effective regulation and self-regulatory codes and by the company’s commitment to quality.

4.2 A high proportion of prescribed medicines are not taken as intended by the prescriber. Updated regulatory interpretations could help companies to provide more, quality controlled, non-promotional medicines information to patients and carers. AstraZeneca already plays a valuable role in medicines and health information provision and we believe this has a positive influence on health and wellbeing. However, the full potential to maximise patient benefits has not yet been realised.

5 www.hm-treasury.gov.uk.
Provision of Drug Information

4.3 Pharmaceutical companies can contribute to the safe and effective use of their medicines through high quality Drug Information Services and through Patient Information Leaflets (PILs) in packs. However, current interpretation of the regulations prevents further provision of non-promotional information to patients, which could lead to more informed decisions about treatment choices being made.

4.4 AstraZeneca operates a 24-hour medical information service to respond to queries about our medicines. Around 16,000 enquiries are answered annually in the UK using the company’s extensive information resources and expertise—we know more about our medicines than anyone else. Most enquiries are from health professionals. Health professionals are able to seek medicines information from password-controlled company Internet sites.

4.5 However, the majority of enquiries about their medicines that comes directly from patients and their carers cannot be fully answered because this would be construed as an illegal promotion of a prescription only medicine to the public. At present patients can find out more information about the safe use of tamoxifen (to treat breast cancer) from the Internet than they can from the company who discovered it, despite the fact that most of the information available on the Internet is unauthorised and, sometimes, misleading. The provision by companies of non-promotional information to patients about the medicine they have been prescribed would support other high quality information sources such as NHS Direct. It would contribute significantly to the optimum and safe use of medicines.

4.6 The PIL that is provided in packs is constructed to a design set out by an EU directive with little flexibility to enhance its user-friendliness. AstraZeneca fully supports the recent EU developments with respect to the requirement for user testing of leaflets. We are also actively supporting the CSM working group on patient information that aims to recommend improvements in PILs.

4.7 PILs are continually updated during the life of a product. Up to date texts are provided on the Internet in response to any change. However, since companies are prohibited from including the website address on the leaflet, patients have no way of knowing that there may be more up to date information available to them.

Promotional Activities

4.8 Promotional activities to healthcare professionals are closely regulated and AstraZeneca is committed to promoting our medicines responsibly and ethically. See point 5.2 for additional information.

4.9 The ABPI self-regulatory code of marketing practice provides wider controls than statutory processes. It is regularly updated to reflect the current consensus on acceptability, external developments (e.g. the Internet) and to reflect current best practice. The UK system for ensuring the quality of promotional communications is amongst the most effective in the world with regulation (through MHRA) working alongside self-regulation (ABPI code).

4.10 The ABPI Code covers industry activities where questions could be raised about the level of influence; clear guidelines exist for sponsorship and hospitality arrangements and the provision of promotional aids (low value gifts). This evolves over time and is regularly updated taking full account of the views of professional bodies, regulators, pharmaceutical companies (including AstraZeneca) and other interested parties. For example, promotional reminder gifts (pens, pads etc) carrying a product name are permitted up to the value of £6 providing they are relevant to professional practice. In future the consensus view on the appropriateness of such gifts might change, based on complaints and subsequent judgements based on the existing code. If it does the mechanism is established whereby changes can be rapidly implemented.

4.11 AstraZeneca has in place a rigorous approval system for promotional material and activities. The requirements for this approval process of materials and activities are set out in a regularly reviewed standard operating procedure. One such requirement is that no promotional material or activity can proceed without the signed authorisation of two Prescription of Medicines Code of Practice Authority (PMCPA) and (MHRA) registered company signatories, one of whom must be a medical practitioner. Furthermore, any complaints that are received and upheld are thoroughly investigated and remedial actions put in place to prevent recurrence. The Medical Director must sign a written undertaking that there will be no recurrence of the matter. Our representatives receive training and regular updating on the technical aspects of our products and also on ethical marketing and selling practices. Failure of sales and marketing personnel to comply with high standards is taken very seriously and is a disciplinary offence. Globally AstraZeneca company policies and standards and our corporate responsibility policy cover sales and marketing.

4.12 AstraZeneca does not advocate any change in the law which would permit Direct to Consumer advertising of prescription medicines, including the type of TV and press advertisements seen in the USA. These are not permitted in the EU and this position has recently been reconfirmed in the review of pharmaceutical legislation. Pharmaceutical companies, however, do have a role to play alongside other information providers, in the provision of non-promotional information about medicines and diseases.

directly and indirectly to patients and the public. AstraZeneca supports the development of clear quality guidelines for all providers of non-promotional medicines information. The information provider should always be identified, but the acceptability of a piece of information should be based on its quality, reliability and usefulness rather than its source.

4.13 AstraZeneca believes that companies be encouraged to work with MHRA to find ways whereby their knowledge of medicines and their communication skills are allowed to be used to maximum effect to the benefit of patients.

5. PROFESSIONAL AND PATIENT EDUCATION

5.1 AstraZeneca works hard to ensure that in all activities involving both Health Care Professionals (HCPs) and patients about its products, UK legislation and the requirements of the PMCPA are fully complied with.

Ensuring Appropriate Use of Our Medicines

5.2 HCPs are kept fully updated on the advances in drug therapy through interaction with AstraZeneca’s sales representatives. Representatives educate HCPs on the correct use of the Company’s medicines through reference to data and licensed indications. Before contact with an HCP, all sales representatives must have both a thorough understanding about the medicines they wish to discuss, and have passed an official examination set by the PMCPA on the regulations concerning the interactions they may have with health professionals. The PMCPA sets strict guidelines regulating how sales representatives may interact with HCPs.

5.3 When there are changes to the licences of AstraZeneca’s medicines, its Medical Information Department sends out written notifications to all relevant parties. Occasionally, if there is a change in a licence that should influence prescribing such as a safety concern, AstraZeneca will use the “Dr Doctor” letter format to communicate those changes.

5.4 Our Medical and Market Access and Outcomes Research Departments provide unbiased information on our products to assist formulary applications and decisions, including the provision of health economic/cost-effectiveness data/models.

5.5 AstraZeneca provides supplementary patient and physician educational materials to support the Summary of Product Characteristics and PILs. Last year AstraZeneca participated in the Medicines Guides programme which, in conjunction with NHS Online, provides factual information about diseases and the treatments available.

5.6 In partnership with the MHRA and the NHS, AstraZeneca develops Patient Risk Management programmes, which are designed to support the safe use of our medicines.

5.7 AstraZeneca has supported local educational programmes assisting the uniform implementation of National Service Frameworks (NSFs). Advice from bodies providing National Guidance has also been incorporated into company presentations to local Drug and Therapeutic Committees (DTCs), to help in the implementation of such guidance.

Patient and Disease Awareness

5.8 To support initiatives from Government and encourage patients to take a greater responsibility for their health, it is vital that patients have easy access to good quality lay publications on disease areas to inform them in their discussions with their prescriber. AstraZeneca sponsors disease area websites and other patient educational materials, which are fully compliant with legislation and the ABPI Code of Practice. In one instance a grant was awarded to support an Internet based patient self-management programme run by the Manic-Depression Foundation. This programme has facilitated a wider dissemination of knowledge concerning mania and depression to both patients and carers, and provided a forum for discussion around this important disease.

Patient Group Support

5.9 AstraZeneca is an acknowledged sponsor of a wide spectrum of patient bodies / associations such as the Prostate Cancer Coalition, and the British Heart Foundation. We share information on our medicines with these groups and support the production of patient educational activities and material. The Prostate Cancer Coalition Roadshow programme in 2003 was a good example of such sponsorship.
Continuing Educational Opportunities for Health Care Professionals

5.10 Treatments for diseases are constantly changing. With the increasing demands upon HCPs they have neither the time nor the resource to adequately update themselves on advances in those treatments, which will ensure the optimum benefit for their patients. This is especially the case in those areas not directly linked to the HCPs own practice. Interaction with AstraZeneca’s Medical and Sales personnel and AstraZeneca sponsored local, regional and national meetings enables prescribers to gain access to the information as well as ensuring their continuing professional education. AstraZeneca also supports attendance at key conferences, and post-conference educational meetings. This provides a forum for Key Opinion Leaders to share with colleagues and peers important data emerging from major congresses, such as the American Society for Clinical Oncology (ASCO).

5.11 AstraZeneca has and does sponsor NHS bodies and patient groups to help them develop educational programmes to assist in the roll-out National Guidelines such as those produced by the National Institute for Clinical Excellence (NICE). One such example are those guidelines directed to NHS Mental Health Trusts, where the Company has worked with the National Institute for Mental Health in England (NIMHE) to develop and support the NICE Guideline on schizophrenia at their national conference.

Professional Development

5.12 AstraZeneca supports the further professional development of NHS staff by the sponsorship of tailored educational and training programmes that have been approved by professional colleges / bodies. Asthma nurses working in General Practice have for example received sponsorship to gain the Diploma in their chosen specialty, benefitting both as individuals and their patients.

5.13 The UK pharmaceutical industry widens career opportunities for HCPs—Doctors, nurses, pharmacists—who want to gain exposure to business and research environments. AstraZeneca offers secondments for clinicians in special units, eg rotations between Trusts in the North West and our Clinical Pharmacology Unit. In addition those HCPs who enter the industry either on a temporary or permanent basis use the research and business skills for the benefit of the NHS units/staff they have contact with often acting as mentors and coaches in management.

Clinical Trials

5.14 The pharmaceutical industry offers expertise in clinical trial design and implementation which raises the standards of clinical trials in the wider NHS, through training on key legislation and policies in clinical trial practice, eg Good Clinical Practice, EU Clinical Trials Directive, protocol development, and ethics submission.

5.15 The Company supports numerous research ideas from UK clinicians, allowing the development of research skills in the NHS, and supporting continuing advancement in clinical and scientific medicine. In psychological medicine, the UK focuses on supporting research ideas on a number of key centres such as the world-renowned Institute of Psychiatry in London. Here a number of studies by leading clinicians have been supported by AstraZeneca, many of which have been turned down by Government bodies due to a lack of available funds.

5.16 AstraZeneca commits to the policy that the results of all AstraZeneca sponsored clinical studies whether perceived as positive or not to the Company should be made available to the wider community.

6. Regulatory Review of Drug Safety and Efficacy

6.1 In almost all countries in the world, concerns have been expressed over public health and product safety in a number of areas—pharmaceuticals being only one of them. With respect to medicines, governments have responded by placing requirements on manufacturers to obtain marketing authorisations before placing medicines on the market and to conform to stringent on-going testing procedures. All aspects of activities in these areas are regulated and legally tightly controlled. The pharmaceutical industry is arguably the most highly regulated industry in the UK, and operates within a very effective and comprehensive European and international regulatory framework that is constantly being updated and revised to reflect new medical progress and scientific advances. The amount of pharmaceutical regulation has increased significantly over the past couple of decades and there has been greater international exchange of medicines information between national regulatory authorities, aimed towards increasing the protection of patients.

6.2 The pharmaceutical industry, medical community, patients and government all have a common interest in ensuring that the regulatory system in the UK is transparent, efficient, robust and bases its decisions on a high standard of scientific evidence. Government has a particular important role to play here in ensuring that new regulation is well formulated, targeted and meaningful ie actually responds to a real need. The regulatory system should provide timely access for patients to effective medicines, whilst ensuring patient safety, and stimulating research into new treatments.
Marketing Authorisation Application

6.3 Before a company can market a medicine in the UK, expert committees within the MHRA or the EMEA must assess whether or not the medicine should be authorised. Before a marketing authorisation is issued, the Agencies will carry out close scrutiny of all the technical reports that must be generated during the development of the medicine, and review the proposed manufacturing methods, quality control procedures and evidence of pharmacological activity, clinical safety and efficacy. The average regulatory submission for a new medicine consists of several hundred volumes of technical and scientific reports and data. During this activity, the "assessment", the Agency assessors will critically review all the scientific evidence presented by the applicant company to establish that the medicine's quality, safety and efficacy are fully supported by the data and in accordance with current rules and regulations. Of necessity, these rules and regulations are based upon a complex combination of law, science and medicine and call for specialised training and background to interpret correctly. The regulatory environment is also often subject to rapid change in accordance with the development of scientific methods and new technologies to which the regulatory requirements need to adapt.

Role of Independent Experts in the Provision of Advice to MHRA

6.4 The MHRA is assisted by advisory committees in making licensing decisions and in reviewing the safety of marketed medicines. It is in the interest of all stakeholders to make sure that the highest level of medical and scientific expertise and excellence is available to the MHRA through these committees. There is, however, only a limited pool of experts in any given area at any given time, and it is important to recognise that this national resource of independent expertise needs to be accessible to both industry, and the MHRA. Consequently, it is essential to have in place a robust, transparent and effective system to avoid any potential conflicts of interest for experts in relation to a specific medicinal product. The MHRA operates just such a system, whereby committee members are subjected to a high level of transparency and rigorous declaration of personal interest, to ensure that their expert scientific opinion is independent and unbiased.

6.5 Industry representation on some advisory committees is valuable to provide input to the discussion of the practical consequences of health policy decisions and on the implementation of these decisions such as switching from BANs to INNs, nurse prescribing and improving the quality of patient leaflets based on experience of drug development and manufacture.

Financial Structure of the MHRA

6.6 The Evans-Cunliffe report recommended that the full cost of the then Medicines Directorate should be charged to the pharmaceutical industry. Therefore, the Agency was established as a Trading Fund that had to be self-sufficient and recoup its costs through fees charged to the industry for its assessment and control activities.

6.7 AstraZeneca is supportive of the MHRA being properly funded so that it can operate efficiently and effectively as a centre of regulatory excellence in Europe. There are sufficient checks and balances in place to ensure independence from industry. Fee levels are set by the Treasury, following public consultation, and are detailed in the relevant UK statutory instruments. However, the pharmaceutical industry has asked for greater transparency from the MHRA on how income from fees are allocated, particularly since the merger of the Medicines Control Agency (MCA) and Medical Devices Agency (MDA) as most of MDA’s activities were funded by the Government, to ensure that the fees for control of medicines are not subsidising activities related to medical devices.

Post Marketing Authorisation Phase

6.8 If a medicine is approved and obtains a licence to be marketed this does not mean that the assessment of the medicine is finished but instead marks the beginning for the applicant company of a legal obligation continuing throughout the lifetime of the medicine to provide the MHRA with information about the medicine both at regular intervals and on an ad hoc basis. The benefit/risk assessment of a medicinal product is a continuous process.

6.9 At the time of approval there will be extensive clinical data on the use of the medicine, however, companies have global pharmacovigilance/risk management systems in place to monitor and assess the use of the medicine in the wider population during the marketing phase. Newly approved medicines and significant changes to existing medicines are subject to intensive monitoring by the MHRA as part of the Committee on the Safety of Medicines (CSM) Yellow Card/Black Triangle scheme. This scheme allows rapid monitoring of new safety signals as medicines become more widely used in patients.

7 European Medicines Agency approves medicines for the European market ie all 25 countries including the UK.


9 Medicines for Human Use (Marketing Authorisations, etc) Regulations 1994.
Communication between Industry and Regulatory Authorities throughout the Lifecycle of a Medicine

6.13 A high quality scientific assessment is facilitated by objective scientific dialogue between regulatory authorities and companies. Such regular dialogue is in the public health interest, to ensure that effective and safe new medicines reach the patient as quickly as possible. It is essential that this integral part of the regulatory framework is continued throughout the various regulatory processes, including pharmacovigilance. Good communication channels between the MHRA and the company are also essential when the MHRA requires information from the company, often at very short notice eg paediatric data, TSE,\(^{10}\) safety reviews on particular classes of medicines.

6.14 There are clearly defined legislative requirements, which necessitate communication, dialogue and the submission of data from industry to the MHRA during the life-cycle of a medicine eg expedited and periodic safety reporting. Regular scientific discussion is initially needed between the pharmaceutical company and the MHRA during the development of a new medicine. It takes an average of 12 years to develop a new medicine and various issues of a technical or scientific nature might arise during this process where written guidance is not available. It is important to ensure that the right development program is carried out to enable registration of safe and effective new medicines in the most efficient way and avoid unnecessary clinical trials or delays in getting new medicines to the patients.

6.15 Therefore, during the regulatory review of a new medicine, or a change to an existing medicine, there is an on-going dialogue between the applicant company and the MHRA. The applicant company explains the data, provides clarifications and answers questions based on the scientific evidence provided. Through such dialogue, the MHRA is able to make decisions on the safety, quality and efficacy of the medicine based on the totality of the evidence available and the proposed usage. For marketed medicines, companies and the MHRA need to maintain regular dialogue to ensure the medicine is used safely and effectively and the licence is kept in compliance with all the relevant regulations. Such dialogue takes place between companies and all major regulatory agencies worldwide.

6.16 A more specific example of where it is important that industry and the MHRA work together is the optimal provision of clear and effective information to patients about their medicines. This is occurring currently with industry representation on the CSM expert working group reviewing the quality of patient information leaflets.

6.17 Input from the Industry and other stakeholders during the drafting of guidelines is critical to highlight the practical implications of guidance in relation to current and future development standards, in addition to the ability to provide comments during the formal consultation stage. The ICH\(^ {11}\) process is founded on the basis whereby authorities and the industry from the US, Japan and EU work together to generate and harmonise regulatory guidelines that will be used in the three regions.

Areas for improvement

6.18 Not only is a strong, efficient and effective UK regulatory agency necessary for ensuring the safety of public health, it is also fundamental to drive a competitive locally based pharmaceutical industry that can develop medicines to better meet the needs of patients. The impact of the establishment of the EMEA on the European regulatory environment has been significant. Companies now have the possibility to select any one of the 25 Member States to assess their medicines. Experience shows that companies select European regulatory agencies that not only provide high scientific excellence, but also consider customer service and performance.

\(^{10}\) Review of all medicines to minimise the risk of transmission of Transmissible Spongiform Encephalopathies.

6.19 The MHRA is considered to be one of the 4 or 5 leading regulatory agencies in Europe. The MHRA has to ensure that it takes a leadership role in developing the future network of regulatory agencies, and dedicates sufficient resource and support to the European system. Findings in the National Audit Office (NAO) Report on the MCA12 indicated that the Agency would be looking to improve the quality of the services it provides to industry in order to attract more business.

6.20 AstraZeneca recommends that the Health Committee supports the ongoing development of the MHRA as the leading regulatory agency in Europe, assuming that this is the Government’s intention for the future role of the MHRA.

6.21 Greater transparency is being called for from regulatory procedures. The industry supports a robust and transparent regulatory procedure, but recommends that the Health Committee does not only consider transparency towards the public. Increased transparency for companies during the assessment process allows better understanding between the company and the MHRA of any issues, and results in more efficient processes for dealing with them. It also ensures that patients are provided with high quality, safe and effective medicines to combat diseases that would otherwise remain untreated.

7. PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY

7.1 AstraZeneca are committed to working with all Health Technology Assessment (HTA) bodies (NICE, SMC and AWMSG) to ensure equitable access to medicines. We are actively engaging with each of these bodies through a range of activities including submission of evidence, responding to consultations on matters of process and membership on a number of committees. In addition to providing information and technical expertise we are, via our work and interactions with each of the HTA bodies, able to share our experiences of best practice. Each of these activities are vital towards ensuring that clear and credible guidance is issued benefiting both patients and the NHS and ensuring equitable access to medicines.

National Institute for Clinical Excellence (NICE)

7.2 Since the conception of the NICE in 1999, AstraZeneca have played a key role in submitting data for both the appraisals and guideline programmes, participating in the consultations on NICE processes and representing industry on both the appraisals and guideline committees.

Health Technology Appraisals

7.3 To date, AstraZeneca have submitted evidence for five health technology appraisals and we are currently involved in preparing four further submissions.

7.4 AstraZeneca are committed to providing information to NICE in a transparent manner in accordance with the agreed framework on the use of confidential data. Industry submissions, such as those provided by AstraZeneca enhance the information available to the HTA groups. In addition to providing information on clinical data industry submissions include detailed information on cost-effectiveness including the provision of QALY values and in-depth health economic modelling. Information on NHS resource implications is also provided. In the case of new medicines, which are due to be appraised near to launch industry submissions may be the primary source of detailed information available to the HTA groups. NICE have themselves recognised the value of industry submissions in the appraisals process and did not adopt the WHO’s recommendations that the Appraisals Committee should be presented with a single set of analyses.13

7.5 In addition to submitting data AstraZeneca also critically reviews and comments on all appraisal documentation released for consultation with the view to ensuring the final guidance is clear, credible and robust.

Guidelines

7.6 AstraZeneca also actively contributes to the clinical guideline programme by both submitting evidence and critically reviewing drafts for a wide range of guidelines. In submitting evidence, in addition to providing details of current data, we also provide information on data/publications that will become available within the development time of a guideline—By doing so, the National Collaborating Centres can develop a final guideline which takes into account all the data which will be available at the time the guideline is published.


7.7 AstraZeneca are, however, concerned about the lack of appeal within the clinical guideline process. While stakeholders, including industry, are able to comment on the draft guidelines there is no course of action, which can be taken to challenge the final guideline.

**Representation on NICE committees**

7.8 NICE welcomes the contribution of pharmaceutical industry consultees on a number of their committees. Currently AstraZeneca represent the industry on a Clinical Guideline Review Group and have previously represented the industry on one of the Appraisals Committees.

7.9 It is our view that such industry representation enhances the depth and quality of the committee discussions.

**Processes/procedures**

7.10 AstraZeneca play an active role in developing and improving NICE procedures and processes, via both participation in consultations and also via membership of the ABPI’s National Health Technology Assessment/Clinical Guidelines (NHTA/CG) User Group. Our aim is to work with NICE to ensure that the NICE processes are efficient, fair and transparent and result in robust and sustainable guidance.

7.11 In working towards improvement AstraZeneca have participated in all NICE process consultations since 1999, including the recent appraisals Process and Methods consultation. We are currently responding on the recently announced consultation for interim appraisals.

**Implementation of NICE guidance**

7.12 We look forward to collaboration with NICE on the issue of implementation. In the review of implementation to date, AstraZeneca have provided information to inform the report produced by Professor Mike Richards.

**All Wales Medicines Strategy Group (AWMSG) and Scottish Medicines Consortium (SMC)**

7.13 AstraZeneca works closely with both of these groups via membership on the relevant ABPI User Groups and, in the case of the SMC, participation in appraisals. As Scotland and Wales are outside of the remit of the Health Select Committee we will not discuss our collaboration with these groups in detail but would be happy to discuss at a later date if required.

**Areas for improvement**

7.14 While improvements to NICE processes have been progressed since the Health Select Committee review there remains area where further improvements could be made. In focusing on these AstraZeneca suggest the following recommendations:

7.15 The Department of Health in conjunction with NICE, the Healthcare Commission, the NHS and industry continue to focus on implementation taking into account the recommendations of Professor Richard’s report.

7.16 NICE continue to address and avoid the potential issue of “NICE blight” in those instances where guidance will not be available at launch. We recognise the step taken by NICE to address this by working with the National Prescribing Centre on the production of drug monographs, however, we would recommend that NICE both work to actively direct the NHS to these monographs and monitor the effectiveness of these in reducing NICE blight.

7.17 NICE to provide clarity about the relationship between technology appraisals and clinical guidelines and the criteria used to define how technologies are assigned to each. We would particularly welcome further clarity and transparency on how the decisions to review and update existing HTA guidance within the context of a clinical guideline are made.

7.18 The DoH and the National Coordinating Centre for Health Technology Assessments review each HTA group for quality and consistency and ensure each has the necessary resource capability.

7.19 The Department of Health, Welsh Assembly Government and Health Department of the Scottish Executive review the processes of the three separate technology appraisal systems and, in order to avoid the current duplication of effort that currently exists both for the three HTA groups and stakeholders, devise a mechanism for sharing best practice.
AN OVERVIEW OF THE CLINICAL TRIALS AND PUBLICATION PROCESSES

A. THE CLINICAL TRIALS PROCESS

Introduction

AstraZeneca is committed to conducting clinical trials to international standards of safety, scientific and medical integrity. There are currently within the UK in excess of 30,000 regulations and guidelines that apply to the drug research and development process. AstraZeneca adheres to these, as monitored through a comprehensive series of internal checks and external quality assurance checks.

The R&D Process: A Highly Regulated Environment

The MHRA conducts statutory Good Clinical Practice (GCP) inspections. AstraZeneca (UK and Global) underwent such an inspection in November 2004 and it received very positive feedback on the quality of its clinical research organisation.

The Research and Development Process

Research and Development encompasses discovery, pre-clinical development, clinical evaluation (Phase I–IV), which leads to licence submission, and lifecycle development. It currently takes in the region of 10–13 years for a candidate drug to be licensed and to receive its marketing approval:

Currently approximately 10,000 chemical entities are investigated to successfully develop one drug through to licence approval. Of these 10,000 chemicals, typically 1,000 demonstrate the necessary biological activity, and only 10 proceed through to clinical trial development, only one of which will successfully receive approval.
The Clinical Trial Process

There are 4 key stages of the clinical trials process following successful pre-clinical development:
- Phase I: This stage is concerned most with safety of the candidate drug and examines the pharmacokinetics of the drug in healthy volunteers (usually 10–50 patient studies).
- Phase II: This stage is examining safety and efficacy of the drug in diseased patients (patient numbers in the 100’s). Within this stage dose-ranging studies are conducted.
- Phase III: This stage examines the efficacy and safety of the drug in much larger populations of diseased patients, usually numbering thousands.
- Phase IV: These studies examine the licensed drug in large everyday settings and populations and may compare the drug with appropriate competitor drugs (possible in Phase III as well).

The Clinical Trial

There are several key phases in a clinical trial from design (involving external investigators), approval from relevant authorities and ethics bodies, study set-up, patient consent and enrolment, treatment, data collection (throughout), data analysis, report writing, and publication (which is reviewed in depth below). Depending upon the treatment period a single study will take a minimum of several months to complete the cycle; most will take in excess of two years and many will take considerably longer:

Key milestones in clinical studies

- Protocol Approval
- First patient enrolled
- Last patient enrolled
- Last patient last visit
- Database lock
- Report approved
- Study start-up
- Patient enrolment
- Treatment period
- Data clean-up
- Analyses & report writing
- Statistical analyses available

24.5 months

Source: CMR International

At each stage of the study design and clinical trial there are numerous patient safety, data quality and process review checks to ensure that high standards of scientific, medical and ethical integrity are being upheld. Herewith a schematic representation the quality control and quality assurance to AstraZeneca studies.

In-Process Quality Control

Data Checks

Document Review

Monitoring

Document Review

Audit

Audit

Audit

Audit

Independent Quality Assurance

It is normal practice for large-scale trials to have independent data safety monitoring boards (DSMB) that comprise independent statisticians and physicians of international renown. Their role is to monitor the safety and efficacy outcomes of the study on an ongoing basis, and to validate the statistical analysis and interpretation of results.
AstraZeneca has had a long standing publication policy. It is AstraZeneca policy to encourage the appropriate communication of information on its products and research and development activities to the international medical and scientific community and AstraZeneca endeavours to publish the results of all its clinical trials.

Below is an illustration of how a manuscript is developed for submission to the *Lancet* for publication. This demonstrates the lead and accountability for authorship taken by the study Steering Group and the input of AstraZeneca at both the review stage before submission and before *Lancet* editorial review.
Further information is provided in the following section on the publication process.

B. THE PUBLICATION PROCESS

The AstraZeneca Philosophy

AstraZeneca is committed to providing healthcare professionals and patients with relevant information that enables them to make the best treatment decisions. To that end, scientific and medical publications are an important means of communicating the results of the company’s research and development. Hence, AstraZeneca has put in place a mandatory Publication Policy that outlines the company’s principles with regard to external communication of scientific and medical information. Specifically this policy describes the company’s aim to publish the results of AstraZeneca-sponsored clinical trials; our commitment to maintain high standards of medical and scientific integrity by presenting results in an accurate, objective and balanced fashion; and states that selective publication that would misrepresent the medical profile of an AstraZeneca product is not acceptable (ie, we must not selectively publish only those trials that have a positive outcome for AstraZeneca products and suppress those that appear unfavourable). Compliance with this policy is formally monitored.

Relationship between AstraZeneca and External Investigators

AstraZeneca works in collaboration with external investigators in the design and conduct of a clinical trial, and in preparing publications from that trial. Whilst AstraZeneca plays an important role in coordinating the publication process, the lead author (usually an external investigator) will play the major role in terms of publication content. This is only right and proper since it is that lead author who through authorship takes public responsibility for the overall design, data and conclusions in the publication.

External Publication Guidelines

There are a number of well-established external guidelines developed by professional bodies to improve the quality and ethical transparency of publications. Probably the best known are the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (www.icmje.org). Publications on AstraZeneca-sponsored trials in biomedical journals follow the ICMJE guidelines and in addition will comply with individual journal’s policies and Instructions for Authors.

Data Access and Analysis

The database for a clinical trial is usually created and maintained by the pharmaceutical company. Expert AstraZeneca statisticians and programmers are responsible for managing these trial databases. To give a sense of the size and complexity of these databases, for just a single AstraZeneca trial (Exanta, SPORTIF III) there were 12,500,000 pieces of data collected that resulted in 200,000 pages of study data. Once the trial is completed, AstraZeneca would supply authors with the statistical tables and figures that relate to any planned publication.

It is normal practice for large-scale trials to have independent data safety monitoring boards (DSMB) that comprise independent statisticians and physicians of international renown. Their role is to monitor the safety and efficacy outcomes of the study on an ongoing basis, and to validate the statistical analysis and interpretation of results. In the Exanta study quoted earlier, the DSMB reviewed all data monthly on an ongoing basis throughout the trial.

Despite the safeguards afforded by rigorous internal and external quality controls, some critics remain concerned that the pharmaceutical company “owns” the database. AstraZeneca believe they have nothing to hide. For registration trials, AstraZeneca routinely make the electronic database available to registration agencies such as the FDA, and have complied with requests from medical journals for a further additional independent statistical analysis as part of the journal’s peer review process.

Authorship

The authorship of publications carries significant responsibilities and must be approached in a rigorous manner. For any publications involving AstraZeneca-sponsored trials, authorship is determined by strict criteria contained in ICMJE guidelines. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. In particular, authorship credit should be based only on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Conditions (1), (2), and (3) must be met. Hence, it should be clear that the practice often referred to as “gift” authorship is not acceptable practice within AstraZeneca.
Where AstraZeneca scientists, physicians and statisticians have played an important part in a study (eg, the conception and design, or analysis and interpretation) they will also be listed as authors. We continue to do this because we believe in transparency despite disturbing evidence that declaring competing interests negatively affects readers’ perceptions of studies in terms of their importance, relevance, validity and believability (BMJ 2004, 328, 742–743).

AstraZeneca believes it is proper for company authors to engage with external authors in discussion on sound scientific grounds, but that there should be no attempt to influence inappropriately the scientific or medical opinions of these external investigators.

**Role of Professional Medical Writers**

Ghostwriting is the practice whereby someone other than the named author (eg, a professional writer) has been responsible for preparing the publication, typically with little or no involvement from the named author, and the contribution of the actual writer—the “ghost”—is not disclosed. AstraZeneca does not support “ghostwriting”. However, we do believe that professional writers have a legitimate role to play in assisting authors, providing any such collaboration follows ethically acceptable practice.

In an ideal world, the scientists, statisticians and physicians who were involved in design, conduct and interpretation of a study should be the people preparing the publication. However, the best clinical investigators do not necessarily make the best writers. They may lack the time, expertise or language skills to produce a well-written publication promptly (for example, many of the investigators will not have English as their first language). In these circumstances, most pharmaceutical companies, including AstraZeneca, may use professional writers and editors (internal staff or agency/freelance) to assist in publication development. The use of professional writers may be particularly helpful to aid the process of publishing results from large multicentre studies involving many contributors.

AstraZeneca believe that the named authors must retain responsibility for the article’s content, this is achieved by the named authors being fully involved from the outset; the principal author should determine the extent of involvement of professional writer and, importantly, surrenders no responsibility for the content of a manuscript by accepting this help; and finally there must be no attempt by the writer to manipulate the opinions of the named authors.

If pharmaceutical companies did not provide this service to external investigators, a number of negative consequences are likely. Namely, publications would take longer to get out into public domain; more publications would be rejected because of poor quality; some publications would never see the light of day—individual investigators would have little incentive to publish “worthy but dull” studies; critics believe there is publication bias in the medical literature now—this situation would worsen if pharmaceutical companies did not provide writing or editorial support to busy clinical investigators.

**Acknowledgments and Disclosures**

It is AstraZeneca policy to ensure adherence to the principles of good publication practice that are described by International Committee of Medical Journal Editors (www.icmje.org) and hence all authors should provide details of any conflict of interest, or financial support/financial connections to the work. Again, we continue to do this because we support transparency despite evidence that this declaration unreasonably biases readers’ perceptions.

**Products Withdrawn from Development**

The pharmaceutical industry is often criticised for not publishing clinical studies that cease to be of direct commercial relevance to them. Since the merger of Astra and Zeneca in 1999, we have withdrawn a number of products from development. One such example is Viozan (sibenadet), a dual dopamine D2-receptor and beta2-adrenoceptor agonist that was being developed for treatment of chronic obstructive pulmonary disease. The lessons learned from this failed development were published in a supplement to Respiratory Medicine. The following quotation from Stephen Rennard MD in the introduction to that volume (Respiratory Medicine 2003, Volume 97, Supplement A, pages S1–S79) underlines our ethical policy to share information with the whole medical and scientific community.

“Finally, many drugs that fall in development for one reason or another do not result in compiled publications such as this. AstraZeneca is to be commended for recognising the value of the lessons learned from the sibenadet development programme and for helping to make them readily accessible through the development of this supplement.”

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Ev 292  Health Committee: Evidence
Q659 Chairman: Good morning. Can I welcome our witnesses and express the Committee’s appreciation for your co-operation with our inquiry and the written evidence which you have supplied. Can I ask you each briefly to introduce yourselves.

Dr Patterson: I am John Patterson and I am Executive Director of Development for AstraZeneca in the UK.

Mr Gray: I am Eddie Gray, the General Manager for GlaxoSmithKline in the UK.

Mr Brinsmead: I am Chris Brinsmead and I am the Senior Vice President and General Manager, and Marketing Co-President, and Executive Director, Development, AstraZeneca, were examined.

Q660 Chairman: Can I begin by asking a question, which in a sense is at the heart of this inquiry, which is achieving the balance between the commercial imperatives that you people have to work to and the business issues that you have to address and the wider public health concerns that we have had put to us during the course of this inquiry. I am sure that you will probably have looked at some of the evidence that we have had so far and understand the kind of tensions that we are addressing: that, from a public health perspective, the concerns occasionally that the public health interest is not served well; concerns on the other side that obviously you are a major, a key player in the UK economy and a very important employer of very many people. How do we achieve this balance that kind of is at the heart of the issues we have addressed in this inquiry?

Dr Patterson: I would like both to echo, Mr Chairman, you could give us an opportunity to add one or two things of my own. I am a physician by training. I joined this industry 30 years ago and was prepared to bring a perspective, the concerns occasionally that the public health interest is not served well; concerns on the other side that obviously you are a major, a key player in the UK economy and a very important employer of very many people. How do we achieve this balance that kind of is at the heart of the issues we have addressed in this inquiry?

Q661 Chairman: I am sure you will want to make those points as we go on with some of the questioning?

Mr Gray: We will try to do so, yes.

Q662 Chairman: Does anybody from AstraZeneca want to add to that?

Dr Patterson: I would like both to echo, Mr Chairman, what Eddie Gray has said, but also to add one or two things of my own. I am a physician by training. I joined this industry 30 years ago and the reason that I come to work every day along with my 60,000 colleagues in AstraZeneca is because we believe that many of the objectives of public health are shared by ourselves. In fact we are not working in the opposite direction in terms of treating disease and preventing disease wherever possible, so it is the desire actually to find new medicines and improve public health that makes most of us excited and interested in coming to work every day. Yes, we do it in a commercial environment, but that does not necessarily put us at odds with the Government and there are lots of good examples where the Government’s priorities, the key areas, whether it is coronary heart disease, mental health, are exactly in line with our priorities for developing new medicines. Something like just under half of the new medicines introduced in this country in the last 10 years fit with those key priorities that the Government has expressed.

Q663 Chairman: So with your medical background then and your past experience, do you feel that the balance that I referred to is struck about right at the present time or should it be shifted in one direction or the other from your own standpoint?

Dr Patterson: I do not think there is a balance at the moment. I think in the last two or three years things seem to have gone completely out of balance...
in terms of public perceptions, in terms of people taking some seemingly very polarised stances in these areas, so I think it is useful to have a discussion about where the balance should stand. We are going through a period of dramatic change, a dramatic desire from patients and the public for more openness than there has been previously, a desire for perhaps the risk:benefit ratios to be different from how they have been perceived previously, and I think it is time to have an open dialogue about those kind of things and see how we can work together going forward.

Mr Gray: I would just support that point. I was particularly struck in one of the previous hearings of that disease and what the current problems of that disease are does not always fit well with the 21st Century public values. I think within the industry I support John’s comments and I think there is a feeling that actually the expectations have shifted quite quickly and quite significantly and to some degree trying to catch a train that is already moving is the kind of experience that most people would feel some commonality with.

Q664 Mr Jones: I was going to raise this later, but, Dr Patterson, you just spoke about the balance having moved very rapidly in the last couple of years. Could you reflect on why there has been that change and why it is not a change which is peculiar to the attitudes that people have of the pharmaceutical industry in this country? I note from a poll conducted in America that confidence in the industry and the public perception that the industry is doing a good job has fallen from 79% of the public in 1997 to 44% of the public now, a huge change in a very short period of time and the conditions in the United States would seem to be very different from the conditions in this country, so why?

Dr Patterson: I do not know that I have all the answers, but I can try and give you my own perception. I think health has become a much, much greater topic in the media than we have ever had previously. Every time you turn on the television or the radio, even the major news programmes are covering significant health issues, so it has become a much more public topic than ever previously. There is a tendency of course to polarise and things are either, certainly from our perspective, wonder cures or killer medicine and there is very little seemingly in the middle. Therefore, every time something happens in our world, a new medicine is introduced, there is a huge media outburst, shall I say, associated with it and, equally, when something happens with one of our medicines, that is also very much more public than it ever used to be. One of the issues that I think is that as we bring very effective, modern, potent new medicines to the marketplace, inevitably we are starting to see more evidence of issues of tolerability and side-effects. It is certainly true that as you innovate, you do not always know from either the laboratory work or from the clinical trials exactly what the profile of the medicine is and we have had a number of high-profile failures as an industry over the course of the last few years which have been very, very visible in the public domain, particularly as they got picked up often early in their life and perceived as being the next panacea, if you like. There is a more rapid rise and a more rapid fall going on than we have ever seen previously and these issues have been debated and people are not well versed, as we know, in many fields in talking about relative risk, so when there is an issue with tolerability of a product, to try and put it in the context of how many people are dying of that disease and what the current problems of that disease are does not always fit well with the 20-second soundbite on television.

Q665 Chairman: What you are saying then, Dr Patterson, in a sense is that perhaps the increased media awareness of, and interest in, health has a bearing on your industry’s image. I was going to move on to one or two comments that we have picked up on perceptions of the industry’s standing. There was somebody from Mr Gray’s company who was quoted in a conference recently who likened the industry’s standing to that of big oil or big tobacco firms, and I think you may recall that reference. Richard Sykes said to our Committee when he gave evidence that the industry is getting, “a very bad name, possibly because of its competitive nature”. Now, the impression that Dr Patterson is giving us is that perhaps this is an unfair image and these comments arise very much because of the media’s focus on health, but is there some justification for this image and one of the reasons for the image that appears to be one that is fairly widespread?

Mr Gray: I think John makes a valid point about the publicity and the impact that has and I think he does make an extremely good point around the concepts of risk and benefit. If I can simplistically put the position, society’s attitude is, “This is a huge change in a very short period of time and the conditions in the United States would seem to be very different from the conditions in this country, so why?”

Q666 Chairman: So to pick up that point and your point earlier on about engaging with the patients, what you are implying is that people need to understand more about the industry, but I would come back and say that perhaps the industry needs to be more transparent, so how could it become more transparent and more engaged with the people it serves?

1 Note by witness: “mark down” is used in this context to mean to view negatively, rather than simply to take note of.
Mr Gray: I think in terms of what I was trying to say earlier about a kind of moving train and trying to catch that, I do not think I would argue about that as a direction. I think it is how we balance that movement against the fact that the situation is not any less complex than it was, so we are having to do that in an area that remains. It is still science and it is still the balance of risk and benefit that has to be assessed, but I do not think I would argue with that. I think a positive thing is that having realised that that train is on the move, we have started to respond, so I think the most obvious example of that would be the clinical trial registers, et cetera, and it is a little disappointing that that then gets reported as some kind of PR exercise when I actually think it is a genuine attempt to respond to this kind of new expectation and agenda. I think as a broad principle, how do we move forward, improving the kind of transparency and scrutiny, but doing it in a way where actually we can still arrive at good public health patient-centred risk/benefit balances absolutely is the broad challenge and doing it in a way which allows the industry to be an adult in that and play its role, not that the only way is to exclude it in some way or fence it off, I think that is the challenge, I would agree.

Q667 Dr Taylor: Can we move on to information and the promotion side. The industry has got codes and standards that relate to the control of the quality of drug promotion. Are there any controls on the quantity of drug promotion? Witnesses have told us in other sessions that whereas research staff in companies are only increasing very slowly, marketing staff are increasing extremely rapidly. Have you any comments on that? Are there any controls on the actual quantity of promotional material you can use?

Mr Brinsmead: I think the first thing to say is that if they are talking about the number of people employed in research and development and marketing, in our company, broadly speaking, those numbers have remained broadly consistent over the last sort of five to 10 years, so I am not sure that would be true for AstraZeneca. In answer to your question around the amount of promotion, the quantity as opposed to the quality, there are limits on that both in the code and in companies, so, for example, the number of times that we can visit a general practitioner in a year is prescribed by the code, so we do not have any limits, as far as I am aware, on the amount of material that we may provide, and the material provided would obviously be down to what material you need to provide to explain the disease and some of the ways that the product works.

Q668 Dr Taylor: So the number of visits to a particular general practitioner is limited, is it?

Mr Brinsmead: Yes, it is, by the code of practice.

Q669 Dr Taylor: And the amount of money that the representative can spend on hospitality, is that limited too?

Mr Brinsmead: I think, talking about the question of hospitality, we would only provide any hospitality if it was in association with a scientific or an educational meeting, so to give an example, it may be that a sales representative would have a meeting with some GPs at lunchtime and in the case of our own company, we would limit them to spending no more than £10 on the sandwiches and drinks that they would provide at that meeting for the GPs, so yes, there is a limit, but I would make the point that hospitality is really just secondary. The purpose of the meeting is to talk about the medicine and how it might be used.

Q670 Dr Taylor: Any other comments?

Dr Dollow: Maybe I could give a bit of context about the development process because I think I would echo Mr Brinsmead’s comments that the number of medicines in development in GSK has increased rather than decreased, so the R&D expenditure we expect to have increased, so although I do not have exact figures, I do have figures on the number of medicines in the pipeline which has increased since the time of the start of GSK. At the moment GSK spends 40% of its R&D in the UK, about £1 billion, and 6,000 employees are working in R&D in the UK. Additionally, we recognise that many of the products which are coming through in our pipeline actually have a very high attrition rate, so only one in 10,000 of the compounds that are synthesised will get to the marketplace to be medicine and only one in 10 that gets into man will be a medicine, and I think that is an important one to remember as well.

Q671 Dr Taylor: So that is your firm—6,000 in R&D?

Dr Dollow: That is correct, yes, in the UK.2

Q672 Dr Taylor: How many in marketing?

Mr Gray: In marketing, maybe about 120 or something like that, 120 or 130. There is one other point, if I may, or viewpoint of this which I think is worth thinking about and that is to kind of put the position of activity and promotion within the context of what actually seems to be happening within the UK as a health service and if I look across that big picture, then I see the rate of generic prescribing at 78% and a target of 85; and I see the uptake of new medicines generally because one of the slowest in western Europe, and acknowledged by everybody as being the case. The last time I appeared before this Committee it was about NICE and one of the recommendations was about implementation because NICE was making recommendations, so here it is effective and safe and it is cost-effective to the National Health Service and we still cannot get it taken up, so the broad picture would not suggest that the level of promotion is bracing things away in any one direction. The big picture tends to suggest that the checks and balances are working pretty well.

2 Note by witness: The figure of 120-130 refers to GSK’s UK Operations, ie those involved in marketing to the NHS.
Q673 Dr Taylor: Is it because we in this country are slightly more cautious than other places?
Mr Gray: Well, I would take your advice, as a medic, on that!

Q674 Dr Taylor: Witnesses in previous sessions have suggested that some drug firms are guilty of having a drug and actually looking for an illness, an extra illness for it to work on. Are there any comments on that?
Dr Dollow: Maybe I could respond to that. For any medicine to be approved, it has to be treating a valid condition, so any condition that we seek to investigate has to be a condition that is recognised internationally, otherwise the regulators will not approve it. I do not recognise the fact that people are suggesting that we are inventing diseases. That is not something that we would do. Any medicine that we have which has an indication is certainly related to an indication which is well recognised by the medical community.

Q675 Dr Taylor: We have got here two of the largest and, hopefully, most reputable firms. Do you think any of the other ones are trying to popularise an illness among people so that one of their drugs would be used more? That is the sort of thing people have suggested to us.
Dr Patterson: Can I come in on top of what Stuart said. There is, first of all, a licence and anything that any company sells has to be within its licence, otherwise it is breaking the law, and those licences are given for specific diseases which are usually within what is called “ICD”, the International Classification of Diseases, so they have to exist to get a licence. Now, it is certainly true that in order to make it more acceptable sometimes for patients to talk about their disease, we may give them a nicer name as an industry, and I will give you an example. No male around this table, I am sure, wants to say, “I’ve got impotence”, but by calling it “erectile dysfunction”, it has become a little bit more acceptable, but we did not invent erectile dysfunction; impotence has been there for centuries and is a considerable issue for many people. It is maybe part of the semantics of giving it a nicer name, but you cannot invent a disease against which you promote a medicine in this country because we have licences.
Mr Gray: I think in watching all the tapes of the earlier hearings, this is perhaps the kind of thread of questions which has actually left me most confused, if I am honest, and I think that there has been a degree of confusion as to what are the kind of accusations, so to speak. I think this one about inventing diseases has been answered and I will not touch on that, but the other one has been this idea that it is the industry or certain members of the industry in some way trying to kind of expand the criteria by which patients gain inclusion. I think clearly there are separate conditions, if I look at the ones that we are involved in, where the symptomatology is clear and either you have this disease or you do not or there are well-established tests for asthma, et cetera, to test lung function, et cetera. I think the other thing which is changing a lot now which again is important is that the National Health Service itself, either through national service frameworks or through the GP contract, is actually setting the target and the standards which apply, so if I think about Type 2 diabetes, for example, within the GP contract they are targeted to have all Type 2 diabetes patients at 7.4%, so there is absolutely no credibility whatsoever in me going out and arguing that it should be 5%, so I think there is again in the way in which individual disease comes forward to a doctor, supported now by things like NICE guidelines, NSFs and GP contracts, et cetera, clearer definitions than there have ever been as to what constitutes an individual condition.

Q676 Dr Taylor: Can you give us any idea of when a major drug is invented and discovered for one particular illness and quite legitimately it is discovered that it has actions on other things? I am thinking particularly of the hypotensives that were discovered to work well for prostatic hypertrophy. Have you got any idea of the sort of proportion of money your firms make from the big blockbuster discovery as opposed to the sort of creeping growth on to the other indications?
Dr Patterson: Perhaps I can try and answer that, not quite in the terms you put it. Most medicines get into the marketplace for a licence in a single indication. We then continue to work with that product throughout its life cycle, often looking at new indications, new formulations, new ways in which it can be of value to patients. It is quite common for medicines to be used ultimately more in an indication that was developed later on. An example would be the angiotensin-converting enzyme, the ACE inhibitors, which started off as anti-hypertensives and then went into heart failure where they are used fairly uniquely and are successful. Our job is to continue to do that and, for instance, this year on a global basis AstraZeneca will spend about 40% of its total clinical development budget on actual life-cycle management of products that are in the marketplace, so it is very common for us then to look at the indications and we have to do that into special groups who are not indicated in the first licence. There were papers, I think, in The Lancet at the end of the 1990s which showed that something like half of the top 20 medicines in the world are actually being used more for indications that came after they had been put in the marketplace than their first indication, so it is an ongoing process. We live with these products for the whole of their life cycle to the point where they go off patent and disappear or are superseded.

Q677 John Austin: I was tempted to ask Mr Gray if there is any empirical evidence that watching tapes of proceedings of this Committee might be a cure for insomnia! My real question is directed to Mr Brinsmead because in your marketing campaign for Crestor entitled “Right First Time”, you mention the desire to exploit the emotions of
prescribers. I wonder if you could explain that and perhaps describe other means of stimulating the use of your products.

**Mr Brinsmead:** Perhaps I can just take a step back and say that heart disease and problems like that are a government priority and clearly having a high level of lipids is something that the Government and doctors and patients want to reduce because you can prevent heart attacks and strokes, so we are very proud that we have a statin called Rosuvastatin, which we brought to market a couple of years ago that does this more effectively than the statins that are already in the marketplace. Now, if you think about why people make a prescribing decision, well, they will make a decision on a rational basis and they will think about the data, they will think about the patient in front of them and what this patients needs to do. However, doctors are also human beings like anybody else and they have feelings and needs and what we find in the emotional sense is that it is important that we understand how people feel so that we can actually make sure that the messages we give them are appropriate. If I gave you an example, if someone was saying that they were feeling a bit cautious, a bit uncertain, and we talked earlier on about whether English doctors were perhaps more cautious than their counterparts in other countries, then it is important that we make sure we provide all the tolerability data and the safety data to try and address that feeling. I think the emotional aspect of the marketing is particularly important.

**Dr Patterson:** I think there is an emotional reaction in this country against using new medicines. The Government’s own figures show that in things like coronary heart disease, only a small percentage of the patients who should be receiving those kinds of medicines are doing so, so you have to look at what it is that is part of the decision-making of that doctor and appeal to the relevant senses.

**Q679 John Austin:** Could I go back to the issue of companies to get new drugs on to the market fast, but I think from something Dr Patterson said earlier, should we not be concerned about the intensive promotion of new drugs which typically follow the launch of a new product when we are not really sure of the side-effects or long-term effects of the use of that drug?

**Dr Patterson:** I think all new medicines carry potential risk because new medicines are effective and they hit pharmacological systems, some of which we do not fully understand. I think it is very important though that we, as an industry, who have spent the last 10 or 11 years developing those medicines, are the people who can carry that information in to the doctors and allow them to make an informed decision as to how that new medicine might fit into their therapeutic armamentarium compared with something they have been using previously. The issue that you raise is the intensity with which we do that and I am not sure on what basis we are saying that we are any more intense than we used to be in that activity. I think we often have more data, so if you take the medicine we are talking about here, whereas when I first started working in this industry at the most 1,000 patients would be treated prior to a licence, while with Crestor we had something like 30,000 patients treated in clinical trials before we came to the licence, so we knew a lot more about it than we did with medicines coming in 10 years ago, so there is a lot of data and a lot of information to be shared, all of which did not exist in the textbooks when those doctors were trained and none of which are pieces of information that they will have seen previously or the people whom they work with in hospitals will have seen previously, so we have to carry that information and that requires some kind of a process for getting that message across.

**Mr Brinsmead:** Sadly, in this country only about half of the people who should be treated and achieved the levels that the Government’s targets stated, only about half of the people treated reach those targets, so there is a positive outcome of intensely promoting a new medicine and that is if you can actually prevent more people having heart attacks and strokes, that must be a good thing. The other thing I would like to say is that there is the Black Triangle system in this country whereby all new medicines have a black triangle and that is an indication to the healthcare professionals that if they see any side-effects, they must be reported to the regulatory authorities, so there are ways with a new medicine where the safety of the patients and the safety of that particular medicine are picked up through that system.

**Dr Patterson:** And the data show that Britain is still the slowest to take up new medicines in Europe. We take up new medicines at about the same rate as Croatia, so again we may be being intense in your eyes, but the reality is that the speed of uptake of new medicines in this country is slow.

**Q679 John Austin:** I can understand the desire of Crestor. In July 2004 you developed a PR campaign to reinforce the positive risk:benefit profile of Crestor when a month earlier, in June, the MHRA had issued new prescribing advice for the 40mg dose and a revised pack insert had been introduced presumably because there was more awareness of risk. Why, a month after that was identified by the MHRA, did you have a positive PR campaign to reinforce the positive risk:benefit?

**Mr Brinsmead:** Well, let me talk a little bit about that. I think the fact is that as we launched Crestor and as we got more experience in the marketplace, it became clear to us that the drug was not always being used appropriately at the correct start dose and we actually had a series of campaigns, not just the PR campaign that you refer to, but also we worked very closely with our sales team and very successfully to make sure that the drug was used at the correct start dose. I do not think that there is any negative implication of having a PR campaign aligned with a change to the prescribing information of the MHRA. I think it is important that we, as a company, when we get the
information on the drug when there is a change, we make sure that we tell people about that very, very quickly.

Dr Patterson: We are actually very proud of that campaign because the start dose for Crestor has always been 10mg in this country and quite a significant number of patients, who are often patients who are having side-effects from other statins or failing to get control, were being put on by doctors at higher doses than 10mg, so exactly in line with the agreement with the MHRA, we actually went out with that campaign and made sure that people started at 10mg and we have reduced the number of patients on the higher doses in this country by a significant number, and we can show you the data, as a result of that campaign. PR is not always bad, sell, sell, sell, but PR can actually be about the proper use of the product in the right circumstances for better patient safety.

Q680 John Austin: Can I go back to something you said earlier about when there was a discussion about the media and the way in which the pharmaceutical industry may be now viewed because of high-profile and perhaps exaggerated claims in the media, for example, “New blockbuster drug—miracle cure”, et cetera. You seem to be suggesting that the media were at fault here. Is not the industry sometimes at fault by having sort of over-inflated claims for some of its new products? Perhaps I could put the question back to AstraZeneca and let’s take Iressa, an innovative cancer drug which you say in your evidence to us has been described as “the biggest advance ever in the treatment of lung cancer”, yet I understand that last month the Food and Drug Administration indicated it was considering withdrawing Iressa from the market after the drug had failed to prolong the lives of people with advanced lung cancer. Are there any lessons which we should draw from this?

Dr Patterson: Well, there are lots of lessons and I could spend a long time talking to you about them. Let me come back to your first point though, that somehow I had implied it was all the media’s fault which I think the Chairman said in response to my first answer. I am not saying it is the media’s fault. I am saying it is an outside world that has changed and that that activity is going on and, therefore, that is why there is so much visibility of what is happening with our products. Let me now switch to Iressa. It is a classic example of where sometimes we are damned if we do and we are damned if we do not. Perhaps later on you will be talking to us about only doing me-too products. Well, here is a very good example of something that is an absolute breakthrough product, brand new type of agent, an EGF (Epidermal Growth Factor Receptor) tyrosine kinase inhibitor, based on very good pre-clinical science and brought to the marketplace in Japan and the USA and a European licence applied for. The early data showed some dramatic responses in patients with lung cancer, many of whom had failed all previous therapies, actually having a complete regression of their disease and some of them going on to live for several years on this product and with very few side-effects, which is something that just does not happen spontaneously. In the open studies in third-line usage in previously failed patients we saw and we treated something like 70,000 patients, stabilising disease in about 40% and about 10% of them giving a very significant response. Now, interestingly enough, there were certain sub-groups who showed a very good response, in particular females and oriental people, Asian people particularly from Japan. We then achieved a licence in the United States under a system that does not exist here, called “Sub-part H” in their procedure which allows you to enter the marketplace while undertaking what are called “the definitive trials”, and in this case the definitive trial was a placebo-controlled mortality or survival study in a very significant number of patients followed all the way through to death. That study was undertaken and unfortunately, (in spite of some of the evidence you have had, to the contrary) our studies are designed to give both positive and negative outcomes, they are balanced, this one showed that although there was the same response rate as we had seen previously, the same time to treatment failure, the survival benefit did not reach statistical significance. As a result of that, our European licence, which was under review, was withdrawn and we had further discussions with the Food and Drug Administration and we will go through some advisory committee processes as to whether it is appropriate to continue to sell that product. We have withdrawn all of our marketing support of the product while those discussions are ongoing. Interestingly enough, within that there is a sub-group of patients from South-East Asia who had a very good survival benefit, some 22%, so we are learning a lot about it. During the course of last year some doctors in the States described some mutation changes that seemed to associate with those people who were getting these very good proven responses, so it may well be we will be back later in the year to say that there is now a sub-group of patients whom we can identify who actually will be the correct sub-group of the population to give this agent to and who will much more likely get survival benefits. It is a rather long answer, but it is a classic example of how we, as an industry, develop modern, very potentially effective, but completely unknown medicines, the kind of issues we can get into and the kind of science we have to keep putting into these products over many years to get all the right answers.

Q681 Dr Naysmith: Maybe the question I am about to ask is perhaps related to what you have just been saying in terms of the information you get from clinical trials, how they are designed and so on and how you get the right answer because we have heard quite a lot of evidence here to suggest that the design of clinical trials and the manipulation of the results is sometimes done in a way which favours the product which is about to be launched,
things like what you actually test the product against, how much you put into negative results, how many negative results are published and that sort of thing. Perhaps Dr Dollow, who must have had a lot to do with a number of clinical trials, would like to suggest, if there is this criticism of the way clinical trials have been carried out in the past and you agree with it, why people, patients and clinicians, should trust the information they get from you in other ways?

**Dr Dollow:** Well, I think it might be helpful if I explained to the Committee how we design our overall clinical development programmes. When we are looking at a potential medicine before it actually gets to even getting to a pill that a patient might take, the programme is designed, first, to see if it has acceptable efficacy and safety in the target that we want and then we design the programme, saying that assuming that these are going to be correct, we will look at our phase two, for example, dose-range finding studies and then our phase three studies. All of these will be pulled together and seen as a global programme. We discuss this programme with regulatory authorities across the world and we discuss it with experts in the field to say that in some cases with some of the studies there is a need to prove that the product has some efficacy, and those will be, for example, placebo-controlled studies. In other cases, it is important to see the incremental benefit that a medicine may bring and those will be comparator studies, and the way we choose our comparators would be looking at which are important medicines which are being used across the world, so because all of our studies or the bulk of our studies are multi-national studies, something that is important in one market may not be important in another market, so we will look at that in the round. The other thing you talked about was around disclosure and, just to reinforce the point that Eddie made earlier regarding the clinical trials register, every single one of our studies for our medicines from the earliest clinical pharmacology studies in healthy volunteers through to every single clinical study that is done subsequently will be made available on the GSK clinical trial register at the time that medicine is first launched, and then subsequent studies will be publicised within 10 months of each study finishing.

**Q683 Dr Naysmith:** I am not saying it is necessarily your fault, but that in this whole process what sometimes obviously happens, and some of our witnesses have told us this, is that results are cherry-picked out of a pool of possible results to establish the effectiveness and sometimes the safety of products and others which might be used for other purposes are kind of ignored and sidelined.

**Dr Dollow:** All I can tell you is our position, that, firstly, we endeavour to publicise the results of all of our studies, be they negative or positive, and, secondly, the clinical trial register will put an equal footing on that for all of GSK’s studies from the year of the start of GSK in 2001.

**Dr Patterson:** Perhaps I could just add a couple of things to that. First of all, when we apply for a licence to sell a product, we submit data on every single patient who has been treated with that product in positive or negative studies, the whole lot, so there is absolutely no selection, whether it is on efficacy or safety, and all licences, therefore, are granted on the totality of the evidence.

**Q684 Dr Naysmith:** So where do you think this comes from, that witnesses have been telling us that sometimes there are negative results which are not published?

**Dr Patterson:** Once the product is in the marketplace, then we continue, as I said earlier, to undertake clinical trials and we have had a policy within AstraZeneca now for a number of years that we want and then we design the programme, first of all, when we apply for a licence to sell a product, we submit data on every single patient who has been treated with that product in positive or negative studies, the whole lot, so there is absolutely no selection, whether it is on efficacy or safety, and all licences, therefore, are granted on the totality of the evidence.
anything else. Post-marketing, then you can do
head-to-head comparisons and most of our
products that are coming to the marketplace now,
unless we have done a head-to-head comparison
with the market leader, and that can be, by the way,
by volume use as well as by value and I suspect
Naproxen is still probably, by volume, the market
leader, then we are not going to get on to
formularies and get acceptance.

Q685 Dr Naysmith: Well, that brings us on to
another topic which, I must say, has really
surprised me since we started this inquiry, which is
the question of ghost-writing and looking around
for clinical scientists and medical scientists who
have the reputation to put their names on papers
which carry data which they themselves have not
had very much to do with and may even know
nothing about. Do you think that this practice is
widespread?

Dr Patterson: It is absolutely not practised in my
company. We have a set of publication policies that
we have had in place for a number of years and we
work with doctors in the outside world in our
clinical trials. Perhaps I can take a step back and
just give you an example which I brought with me
from a phase three clinical trial that we ran on an
anti-coagulant. It was undertaken in 260 hospitals
with some 3,400 patients. The amount of data that
generates is staggering, with 16,000 events
monitored, 30,000 blood samples, 50,000 patients
visits, a total of 12.5 million data points. We then,
as the company, analyse, collect that, quality-
assure it by AstraZeneca personnel to make sure
the data are correct at the hospital sites, and we
then turn it into a report that is some 200 pages
long. Those kinds of studies we start by having a
group of doctors working with us or an individual
who will help us design the study and they will stay
with the study throughout. We will often have a
separate data-monitoring or safety committee
which will look at the data to make sure we are
doing no harm during the course of it, and at the
end of it we do employ professional writers within
the company to turn that 200 pages into a draft
publication, but it is done with the people who are
going to become the authors and they have the
opportunity to question and challenge every single
conclusion and every single table that is put in
there. At the end of the day they have a
responsibility, just as we have the responsibility for
getting the analysis right, in putting their names to
it to say that they have taken adequate care and
worked with us to deal with it, so that is, if you
like, the one extreme.

Q686 Dr Naysmith: I am not going to stop you
saying any more, but if that is an example of what
happens and you are talking about a really big trial,
sometimes there will be, and it is hard to say how
many, but dozens of names of people who have
been involved in the trial.

Dr Patterson: Yes.

Q687 Dr Naysmith: So how would you decide
which names go on the scientific paper?

Dr Patterson: Well, there was actually in the case
of this trial, and I have got a flow diagram which
I can show you, the committee which we had set
up to begin with which met and had a meeting to
decide whose names would go on it. It is often quite
a fight amongst them as to who goes on it, but then
whoever does will get the responsibility on behalf
of the others to make sure it is right. That is no
different from, say, something that the Medical
Research Council runs as one of its major trials or
other co-operative groups outside of the industry
itself, so yes, you will get a small number of names
and if there is a significant AstraZeneca author as
part of that, we would hope and expect that their
name would be there as part of that report.

Q688 Dr Naysmith: But you are saying that you
would never seek someone who may be someone
who is also a scientist at an institute where this trial
has been carried out who is a big name and well
known to put their name to the paper, not having
been involved throughout?

Dr Patterson: And not gone and worked through
all the data and not had the responsibility? That is
an absolutely unacceptable activity.

Q689 Dr Naysmith: From what you have said, Dr
Patterson, do you think that the stuff that we have
had describing this, that it would not be an
acceptable practice and do you think it would be
open to abuse, what some of the witnesses have
said to us?

Dr Patterson: If what the witnesses are saying is
correct and they have evidence to support it, then
I think it is an unacceptable activity. The idea of
hawking around a set of results and a cheque book
and saying, “Put your name here and we will give
you some money” is against every principle that we
and the medical journals live by.

Dr Dollow: I was just going to add to John
Patterson’s point that the International Committee
of Medical Journal Editors have set out some
guidelines for authorship and they read that,
“Authorship should be based upon substantial
contributions to conception, design, acquisition of
data, analysis and interpretation, drafting the
article, revising it critically for important
intellectual content and final approval of the
version to be published”. That is something that we
strictly abide by. We may well have people who put
the first draft together, but absolutely those people
who put their name to the authorship must have
been involved at every step of the way. It says,
“Authors should meet conditions 1, 2 and 3”. The
other thing that Dr Horton mentioned in his
evidence was that people who contributed can also
be listed as contributors, if not formal authors, and
again that is something we support as well and is
something we have been doing for many years. The
issue of ghost-writing, as alleged, is not something
I recognise at all.
Q690 Dr Naysmith: So you would say that it is an unacceptable practice if it does happen, trying to get a prominent scientist or a prominent medical person to put their name on it without having any kind of involvement in the process at all?

Dr Dollow: We would not support that in any way, shape or form, absolutely not.

Q691 Chairman: Are you saying in your experience that it does not happen within the industry? You have explained your own company’s position on this, but it does not happen in the industry, as far as you are aware?

Dr Dollow: I can only speak for GSK. My personal experience is that I was working for one other company before I worked with GSK and it certainly did not happen in that company and I have been in the industry for 14 years now.

Q692 Chairman: But you are not making the point that it does not happen at all, but that in your experience of the company you worked for and your current company it does not happen?

Dr Dollow: Absolutely.

Q693 Dr Naysmith: Is that the same for Dr Patterson?

Dr Patterson: It is completely unacceptable in my company, but I cannot say it has not happened in other parts of the industry.

Q694 Mr Jones: I just want to clarify a slight ambiguity that I thought arose in those two answers. When Dr Dollow read from a code of practice, one of the requirements was that the author drafted—

Dr Dollow: “...a substantial contribution to drafting”, so they have to have been involved in reviewing and writing, so absolutely, yes.

Q695 Dr Naysmith: But in Dr Patterson’s answer, he referred to professional writers, so perhaps you forgot about the drafting.

Dr Patterson: Not at all, no. We do employ professional writers and they are involved. Most of them are not experts in that particular field of medicine, but they are very good at writing good English and they also understand what it takes to write an article that can be published.

Q696 Dr Naysmith: Perhaps we have difficulty in understanding what “drafting” means then. If the person whose name is at the bottom did not either write part of the article or how the article would come out, then they did not have any involvement in drafting, as I understand drafting, and, therefore, the code of practice is broken.

Dr Patterson: The way that it works with professional writers is that they will possibly produce a first draft which will then be reviewed by the author or authors or a committee and who will have significant input into that drafting and how it should then subsequently go forward, so we start with a 200-page report, as I described, and the medical writer will then pick that up and try and turn it into something, if it is going into The Lancet, that is in the format that these people recognise, remembering that many of the senior doctors who have worked with this may not have English as their first language or are not going to have the time, the effort and the knowledge as to what it takes to have the right format for these journals. That is drafting, but that is not the whole of the drafting. It then goes through a series of iterations.

Q697 Dr Naysmith: I would guess there would be a problem if you are talking about translators. I think I would not be asking these questions if you said you employed translators.

Dr Patterson: No, this is not a translator who takes somebody’s foreign language into English. This is somebody whose native language is English who is a professional writer who takes a report and turns it into a draft which would be acceptable to a medical journal.

Q698 Mr Burns: Just to clear this up, maybe you could help us with this analogy. Between 1994 and 1997 in particular, but also thereafter, there were dozens and dozens of articles that appeared in papers like The Sun, The Daily Express and The Daily Mail, written by Alistair Campbell or Peter Mandelson, but having Tony Blair’s name on them, although he had never seen the articles! What you are saying is that that does not happen, but there are some people who may not be as fluent in the English language who need a professional draftsman to put their thoughts and their research into English to make a compatible article for reading. Would that be helpful?

Dr Patterson: Yes, or who even collects together the information for a first draft from which you can then present your thoughts.

Q699 Mr Burns: But it is more accurate that way than just having some skivvy writing an article for a newspaper that you have never seen until you read the newspaper?

Dr Patterson: And then putting somebody else’s name to it, correct.

Chairman: Are you making a point there, Simon?

Q700 Mr Jones: Moving on, most countries, in fact almost all countries, do not allow direct-to-consumer promotion of prescription medicines, although notably the United States does, and your pharmaceutical companies are enthusiastic participants in that in the United States, which is what you have to be really within that system. Do you think that direct-to-consumer advertising has much to recommend it to other countries?

Mr Brinsmead: I think my position would be that we in this country are happy with the situation and would not be pushing for direct-to-consumer advertising on behalf of AstraZeneca anyway at this moment. I think what we would think is important is that the provision of medical information about a product to patients should be possible, so I think we have to distinguish between advertising on television and in magazines, that
Q701 Mr Jones: Mr Gray, since your company operates in the United States and in this country and other European countries, you would be in a good position to compare and contrast the values.

Mr Gray: Yes. In addition, I was personally living and working in the United States in the early '90s when the DTC all started. I think I learned from that that any form of communication has to sit comfortably in the cultural context. It was very interesting. The friends my wife and I had when we lived there were the people who lived around us and parents of children in the schools, so they were not industry people. Some of them were doctors in the system. I have to say that those people, pretty overwhelmingly, thought DTC was a good thing. They felt it was consistent with “American life” for want of a better phrase. They wanted the information; they were very, kind of, proactive about which doctor to go and visit and all of that kind of thing. I think my sense of the UK is that the cultural context is not appropriate for direct-to-consumer advertising. I do not think the public want it and as an organisation we are not pressing for it.

Q702 Mr Jones: Do you see, in this country, sponsorship of selected patient organisations and disease awareness campaigns as a substitute for direct-to-consumer advertising?

Mr Gray: I do not see it as a substitute at all. I see disease awareness as a separate and valid activity. I was talking earlier about the issue of: Do we invent diseases and are we trying to stretch the criteria? and I think another part of the element that has got mixed up in that is this issue of whether there are also patients, kind of, being forced or encouraged into the system who should not be. If you look at the current attitude of the National Health Service and how at the moment, particularly in primary care, with its focus and attention on long-term medical conditions, the National Health Service is actively looking and seeking to get patients in as early as possible and that is to the benefit of the patients. If you look at the current new general practitioner contract, for example, various measures which lead to GP payment are around issues like: Do we know if all these patients are in a particular condition? Do we have a register of them? Are we seeing them ever so frequently... on a certain frequency? et cetera—nothing to do with whether or not there is any treatment involved. Those are important measures for the ongoing health of these long-term conditions. The other thing—which sometimes is a bit galling, quite honestly—is that often the best balance of management of a patient only really comes about if you can make the patient aware and get them to access the system early. If I think about diabetes, for example, everybody would say for Type 2 diabetes that the first thing you do is a regime of diet and exercise. Everybody says that, including us: it is on all our materials. But of course the later a person actually is caught and presented for Type 2 diabetes, the less successful diet and exercise is and the accusation is: Why are they on drugs so quickly? Well, actually, because they turned up too late. The earlier they turn up, then the more successful that period of diet and exercise and the more elongated that can be. We do take part in such activities. I have one here: there is no promotion involved in it at all, and we do have examples of people who have responded with words of thanks on the basis of: “I read that and realised some of those applied to me and I have gone and done something about it”—interestingly, including a member of parliament. So it forms a valuable service, and I see it in isolation and not as a substitute for anything, quite frankly.

Dr Dollow: If I could supplement that and reflect on my experience. I used to be a hospital doctor and a general practitioner, and, when you see patients coming in who are informed, it enables you to have a debate with them about their health. So many of the things in medicine are not black and white, they are about making choices, and if patients are informed about how to help make those choices they are engaged with the management of their own disease. That has to be a benefit. If, however, a patient comes in and you find they simply do not have the disease, you can say, “Well, it’s good that you are aware of it, but you don’t have it so I don’t need to worry about it.” I think that individual doctor/patient relationship has to be seen as the final and appropriate gatekeeper of the information that gets to patients through disease awareness.

Q703 Mr Burns: Could I pick you up on that point because there is also a counterview to that, which is that there is a growing problem in the patient/GP relationship because individuals are going into the GP practice, having read some information from a variety of sources, including the internet, and telling the doctor what is wrong with them. Then, when the doctor examines them and does not agree, a blazing row ensues because the patient believes that the doctor has got it wrong. On the argument that a little education is worse than no education at all, a lot of GPs are having serious problems with their relationships with their patients.

Dr Dollow: All I can do is reflect on my experience and the experience of friends and colleagues.

Q704 Mr Burns: With respect, how long ago was that experience?
Dr Dollow: My experience was 14 years ago, but . . .

Q705 Mr Burns: That was before the internet.
Dr Dollow: But friends and colleagues who are currently in general practice I still talk to and I think I can reflect on the discussions that they have had with me. There are occasionally disagreements, but, in most cases, some patients have been sent away, saying, “No, you haven’t got that,” and with some patients saying, “Yes, actually you have got that and it is worth you doing something about it,” which may or may not require a medicine.

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Dr Patterson: We look across, we think, about 80% of medicine in the therapeutic areas in which we research, so most of the areas that you would regard as key priorities or the major causes of morbidity and mortality, but no one company looks at all fields, for instance. Could I pick up on that innovation has decreased. We have seen, in the last few years certainly, a reduction in the number of medicines getting to the market place, but I think amongst them are some very significant and very innovative medicines. People fail to understand just the length of time and the investment required to get them there. Perhaps the best example I can give you is monoclonal antibodies. They were discovered in Cambridge in the UK in 1976 but the first medicines based on monoclonal antibodies only got to the market place in 2000 and it is only now that we have, sort of, 10 or 12 of them out there and actually it is only now that the first fully human monoclonals—because the early ones were antigenic and could not be given multiple times—are beginning to come through. So that is something like 30 years from their discovery. During the 1990s a lot of the human genome work was undertaken. Many exciting new things came out of that and somehow the world expects instant gratification. I suspect, if I am still working in this industry in 2015 and 2020 that gratification will start to hit the market place, but if you add 10 years from when a medicine is first discovered to get into the market place, to the science that is required to turn a SNP or a change into our understanding of the genome into something that has become a medicine, you are talking 20- to 30-year time periods. During the ’90s, in addition to all the classic organic chemistry, small molecule type work that industry was doing, we had to add in all the new science. We have finite resources too. Most companies diverted resources into those things and as a result there was a slowing down of some of the other small molecule work. I hope we are going to see in the second half of this decade the fruits of some of those labours beginning to speed up again and most of us would say our early development portfolios, those products that are in pre-clinical or phase 1 and 2, are now significantly greater than they were five years ago.

Dr Naysmith: I am going to move on to a subject which has been described to us as “pharmacovigilance” although I am not sure what that term really means. Would it be fair to say that, once drugs get licensed and are on the market, companies typically spend a lot more time and money on demonstrating their benefits than investigating and looking at their potential harmful effects? Do you think that is true? If it is true, do you think they have the balance right?

Dr Patterson: I think that is an outrageous statement and it is not true at all.

Dr Gray: I did. I think there is a very pertinent kind of connection with the previous question. Nowadays, I believe I am right in saying, health on the internet is the biggest content behind pornography. From our point of view, in terms of any disease awareness activity in which we have been involved I am extremely confident that we apply to it exactly the same standards that we apply to everything else. I think, if you have looked at any of the health information available on the web, there is a range from very respectable right down to complete and utter cranks. Ours, as a percentage of the total that is available, is actually really very small. So I do believe you are probably right that many General Practitioners, as Dr Heath, I think it was, confirmed in her own evidence, are experiencing this problem, but the idea that it is a function of what we are doing . . . I think the world has well moved beyond that. The sheer amount of information on the internet now on health matters, completely unregulated, I suspect, is much more a contributor to that situation than anything in which we are involved.

Q707 Dr Taylor: Turning to research and innovation, we have all seen a huge explosion of really important new drugs over the last 40 years. There is a list as long as your arm. The discovery of those sorts of huge innovations really seems to have slowed down. Is this inevitable? What fields are you looking at? We have had a very useful paper from the ABPI about polio, river blindness, trachoma, HIV, tuberculosis—all the things in the less well-off countries. What sort of areas are you looking at to increase the rate of innovation?
Q709 Dr Naysmith: Not true at all.  
Dr Patterson: I think we have a legal, moral and ethical duty to follow the safety of our products from the moment they go to the first patient through to the moment we stop producing them or they stop being on the market place. Our adverse reactions programmes and processes are global. We have large numbers of people employed in our organisations whose sole role in life is to collect, collate, examine and analyse those activities. We have a thing in AstraZeneca called the SERM process (the safety, evaluation, review mechanism). It is a community of people who have nothing to do with the efficacy of our products or nothing to do with the marketing of our products. They are doctors and scientists and epidemiologists whose job is to review the data on a regular basis to make sure there are no signals coming out, there are no adverse reactions coming out, and then to make sure that if we see those things they are dealt with appropriately, either by, at the very extreme, stopping selling the medicine, or changing the data sheet or informing health authorities. In addition to that, we have regular safety update reports that we make to the health authorities, and, again, depending on the severity of the adverse event, we report either rapidly or on a periodic basis. When a product is newly in the market place, we often have more onerous needs than before. It is all there. We also monitor not just everything that comes into us spontaneously but the world literature for anything that is reported there, and we take every regulatory authority worldwide database and feed it into ours so that we can get the most comprehensive worldwide database of safety. Then, as soon as we have a signal or an issue, we talk to the health authorities, we vary our licence or we take the appropriate steps.

Q710 Dr Naysmith: That is all very commendable. Have you ever suggested to the Government, in this country, or the Department of Health, that the system they use in this country for reporting adverse effects of drugs does not really work? I am sure Dr Dollow will confirm that the card system, where a card is supposed to be sent in by GPs and hospital doctors when they see adverse effects, is widely recognised to be a bit of a nonsense. Dr Patterson, you would find a lot more adverse reactions being reported to you if we had a proper system for doing that.

Dr Patterson: The UK, of course, represents only about 3% of the sales of our products globally, so it is a relatively small percentage.

Dr Dollow: I think it is important to put it in context. I think it is a good example of how labels change over time; so the labelling, be it in the patient information or the doctor information. I would concur also that withdrawal effects and discontinuation symptoms have always been in the Seroxat label, so it has always been there both in the patient side and in the doctor side. It has, however, been updated over time as more information has become available to us. The fact

Q711 Dr Naysmith: It would be a statistically significant cohort if you were studying something about a drug.  
Dr Patterson: That is certainly true. We would always encourage every country to have the right kind of systems that are as comprehensive as possible. Of course we do have in the UK the Southampton unit which actually prospectively goes out and takes cohorts of patients and looks for specific events. It is not instead of spontaneous reporting but in addition to it, to get these things put into the context of the wider usage. These things are not absolute: you have to put them into the context of the disease and the other medicines that are available.

Q712 Dr Naysmith: Does Dr Dollow agree with me that the card system, on which medics are supposed to send in adverse effects, does not work very well?  
Dr Dollow: Let me reinforce, first, John Patterson’s view. GSK has a system which is essentially similar, in that we absolutely report all adverse effects on a global basis to all authorities worldwide but we can only work with the information that we glean from our clinical trials and spontaneous reports and systems such as yellow cards. We again have a large safety department in the UK and the US and around the world which reports these adverse events. They are individuals who spend much of their day trying to get much more information. I think the yellow card system was a great innovation. I think the difficulty, as people have previously said, is its expansion: whilst supported—and we would certainly recommend that any expansion of it be supported, including patient reporting—the difficulty behind it is getting the robust information. In one of the previous evidence sessions, Professor Vallence mentioned the use of the general practice research database. That is a very good idea and we would certainly recommend that GPRD is expanded to beyond the cohort of patients that it currently has. Currently GPRD works by a diagnosis being put in and the name of a medicine being put in and then the analysis has to be associated by someone specifically doing an analysis. We would recommend not only expanding it as part of National Health Service IT expansion but also people putting in adverse events and labelling them as adverse events so they can go further in. So I think the yellow card system is very good and we support its expansion but I think there is more we can do. Certainly we would be very welcoming of anything the Committee recommend to support that.

Q713 Dr Naysmith: We are getting a bit short of time now, but could I quickly ask GSK about Seroxat and the fact that, up until quite recently, June 2003, the company maintained that withdrawal symptoms from Seroxat were very rare, round about 0.1% was the figure, and now you have to accept that it is nearly 25%. How did that come about? There is evidence that you knew before June 2003 that the figure you were using was wrong.

Dr Patterson: The UK, of course, represents only about 3% of the sales of our products globally, so it is a relatively small percentage.

Dr Dollow: I think it is important to put it in context. I think it is a good example of how labels change over time; so the labelling, be it in the patient information or the doctor information. I would concur also that withdrawal effects and discontinuation symptoms have always been in the Seroxat label, so it has always been there both in the patient side and in the doctor side. It has, however, been updated over time as more information has become available to us. The fact
that more information becomes available to us allows us to make a reasonable recommendation based on the data, so that we can say the frequency of those adverse events and the descriptions used for those adverse events is more appropriately labelled. Additionally, I think, when it comes to patient information leaflets, it is a very good example of how patient information leaflets can be worded more appropriately. Seroxat is an example where we have extensively done user testing. Patient information leaflets, while they legally have to be compatible with a summary of product characteristics, sometimes are written in a way which is unhelpful to patients. We have found through the Seroxat process and through extensive user testing that the patient information leaflet is now more friendly. I think we would also recommend that more user testing happen with patients, such that they are written from a blank sheet of paper whilst still being compliant with the summary of product characteristics.

Q714 Dr Naysmith: Despite what all of you have said, does this episode not indicate looking a bit more closely at some of the harmful effects of drugs—and I know you disagreed with the original question, Dr Patterson—that it might be worth spending a bit more resources looking at that rather than looking at the beneficial effects once you get to the market?

Dr Dollow: Someone who has a patient in front of them recognises that any prescribing decision is taken on the basis of the risks of the disease the patient is suffering from, the risks of prescribing the medicine and the benefits that medicine is going to bring. When we think about the evaluation of our medicines and safety, we have to take it in those contexts. We cannot separate them. People have recommended, for example, that safety evaluation be separated within the MHRA. I would, I think for clarity, recommend to the Committee that it is actually all within the MHRA but is in separate lines at the moment. We would support keeping it within the MHRA but ensuring that the safety and the efficacy are considered together.

Dr Patterson: In terms of the things that are recognised as potential issues, either from the trials or from the literature, we do diligently follow those. I would give you an example. On Crestor which was mentioned earlier, on a weekly basis now I see a graph of the incidents and a report every week as to key events that may have happened, number of deaths, etc., and where that sits opposite the whole literature. That is worldwide on a weekly basis. Where it is an issue is where something is totally new; i.e. it has not been described before. There it comes down to pattern recognition, which might come from a doctor seeing it in several of their patients and often comes from aggregating together experience over a number of trials for the development of longstanding trials in the course of the market place. That will always happen, particularly with the much less frequent side effects. If something happens one in a thousand, and you have 3,000 patients in your database or even 30,000 at the time of launch, unless it is unique, unless the drug turns your ears green or does something like that, it is unlikely to be picked out if it is a slight excess of something that the patient suffers from with that disease anyway, and you need large databases and long periods of time in order to pick it out. We do look for pattern recognition—that is what our SERM process does—but it sometimes takes 10 or 12 trials to be published before that comes together and the signal comes out.

Q715 Mr Burns: The ABPI and its international equivalents have recently announced the launch of a clinical trials register. It is going to go further than the voluntary schemes currently in place. Do both of your companies support the setting up of a public register of all clinical trials registered at inception? Would you be happy to see it run by an independent authority?

Dr Dollow: Our company is on record as going further than the current recommendations, so, yes, we would support that, both for results and from studies from inception.

Dr Patterson: All clinical trials, yes.

Q716 Mr Burns: What about run by an independent authority?

Dr Patterson: I do not think it matters. A register is a register, as long as the right information is there and it is only done once. We have a multiplicity of new registers appearing at the moment.

Q717 Mr Burns: The pharmaceutical industry has told us how it wishes to work closely with government and the regulators. If such a relationship is attractive, why is it apparently that companies from time to time omit to give all the data at their disposal to the regulators or to NICE?—on the assumption that that statement is true.

Mr Brinsmead: We, as a company—and it is the same for every company—would have to submit all of our data to regulatory authorities around the world, so I am not sure that is true.

Dr Patterson: I think what you are driving at is the situation where maybe the work has been done outside the label of licence indication for a product, where the company is not applying for a licence for that indication. With a product coming to the market place for the first time, absolutely everything from everywhere is in there. When a product is out in the market place, people may use the product in other countries or of their own volition for things that are not part of the licence—and they may do that themselves.

3 Note by witness: GSK’s position is that it supports both clinical trials results and studies from inception being available. All relevant information should be on such a register, and the register should be accessible. By whom a register is run seems to GSK largely immaterial. GSK does not rule out support for an independently run register, but remains unclear as to what advantage there might be, or are being claimed for such an arrangement, as compared to the existing position.
Once a product is there, any doctor can buy the product and use it or any hospital can use it for whatever they wish. We do not control that. If they then do that, we may not even have that information to provide it.

Q718 John Austin: I wonder if I could come back to the question on Seroxat. You said in response to Dr Naysmith that there was a period when you changed your view from severe withdrawal symptoms being rare to acknowledging the real level, but is it right that the initial clinical trial showed a significantly higher rate of significant withdrawal symptoms than you were suggesting when you were suggesting they were rare? Why were you acting so defensively, almost in denial, when members of Parliament tabled an early-day motion a couple of years ago regarding the problems of withdrawal from Seroxat when you knew that there were significant symptoms?

Dr Dollow: First, let me respond to the point about the level of withdrawal symptoms from one single clinical trial. That was a control which started putting people on several levels of Seroxat, so it started with 10, 20, 30, 40, which did not mirror clinical practice, and stopped them very abruptly. The levels in that one trial did not reflect the balance of all the evidence that was available from all the dossier that was submitted to the regulatory authorities. At the time that we put the information in our label about the discontinuation symptoms, that reflected the knowledge that we had and that reflected the knowledge that was available across the world. With regard to the evolution, we did not change our label at one point. The label evolves over a period of time, every time that it is being revised when there are safety updates and revisions to the licence. With regard to the early-day motion, I am afraid I do not have specific information about that, so I would probably have to get back to you on that.

Q719 Mr Jones: You are multinational companies operating in the world market and Britain is a very small part of it. What importance do the changes our government might make in the way in which they regulate drugs have to you? Is it more as an example to other governments or is it important in itself?

Dr Patterson: This is our home market for us. We have a third of our global research and development here; we employ some 10,000 people in this country. It matters enormously to us that this is an environment in which science is good, in which scientists can work in academic laboratories or in our laboratories with animals without fear; it matters to us enormously that the national health system is somewhere where we can do what is called translational research. We particularly focus our cancer work in this country and work with people who can then take those products into the early testing in man in a very well organised and scientific manner, and it matters to us at the end of the day that those people who have worked with the medicines in research are able to use them in the market place and able to talk to their colleagues globally about their experience with these products. So it matters.

Mr Gray: I would support that it matters absolutely. I think I would also add that recommendations both from the Government and indeed from inquiries like this one also pertain to the very original questions that the Chairman was putting with regard to our reputation also. I think, therefore, we would take them extremely seriously.

Chairman: Could I thank you, gentlemen, for an excellent session. We are most grateful to you.

Memorandum by The Association of the British Pharmaceutical Industry (PI 35)

The Association of the British Pharmaceutical Industry (ABPI) represents more than 80 pharmaceutical companies in Britain engaged in the research, development, manufacturing and supply of prescription medicines. The ABPI brings together companies producing such medicines, whether branded or generic, many smaller organisations involved in pharmaceutical and bio-pharmaceutical R&D and those with an interest in the pharmaceutical industry operating in the UK. ABPI member companies manufacture and supply more than 80% of the medicines prescribed through the NHS and are major exporters to countries all over the world.

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SUMMARY

Positive engagement between the pharmaceutical industry and the UK health system is both necessary and desirable, on all the dimensions highlighted by the Committee:

— On innovation, the industry is the prime innovator of new medicines. While all major companies operate research globally, it is very much in the UK’s interest to attract as much research here as possible, and to ensure strong UK doctor and patient input into research priorities. A quarter of the world’s top 100 medicines were discovered in Britain, and we want this success story to continue.

— The industry sponsors a large proportion of UK medical research. New initiatives will bring an increasing volume of clinical trials to the UK, increasing patient access to new medicines, especially if some cost and time challenges are tackled jointly by industry and the NHS. The industry spends £10 million per day on research in the UK, and we would like to see this increase further.

— The majority of information and in-service training and education on new medicines is provided by the industry. Responsible, regulated promotion is still the most effective way to get information into the hands of prescribers, the industry is also active to ensure comprehensive medicines information is available online to doctors, patients and their families.

— Stringent regulatory review is a cornerstone of the process for the development of medicines. Since the majority of safeguards are globally, not just nationally relevant, this is increasingly an international activity, but one in which the UK, through the MHRA and the UK-sited EMEA, has a prominent voice.

— Product evaluation for cost-effectiveness is an increasingly important activity, as the need to make difficult choices about priorities rises. In most cases, medicines represent an economically superior solution—earlier, less costly intervention than hospital procedures, for example. However, the industry has provided input to the NHS and to NICE to help reverse the continued lower access to innovative medicines in the UK than in other leading European countries.

All the above interactions are two-way. The NHS and its doctors, patients and administrators have profound impact on the way the pharmaceutical industry operates in the UK. This partnership has helped build a UK industry that directly and indirectly employs over 300,000 people and contributes a surplus of £3.6 billion to the annual UK balance of trade. All the key points of contact between the health system and the industry are subject to regulation through UK and European laws and by mechanisms as varied as NHS ethics committees, new medicine approval processes and promotional codes of practice. There is always room for improvement, however, and the industry looks forward to the dialogue with the Committee about ways in which the two-way partnership can be further enhanced.

1. INTRODUCTION

1.1 Most people will take a prescription medicine at some stage of their lives. Whether commonplace interventions such as vaccination against childhood disease or an antibiotic to clear up a painful infection, through to medicines that prevent the rejection of transplanted organs or sophisticated chemotherapy that improves the life prospects of someone battling cancer, medicines are integral to health care. The gradual increases in life expectancy and quality of life over the past 50 years, with corresponding improvements in people’s overall health, are due in large measure to the success of modern medicines.

1.2 None of which happens by accident. It typically takes 12 years and £500 million of investment to bring just one new medicine to the patient. And the pathway is as precarious as it is long. For every one medicine available to prescribe, many hundreds of thousands of molecules begin the journey. Of the factors that determine those medicines that reach the patient, the health needs of the population is the most important. If there is insufficient clinical need to justify a new medicine then that medicine will not be developed. Safety is equally a key consideration since medicines with unacceptable safety or side-effect complications are worthless. Regulatory authorities rigorously and independently assess all potential new medicines for quality, safety and efficacy. The standards they demand are becoming even higher. To surmount the regulatory hurdle today, a new medicine must not merely be adequate: it must demonstrate that it is at least as good, if not better, than those already available.

1.3 The NHS Chief Executive’s 2003 report said that the increases in the prescribing of medicines “are contributing to improvements in care and, in particular to the improvements in survival rates for cancer and coronary heart disease”. The pharmaceutical industry is proud of what it does. Our goal—to bring to patients life-enhancing medicines—is not only necessary but noble, and there is no reason why the industry should not use all legitimate means to advance it. We respect the fact that both Parliament and the public have the right to know that the medicines they take have been thoroughly researched, independently approved and are promoted to prescribers appropriately within clearly laid-down rules.
1.4 Regulation is a fact of life for the pharmaceutical industry. There can be no industry more closely policed than ours. At every stage of a medicine’s development and then, once it is licensed, during its commercial phase, the industry and its medicines are subject to control. So, for example, experiments involving animals (itself a regulatory requirement since it is illegal, for obvious reasons, to do basic safety tests on humans) are controlled by the Home Office and its Animals Procedures Committee. Clinical trials involving human beings must be properly authorised and require independent ethical approval. The UK is now subject to the EU Clinical Trials Directive which, among other things, bolsters internationally-agreed standards of good clinical practice and has written them into national legislation. Manufacturing is also the subject of very rigorous inspection and legislation.

1.5 No medicine can be promoted to prescribers without a marketing authorisation, which is not granted until the regulatory authority has examined every line of a medicine’s submission dossier, with documents totalling hundreds of thousands of pages. Sales and marketing activity is controlled, mainly through the industry’s own ABPI Code of Practice (like the House of Commons, the pharmaceutical industry works well within self-regulation), and this is backed up in legislation, notably the European Directive 2001/83/EC, which, among other things, prohibits the promotion of prescription only medicines directly to the public. The industry is currently embarking on a further review of its Codes of Practice across Europe and hence in the UK, challenging ourselves to keep our standards high.

1.6 Medicines are regulated for both value and cost. Increasingly, medicines must also prove their cost and clinical effectiveness to the National Institute of Clinical Excellence (and to similar bodies in Scotland and Wales). Prices are controlled through the Pharmaceutical Price Regulation Scheme (PPRS) as well as by various market pressures in an increasingly cost-aware NHS.

1.7 The terms of reference of this inquiry are broad and themselves make the point that the industry is active across a wide range of endeavour. This response from the ABPI, on behalf of the industry, follows the headings in the terms of reference point by point. In each section we seek not only to explain the industry’s approach to the subject matter in hand, but to anticipate points that the Committee will doubtless wish to explore in this inquiry. While we have tried to keep our comments as succinct as possible, the sheer breadth of ground that needs to be covered means that this submission is somewhat longer than the Committee’s guideline.

1.8 The Committee has acknowledged the contribution of the pharmaceutical industry not only to improved health, but to the economic and scientific output of the country. It is worth stressing a few salient facts:

- a quarter of the world’s 100 most-used medicines originated in research and development carried out in the UK;
- pharmaceuticals is by far the largest contributor to R&D in this country (£10 million every day); and
- pharmaceutical companies operating here sustain 83,000 jobs directly and a further 250,000 indirectly.

1.9 Neither the industry itself, nor those responsible for creating the environment in which it operates, can afford to rest on this record. It is an unarguable fact that the focus of innovation in medicines is shifting to the USA and while the UK has been less exposed than some other European countries, such a trend cannot be ignored. The industry is not asking for special favours; nor should we be immune from public scrutiny. However, there should be recognition that the influence of the pharmaceutical industry in this country is overwhelmingly for the good. Where the industry can get better, so we should. Where the Committee, and Parliament more generally, is able to recognise the positive contribution the pharmaceutical industry in the UK makes to health, wealth and to science, so it should. No one should be in any doubt that the benefits of having a strong and thriving pharmaceutical industry in this country are immense.

1.10 As the Prime Minister has said: “A successful pharmaceutical industry is a prime example of what is needed in a successful knowledge economy. The UK’s pharmaceutical industry has an outstanding tradition and has contributed very substantially to our economy and the welfare of our citizens”.14

2. INNOVATION IN MEDICINE

- The UK is a world-centre for pharmaceutical research and development.
- The industry has a strong record of partnership in collaborative research with universities that has brought benefits to both.
- Care must be taken to maintain a UK environment supportive of R&D.
- Innovation in pharmaceuticals takes many forms—from “wonder drugs” to steady improvements that can revolutionise a patient’s quality of life.
- The output of pharmaceutical research is well-aligned to the priorities of the NHS.

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2.1 The UK has a long history of success in pharmaceutical research and development, with 25 of the world’s leading medicines having their origins in this country. This success is due to three factors above all: historically strong research; a strong academic research and clinical base; and a framework that encourages investment in R&D. The recent introduction by the Treasury of tax credits to support R&D is an example of the Government’s positive attitude towards this endeavour.

2.2 The combination of a strong history and favourable environment means that UK pharmaceutical R&D is able to “punch well above its market weight”: only 3% (by value) of the world’s prescription medicines are sold here; yet the UK attracts around 10% of global investment in pharmaceutical R&D. This is more than half of the total pharmaceutical R&D investment in Europe as a whole.

2.3 However, as figure 1 overleaf clearly illustrates, over the past 10 to 15 years, the USA has opened up a commanding lead in pharmaceutical R&D investment. This trend will continue unless a favourable environment exists in the UK, including the supply of suitably-trained scientists and removing attacks on the industry and its suppliers by animal rights extremists.

2.4 Overall, what the pharmaceutical industry spends on R&D has tripled in the last 10 years (over the same period NHS spending has roughly doubled). The UK remains a world-leader in the development of new compounds and R&D productivity is amongst the best in the world. As a proportion of R&D spend, the UK has one of the largest numbers of first patents filed for new molecular entities. Such activity has a benefit not only to medicine, but to science. No other industry sector in the UK comes close to matching pharma’s R&D spend, which represents a quarter of the overall UK total. We are the country’s largest employer of science graduates: 27,000 employees are directly engaged in R&D activities.

Figure 1

COMPARISON OF SHARE OF GLOBAL PHARMACEUTICAL R&D INVESTMENT

<table>
<thead>
<tr>
<th>Year</th>
<th>US</th>
<th>Japan</th>
<th>UK</th>
<th>Germany</th>
<th>France</th>
<th>Switzerland</th>
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<tr>
<td>1990</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
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<tr>
<td>1991</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
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<tr>
<td>1992</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
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<td>1993</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
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<tr>
<td>1994</td>
<td>60%</td>
<td>50%</td>
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<td>30%</td>
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<td>60%</td>
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<td>1996</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
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<tr>
<td>1997</td>
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<tr>
<td>2001</td>
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<td>50%</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

2.5 As figure 2 shows, the pharmaceutical industry funds more healthcare-related research in the UK than every other funder put together—six times as much as the Department of Health; five times as much as medical charities; eight times as much as the MRC.17

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15 ABPI analysis of global sales and historical information on R&D pipelines.
17 ABPI estimates.
Collaborative research

2.6 The pharmaceutical sector is also a significant supporter of academic research. Last year ABPI companies funded over 1,100 collaborations in 80 UK institutions. The Lambert report,¹⁸ an independent review of business-industry links, commissioned by HM Treasury, noted that the UK pharmaceutical industry is an exemplar not just in research intensity, but also in its approach to collaborative research with universities.

Case study: Dundee Kinase Consortium

Six pharmaceutical companies, GlaxoSmithKline, AstraZeneca, Pfizer, Boehringer Ingelheim, Merck & Co Inc, Merck KGaA (German company) have established a consortium collaborating with the University of Dundee to support the Division of Signal Transduction Therapies, led by Prof Sir Philip Cohen. The funding, worth £15 million over five years, brings:

Benefits for Industry

— Access to know-how from > 70 world class scientists.
— Screening facility vs panel of kinases.
— Electronic information storage/transfer. Production of proteins and biological reagents.
— Custom synthesis of antibodies.
— Information on new drug targets.

Benefit to the University

— Access to the most selective chemical tools.
— Joint publications in top journals.
— Intellectual direction from industry.
— Increased efficiency of process through semi-industrialisation and sharing best practice.

Meeting NHS needs

2.7 The pharmaceutical industry’s input into research and development should not therefore be in any
doubt. It is legitimate, however, to ask two questions about all this effort: is the end result genuinely
innovative medicines; and, secondly, how aligned is pharma’s research effort to health priorities, and
specifically to the priorities of the NHS?

2.8 The history of medicines research is punctuated by landmark discoveries in human health. The
discovery of AZT by Wellcome in 1987, for example, was the moment when humanity first began to turn
the tide of HIV/AIDS. The fact that we can now slow, or even reverse, the progression of cancer, or bring
relief to people suffering from the debilitating effects of mental illness, is all due to breakthroughs made by
the pharmaceutical industry. The almost complete disappearance in the UK of childhood diseases, which
used to kill and cripple, could not have been achieved without vaccines the industry has developed.

2.9 Death rates from heart disease have fallen by more than 40% in the UK over the past 10 years alone.
A review of the relevant literature has shown that about 40% of this reduction is due to treatment including
secondary prevention, use of thrombolysins (clot-busters), treatment of angina and treatment of
hypertension. The use of statins to reduce cholesterol levels is estimated by Government to be saving 6,000
lives a year.

2.10 Nevertheless there is still no “cure” for many cancers, no “cure” for Alzheimer’s disease, no “cure”
for acute psychoses, and no “cure” for arthritis. These can come in time if the pharmaceutical industry funds
the necessary research and development.

2.11 In the meantime, incremental (and important) advances are being made. The industry is working
closely with the medical profession in chronic disease management—emerging as one of the most important
priorities for the NHS. Conditions such as diabetes, asthma and arthritis cannot (at the moment) be
eliminated. However, the quality of life of people with these conditions can be substantially improved, for
example, by medicines that have fewer side-effects or provide better symptom control or that are easier to
take (which in turn improves compliance). Table 1 below gives a number of examples where later medicines
in a class have provided innovative advances to patients over and above those of the first medicine of
their type.

2.12 We are also now discovering why different patients respond differently to different medicines (the
so-called “pharmacogenetic” effect). This knowledge is being used increasingly to choose the right medicine
for the right patient and to discover even more specific therapies.

Table 1

BENEFITS OF INNOVATION

<table>
<thead>
<tr>
<th>First to Market</th>
<th>Follower</th>
<th>Class</th>
<th>Benefit of Follower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accolate</td>
<td>Singular</td>
<td>Leukotriene modifiers</td>
<td>More convenient dosing (once a day vs twice a day)</td>
</tr>
<tr>
<td>Beconase</td>
<td>Flixonase</td>
<td>Intranasal steroid</td>
<td>Potency; fewer adverse events</td>
</tr>
<tr>
<td>Zovirax</td>
<td>Valtrex</td>
<td>Herpes anti-viral</td>
<td>More convenient dosing</td>
</tr>
<tr>
<td>Mevacor</td>
<td>Lipitor</td>
<td>Cholesterol lowering</td>
<td>Potency</td>
</tr>
<tr>
<td>Tagamet</td>
<td>Zantac</td>
<td>H2 antagonists</td>
<td>More convenient dosing; fewer drug interactions</td>
</tr>
<tr>
<td>Cozaar</td>
<td>Diovan</td>
<td>Angiotensin Receptor Block</td>
<td>Potency</td>
</tr>
</tbody>
</table>

2.13 The research output of the pharmaceutical industry is well-aligned to the priorities of the NHS.
Some 43% of new medicines introduced over the past 10 years by the industry are designed to support four of
the NHS’s key health priorities—cancer, coronary heart disease, mental health and illnesses of the elderly.19

Table 2

MEDICINES LAUNCHED OVER PAST 10 YEARS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number launched</th>
<th>Proportion of total new launches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>111</td>
<td>14%</td>
</tr>
<tr>
<td>Cancer</td>
<td>48</td>
<td>6%</td>
</tr>
<tr>
<td>Mental Health</td>
<td>119</td>
<td>15%</td>
</tr>
<tr>
<td>Elderly conditions excluding the above (eg Type 2 diabetes, arthritis)</td>
<td>63</td>
<td>8%</td>
</tr>
</tbody>
</table>

19 IMS Dataview.
2.14 Hence, in the area of innovation in the UK, the NHS and the pharmaceutical industry have essentially a common cause—an ambitious role for the UK in researching and developing both “breakthrough” and “better performance” medicines.

3. THE CONDUCT OF MEDICAL RESEARCH

— The UK is a world centre for clinical research which has helped to develop major innovative advances in medicines.
— Clinical trials are conducted ethically and safely and to the highest standards of Good Clinical Practice.
— All trial data are provided to the regulatory authority for its independent assessment.
— Publicly-funded research benefits from collaboration with industry.
— Government action is required, however, to ensure that the cost of clinical research in the UK is not prohibitive or it will be driven abroad.

3.1 The UK is acknowledged as a world centre for clinical research involving medicines. The basis of this success is collaboration between the industry, the NHS and academic institutions. And the contribution of industry is vital. Industry funding of research in the UK has helped many research units within NHS Trusts to continue functioning at a high level. Industry sponsored clinical trials made up about 40% of all applications to the London Multi-Centred Research Ethics Committee in 1997–2000, easily the largest grouping of research applications involving clinical trials.20

Sponsorship*

\[(n=276^*\text{ for } 263\text{ studies})\]

<table>
<thead>
<tr>
<th>Sponsorship</th>
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* may be partial, complete, indirect or direct sponsorship
** some studies had more than one sponsor

3.2 In April 2000, the Prime Minister set up the Pharmaceutical Industry Competitiveness Task Force (PICTF), a joint Government/Industry task force examining the competitiveness of the UK with regard to the pharmaceutical industry. One of its work streams related to clinical research. The group continues to meet to foster collaboration between the industry and the NHS.21 Among its outputs is a partnership agreement22 published in March 2002. It sets out guidance for partnership between the NHS and industry both for commercially sponsored research and the role of industry in supporting non-commercial research.

3.3 Clinical trials in Britain will receive a major boost from the recent establishment of the UK Clinical Research Collaboration (UKCRC). The new body aims to speed up the development of new medicines from the laboratory to the patient by expanding the number and range of clinical trials.23 It has been developed as a direct result of recommendations from reports of the Biosciences Innovation and Growth Team24 and the Academy of Medical Sciences.25 The ABPI welcomes the fact that the pharmaceutical industry is recognised as a partner in the UKCRC and looks forward to working to improve the competitiveness of the UK in global medical research for the benefit of patients, the NHS and, ultimately, the industry in the UK.

25 Strengthening Clinical Research, Academy of Medical Sciences, October 2003.
**The Development Process**

3.4 Following discovery and laboratory research, new chemical entities (NCEs) undergo toxicological and animal testing. Animal research is conducted under strict regulation and licensing by the Home Office and is only conducted when there is no practicable alternative available. These pre-clinical phases take about three years but with a high attrition rate.

3.5 Only those compounds that have a positive benefit/risk ratio go into clinical studies. These begin with healthy volunteer studies (phase I) involving people, usually under 45, during which data on how the medicine works and its effects on human systems are collected. Some early safety data and information about likely dosage are also collected.

3.6 If the benefit/risk ratio remains positive and there have been no severe adverse effects, the medicine will now be given to patients with the disease it has been designed to treat (phase II) to determine that the medicine works as expected. If this is confirmed and there are again no major safety issues, the medicine is used in large phase III trials of up to several thousand patients to determine its efficacy (that it works) and safety. A clinical trial will often have two arms, one containing the investigative medicine and the other a comparator, either a placebo or current best treatment. Patients entering the trial are randomly allocated to one arm or other. In a single blinded trial, the patient doesn’t know which arm they are in and in a double blinded trial, neither the investigator nor the patient knows, thus eliminating bias. At the end of the study, the blind is broken and the data analysed. If the outcome of all the clinical studies together is positive with a good safety record, then a marketing authorisation is sought from the relevant regulatory authorities. At the end of the clinical trial process, several thousand patients will have volunteered to take part in the clinical trials.

**The Governance of Medical Research**

3.7 All clinical studies involving medicines are conducted ethically and safely and the high standards of Good Clinical Practice (GCP). Standards are international, based upon the Principles and Guidelines for Good Clinical Practice (ICH GCP) developed by the International Conference on Harmonisation and launched 1997. Both the ABPI and the UK regulatory authorities are fully signed up to the standards and there is little or no chance of a product being licensed if its trials have not complied with them. Before 1997, other guidelines were in place, including those developed by the ABPI itself.

3.8 On 1 May, 2004, the UK implemented the European Clinical Trials Directive, which introduced in the UK the Principles of ICH GCP into legislation. This means that all clinical trials, both commercial and non-commercial, covered by the Directive will be performed to an equally high standard.

3.9 The Directive means that all industry trial protocols will be scrutinised by both the MHRA and, as previously, an independent ethics committee before approval will be given. In addition in the UK, trials involving secondary care and many involving primary care also have their protocols assessed within the relevant NHS Trust. The timelines for scrutiny are laid down in the legislation for the MHRA and ethics committees but not for the NHS Trusts, which have now become the major time-limiting factor in clinical trial start-up. Delay in the NHS Trust process makes the UK less competitive in comparison with its European neighbours. As a result, the ABPI and Department of Health jointly launched a Model Clinical Trial Agreement (MCTA) in January 2003 with the specific aim of speeding up the contracting process at NHS Trust level and thus speeding up start-up times for trials.

3.10 The ABPI has recognised for many years the importance of publication of clinical trials. In 1996, the ABPI published its guideline on Good Clinical (Research) Practice and stated: “The investigator must agree a publication policy with the sponsor before the start of the study”. The Model Clinical Trial Agreement, published by the ABPI and Department of Health contains a section on publication of the trial and makes this a contractual duty.

3.11 In May 2003 the ABPI launched its Clinical Trial Register (https://www.cmrinteract.com/clintrial), which is a voluntary register of completed phase III trials involved in a marketing authorisation application three months after launching the new medicine in its first major market. A number of individual pharmaceutical companies have also announced proposals to make public details of their clinical trials.

3.12 In a small minority of cases, standards full below those required. The ABPI has been at the forefront of prosecution of research misconduct in the UK. Since 1988, it has reported 26 doctors to the General Medical Council (GMC) for research misconduct and 25 of these have been found guilty of serious professional misconduct and about half have been erased from the Medical Register.

28 The Model Clinical Trial Agreement www.abpi.org.uk.
The cost of research

3.13 The UK is one of the most expensive places, in the world, to undertake research. An international annual assessment of cost comparisons of clinical trials, FastTrack for 2002, showed that of our major competitors, the UK was second most costly in both the trials monitored.

3.14 These facts seriously reduce the competitiveness of the UK. The key factors for a company in placing its research are the speed, quality and cost of the research. The Clinical Trials Directive has had a positive impact with regard to speed in the UK as the MHRA is one of the most efficient regulatory authorities in Europe for processing clinical trial applications and plans to approve 80% of its applications within 30 days (14 days for healthy volunteer studies). As outlined above, the key factor in timing is now NHS Trust approval. Equally, government action is required to ensure that the cost of clinical research in the UK is not prohibitive with regard to the application of general overheads and payment for standard care.

Research and Paediatric Medicine

3.15 One of the priorities for the UKCRC, referenced above, is children’s medicines. Millions of children receive medicines every day that are safe and effective. But many older medicines have not been tested on children, although experience over many years provides a sound evidence base for their continuing and safe use. Children may respond differently from adults to medicines so it is necessary to conduct proper clinical trials in children of different ages.

3.16 For many medicines, it would be ethically inappropriate to carry out experimental trials in children of different ages from new born babies to toddlers to teenagers, before its effect is well established in the more robust adult population. Parents have been understandably reluctant to allow their sick child to participate in the clinical trial of a medicine that is, to a degree, “experimental”. The UK-based pharmaceutical industry, through the ABPI, has been at the forefront of trying to improve the situation.

3.17 The pharmaceutical industry is the leading sponsor of UK clinical trials for children.29

Sponsorship* of studies in children only

(n=30 for 28 studies)

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*some studies had more than one sponsor

3.18 The introduction of a new European Regulation on Paediatric Medicines in 2006 will require more medicines to be licensed for use in children. This will mean that more clinical trials will need to involve sick children in order to ascertain the safety and efficacy of new medicines that will have potential benefit for those children. The pharmaceutical industry will inevitably fund the majority of paediatric trials and we therefore welcome the principle of incentives in the draft regulation.

3.19 In the UK, paediatric centres that are experienced in carrying out clinical trials in children are at present few and far between. Although paediatricians are well versed in managing the clinical and psychosocial problems that children have, and have an understanding of the difference in physiology between children and adults, some of these potential investigators may be inexperienced in running a clinical trial and there may be a lack of necessary resource and staffing. The pharmaceutical industry is keen to work with the Government and regulatory authorities in developing a better research environment for children.

Clinical Pharmacology

3.20 In the mid-1990s, the ABPI recognised that there was an increasing shortage of clinical pharmacologists in the UK, who are vital in the early clinical development of a medicine. The UK has traditionally led the world in clinical pharmacology research—half of European healthy volunteer studies are done in the UK. Following negotiations involving the Department of Health, the Royal College of Physicians of London and the ABPI, a joint training programme has been set up in Clinical Pharmacology with the industry partner funding half of the trainees' salary. So far, 20 trainees are undertaking or have completed the course at a total cost to industry of over £2 million. Two of the supported trainees are in Paediatric Clinical Pharmacology.

4. Provision of Medicines Information and Their Promotion

Information and promotion are necessary and valid activities for the pharmaceutical industry:

— Informing doctors of new medicines and new indications for existing medicines for the benefit of patients.
— Ensuring that health professionals are aware of the medicine dosage, side effects etc, allowing them to optimise their use of medicines for the benefit of patients.
— Encouraging value for money and better patient outcomes.
— Strictly regulated by the ABPI Code of Practice.

4.1 Medicines information and promotion are strictly regulated by UK and European law as well as by the ABPI's own Code of Practice. Promotion of prescription only medicines (POMs) to the general public is prohibited in the UK. The provision of accurate information through marketing to health professionals is an essential element of a successful pharmaceutical business and is conducted in an ethical, responsible and professional manner.

4.2 Doctors, pharmacists and other health professionals need to keep up to date with scientific understanding and new developments in treatments to ensure that patients can benefit from advances. Pharmaceutical companies know more about their own products than anyone else, so the industry has an important role to play in providing information for prescribers and dispensers, including about potential side effects to help ensure their proper use of medicines.

4.3 A recent Taylor Nelson study\(^\text{30}\) of 205 GPs showed that family doctors consistently rated representatives amongst their top three sources of information:

— First as most effective source of awareness of new medicine information.
— First as most effective source supporting educational or medical meetings for GPs.
— Second most effective source of medicine information (withdrawals, dosage etc).
— Third most effective source of clinical trial results.

4.4 The ABPI Code of Practice is drawn up in consultation with the British Medical Association, the Royal Pharmaceutical Society and, importantly, the Medicines and Healthcare Products Regulatory Agency. It reflects the legal requirements controlling the advertising and promotion of medicines and extends well beyond them.

4.5 It is a condition of membership of the ABPI that companies abide by both the letter and the spirit of the Code. Observation of the Code is a priority for pharmaceutical companies. Any breaches have a damaging impact on the company concerned in terms of both sanctions and company reputation. Companies also have to divert valuable resources, often over several months, into investigating every complaint in detail.

4.6 Self-regulation has proved effective for well over 40 years. The industry's own vigilance in observing the Code results is reflected in the fact that nearly half the complaints made to the Prescription Medicines Code of Practice Authority emanate from pharmaceutical companies themselves. The overall number of complaints (upheld or not) is some 125 a year over the past decade. This is a modest level, given the scope of the Code and the fact that it covers relationships and activities with more than 90,000 GPs and hospital doctors and 40,000 pharmacists as well as other health professionals.

4.7 The pharmaceutical industry worldwide holds the ABPI Code of Practice in high esteem and actively promotes its use. In the UK the ABPI and its member companies routinely explain to health professionals how the Code operates and welcomes comments on how it could be improved. The ABPI is publishing in September 2004 guidance notes on the Code for health professionals that will be distributed to all Primary Care and Hospital Trusts.\(^\text{31}\)


\(^{31}\) Controls on the Promotion of Prescription Medicines in the UK—guidance notes for health professionals, ABPI, September 2004.
4.8 All national codes in Europe are currently being reviewed by the European Federation of Pharmaceutical Industries and Associations (EFPIA). As part of this the ABPI is carrying out its own review of the Code and its operation. This will involve external consultation and the conclusions of the Health Select Committee inquiry will be taken into account.

Industry representatives—training and qualification

4.9 There are approximately 8,000 pharmaceutical company medical representatives operating in this country, a number which has remained fairly stable over the past five years. The medical representative plays a key role in promoting medicines to health professionals. Representatives traditionally have scientific or health-related backgrounds, and receive intensive training within their own company. All training material has to be approved on behalf of the company by an employee who is a registered doctor and one other senior person to ensure that it complies with the ABPI Code of Practice.

4.10 Company representatives have to pass the ABPI medical representatives exam within two years of being employed in such a role. The ABPI course and exam covers:

- Basic physiology and anatomy.
- In-depth education on their relevant disease area.
- Understanding of the NHS and how it operates.

Visiting health professionals

4.11 Health professionals need to balance the responsibilities of dealing with patients’ needs together with administrative and managerial duties. In addition they need to set aside time to keep up to date with the latest medical innovations. Information learnt from visits by medical representatives helps health professionals to be aware of the latest changes in treatment regimes in a very time-efficient manner.

4.12 The number of visits by a representative to a doctor during any year is controlled by the Code and should not normally exceed three. The primary care medical representative calls on GPs, usually through a well-managed appointment system. This may sometimes be with a single GP or a larger group of doctors. Nurses are increasingly included in such meetings as their involvement, including prescribing decisions, has grown in recent years.

4.13 During the discussion the representative will use detailed material to explain the appropriate use of the medicine, provide data on clinical trials and relevant comparative information. Promotional material must also contain prescribing information which states the cost of the medicine and be consistent with the medicine’s marketing authorisation. All material is checked for factual accuracy and must comply with the Code.

4.14 Secondary care representatives use material especially designed for this level of care. A discussion about cost benefit or cost effective data allows health professionals to quantify the potential effect of a new or different medicine on their budgets.

4.15 The Code permits promotional aids to be given to health professionals provided they are both relevant to the recipient’s work and inexpensive (costing no more than £6).

Wider promotional activities

4.16 Companies regularly advertise in medical journals to create awareness of a medicine and its role within effective therapy. All information and comparisons must be accurate, balanced, objective and unambiguous. They must not mislead and must be capable of substantiation. Direct mailing is used, often to inform the profession of changes to prescribing information, new medicines or new clinical data.

Further improvements

4.17 In providing information to the medical profession it is becoming increasingly clear that:

- there is greater pressure than ever on doctors’ workloads;
- the benefits that increased prescribing can bring in better patient health and lower overall costs to the NHS need more emphasis alongside the steady feedback to doctors on prescribing costs alone; and
- more efforts are also required to widen patient access to many newer medicines.

The pharmaceutical industry believes it has a powerful role to play in partnership with the NHS in delivering better healthcare for patients.
5. Professional and Patient Education

— No one knows more about a medicine than the people who discovered, developed and made it available.
— Our principal objective is to provide factual information for professional and patient education to achieve the best outcome for patients.
— The UK-based pharmaceutical industry funds more than half of all further education and training for NHS doctors.
— Industry collaboration with patient groups under agreed “rules of engagement” can result in real benefits for patients.
— Patients’ own search for more information about their medicines could be met in part by industry, given some relaxation of current communication restrictions.

Information Requirements and Offerings

5.1 Professional and patient education is vital to achieving the best outcome for patients from the most appropriate use of medicines. As in other areas, in the provision of education and information, the pharmaceutical industry operates in a highly regulated environment.

5.2 Pharmaceutical companies are required to provide information about their medicines, on request, to health professionals under the terms of the ABPI Code of Practice. Companies are obliged to have a “scientific service responsible for information” (Clause 13 of the Code). Over the course of a year, large pharmaceutical companies in the UK each deal with between 15–26,000 requests for information directly from health professionals and administrative staff and some 12,000 indirectly through sales representatives. This obligation to provide information continues beyond the end of data and patent exclusivity.

5.3 The industry provides information about medicines in a variety of other ways as well. It contributes to both the British National Formulary and the Monthly Index of Medical Specialities, the two most important and commonly used UK reference works on licensed medicines. The industry also supports the development of the Medicines Compendium and its electronic edition, which provides, via the internet (www.medicines.org.uk), comprehensive, up-to-date, government-approved technical data on individual medicines, including safety and dosage information, and patient information leaflets on individual medicines. This service delivers over 2.5 million documents about medicines per year to health professionals and to members of the public. The electronic Medicines Compendium is being incorporated into the National Electronic Library of Medicines and is widely used throughout the NHS as a primary and definitive source of medicines information.

5.4 Medicines Guides produced by the industry, both electronic and in print, are now being developed as additional sources of information for the general public via NHS Direct.

Professional Education

5.5 Professional education is largely provided through regulated medical education programmes conducted in various partnership activities between the industry, academia, health professionals and their professional bodies, medical publishers, the Government and the NHS. Such education is directly supported by the industry, whether by donation, unrestricted educational grants or partnership programmes, and is of considerable value to the NHS. Without this high quality educational support from the industry, an additional heavy burden will be placed on NHS resources.

5.6 In fact, the UK-based pharmaceutical industry funds more than half of all further education and training for doctors in Britain and of a quality standard at least as good as non-sponsored education. This provides an essential role in helping to build a culture of innovation and medical knowledge to help the NHS deliver a modern health service. Internationally, the industry supports symposia that bring together leading experts from the UK with their counterparts around the world.

Patient Education

5.7 The industry is prohibited from providing information, directly to patients, outside the relevant clause in the Code (Clause 20). This does permit the tightly regulated and formulaic information available in the summary of product characteristics, the patient information leaflet inserted in the pack and information on the packaging of the medicine itself.

5.8 However, under current legislation and guidelines, pharmaceutical companies can run, partner or sponsor certain kinds of regulated and strictly non-promotional public health education and disease awareness activities. This helps make people aware of the availability of treatment options for a condition and advises them to seek the advice of a health professional. Any such communications cannot speak solely

about the availability of a specific medicine or encourage patients to ask their doctors for a specific brand. Guidelines agreed between the industry and the MHRA mean that these communications must clearly have public or patient education about a disease and treatment options for it as their objective.  

5.9 This kind of education usually involves partnership with public and or voluntary sector bodies and informal but wide consultation with interested stakeholders. Successful public health education and disease awareness programmes in the UK have covered subjects such as: allergies, cancer, cardiology, central nervous system diseases, dermatology, epilepsy, glaucoma, men’s health, multiple sclerosis, respiratory disease, urology and women’s health. The ABPI has produced a CD ROM with examples of such successful collaborations. A copy is being submitted to the Committee. Patients often benefit through these disease awareness programmes by having previously unidentified and sometimes serious conditions diagnosed and treated in good time.

Working with Patient Groups

5.10 Relationships and partnerships with patient groups, voluntary sector and other stakeholders are governed by the prohibition in UK law on advertising prescription only medicines to the public. Furthermore, they are conducted in accordance with strict published guidelines or operating principles, such as the Long-term Medical Conditions Alliance’s guidelines for voluntary health organisations working with pharmaceutical companies. Many pharmaceutical companies also have in-house rules for working with patient groups. Above all, companies wish to avoid either the reality or the perception of improper or undue influence.

5.11 Pharmaceutical companies and patient groups share a common interest in wanting patients to receive the most effective, evidence-based treatments, and to do so without unnecessary delay. It is desirable for patient groups and pharmaceutical companies to work together towards this end and to educate and inform their members or a wider public, about particular chronic medical conditions, their prevention, and new developments in therapy. This co-operation can take the form of funding by way of donation or unrestricted educational grant, administrative and technical or logistical support, advice and consultancy in specific areas of business or healthcare expertise etc. Two examples are given below.

Arthritis Care has been supported by Pfizer in raising awareness of the availability of treatments and methods for the management of arthritis with materials which are comprehensive and go well beyond the availability of medicinal interventions, looking at diet and lifestyle etc. A “state of the nation” report to quantify and provide evidence of the extent of the problem of arthritis in the UK and a programme to assist in the implementation of NICE guidelines have also been delivered.

Eleven pharmaceutical companies have worked with CancerBACUP over the last year to utilise their oncology representatives to help raise awareness of the new CancerBACUP information and support line phone number by distributing cards and posters to oncology centres across the UK.

Working with the NHS

5.12 The relationship between the NHS and the pharmaceutical industry is constantly changing. To support these changes teams within pharmaceutical companies work with NHS management to develop NHS partnership activities.

5.13 The ABPI and the NHS Alliance have recently produced a suggested framework for joint working between the pharmaceutical industry and the NHS. Among its provisions are:

— The interests of individual patients should be protected.
— Clinical aspects of care should be under NHS control, although industry input is legitimate and offers benefits to patients and the NHS.
— Joint working should not be seen as an endorsement or promotion of a specific medicine or technology.

5.14 The framework also includes a selection of case studies of successful partnership working in a variety of different areas, ranging from educational support to the implementation of National Service Frameworks. A copy is being supplied to the Committee but an example is extracted overleaf.

In 2003 Lilly launched the “Well-being Support Programme” as a pilot scheme for mental health services in the UK. Organisers from various PCTs will seek to enrol a total of 1,200 patients over two years at eight sites across the UK. The programme will aim to improve the lifestyles of patients suffering with a serious and enduring mental illness. These objectives comply with the recommendations made by the National Institute for Clinical Excellence and the NSF for Schizophrenia. Lilly’s programme addresses these issues by concentrating on three key areas:

— Lifestyle assessments and interventions—e.g. smoking, weight management and physical activity.
— Side effect assessment and management—e.g. understanding the impact of side effects and helping patients manage them.
— Physical health assessment—providing a basic physical health check including blood pressure, weight, height and pulse rate.

The outcome—by the end of 2003, eight national sites had enrolled over 1,000 patients. Each trust has set up groups for weight management and physical activity. Over 100 patients are now benefiting from these groups each week.

Areas for development and improvement

5.15 The Government recognises that better health outcomes are generated when patients are entrusted with responsibility for their own healthcare. Through initiatives such as the Expert Patient Programme or NHS Direct, it is promoting policies that focus on increasing patient choice and advancing the self-care agenda. At the same time, the desire of patients for reliable and balanced information about their health needs and the options available for treatment has never been greater. Health-related subjects are at the top of the list of the most searched for items on the Internet. It is in this context that the debate about whether the pharmaceutical companies should be allowed to communicate directly with patients becomes significant.

5.16 The ABPI’s Informed Patient Initiative Task Force, believes that pharmaceutical companies could help patients be better informed if current restrictions on industry providing scientifically reliable information on healthcare, medicines and treatments directly to patients were relaxed.

5.17 This position is supported by many patient groups and is consistent with the position of the MHRA on the provision of health information to consumers. The UK government does not support direct to consumer advertising of prescription medicines but is supportive of the provision of information to patients. This shows that there is common ground between regulators, Government, and industry.

5.18 An opinion survey conducted by MORI last year asked the general public if they thought it was valuable to have a range of different types of information about medicines from different sources. An overwhelming 81% agreed with the statement.

5.19 There are still understandable concerns about the regulation of patient information on the Internet. The Times reported (3 August 2004) a study warning that thousands of cancer patients are risking their health by following the advice of websites promoting bogus cures. The industry could play an important role here, working in conjunction with the regulators, health professionals and patients.

5.20 This greater public demand for information about their health is also reflected in increasing coverage of healthcare issues by the press and broadcast media. Everything that the industry says to the media about medicines is governed by the Code. The media has a genuine interest in reporting health news and producing features on healthcare and related advice. However, editorial control rests with the media organisations and companies have no control over final headlines, content or slant.

5.21 Given the above, a key issue facing the industry is how best to legitimately (and legally) participate in the healthcare information revolution. Industry and Government are therefore in active discussion to explore ways to improve public access to good quality information on licensed medicines.

5.22 For example, within the NHS Strategy Document “Pharmacy in the Future—Implementing the NHS Plan”, the Government has established a joint task force to lead the implementation of a national strategy on partnership in medicine taking. There is pharmaceutical industry representation on the task force and its working groups. For the first time last year this partnership supported a very successful “Ask About Medicines Week” campaign for the general public. The ABPI and individual pharmaceutical companies participated in this event, which will be repeated later this year (November 1–6, 2004). We would support changes to allow pharmaceutical companies to communicate scientifically reliable information directly to the ultimate consumers of its medicines and would welcome the opportunity to explore this in further work with regulators, policy makers and other stakeholders. No one knows more about a medicine than the people who discovered, developed and made it available.

6. Regulatory Review of Medicine Safety and Efficacy

— The pharmaceutical industry operates within one of the most complex and stringent regulatory frameworks of any industry.
— Good communication between regulators and companies is essential to ensure the regulatory system is efficient and effective.

36 The remit of the IPTF is to work with the Association of the British Pharmaceutical Industry (ABPI) to make recommendations to the Medical and Healthcare Products Regulatory Agency (MHRA) on patient information.
37 MORI survey of 2,000 adults, July 2003.
— Companies are legally required to monitor continually the use of a medicine throughout its lifetime to maintain a positive benefit/risk balance.
— Future funding models for the MHRA must ensure that the agency can continue to operate as a European Centre of Excellence.

**Regulatory Framework**

6.1 Public health and medicine safety are important issues around the world. Governments have responded by placing requirements on manufacturers to obtain marketing authorisations before placing medicines on the market and to monitor them closely thereafter.

6.2 All aspects of activities in these areas are tightly regulated and legally controlled, and the European and international regulatory framework is constantly updated to reflect new scientific and medical progress. The amount of pharmaceutical regulation has increased significantly over the past 20 years with greater international exchange of medicines information to increase the protection of patients.

6.3 The pharmaceutical industry, medical community, patients and government all have a common interest in ensuring that the regulatory system in the UK is transparent, efficient, meaningful and robust, and bases its decisions on a high standard of scientific evidence. The aim should be to regulate effectively but efficiently: over-regulation is a disadvantage to both to patients and industry. The regulatory system should provide timely access for patients to effective medicines, while ensuring patient safety and stimulating research into new treatments.

**Marketing Authorisation Application**

6.4 Before a company can market a medicine in the UK, it must be approved by expert committees within the Medicines and Healthcare Products Regulatory Agency (MHRA) or the European Medicines Evaluation Agency (EMEA). Before a marketing authorisation is issued, the agencies will carry out close scrutiny of all the technical reports that must be generated by a pharmaceutical company during the development of the medicine. They will also review the proposed manufacturing methods, quality control procedures and evidence of pharmacological activity, clinical safety and efficacy.

6.5 The average regulatory submission for a new medicine consists of several hundred volumes of technical and scientific reports and data, including details of animal research, clinical trials and manufacturing processes.

**Role of Independent Experts and Industry in the Provision of Advice**

6.6 The MHRA is assisted by advisory committees in making licensing decisions and in reviewing the safety of marketed medicines. It is in the interest of all stakeholders to make sure that the highest level of medical and scientific expertise and excellence is available to the MHRA through these committees.

6.7 There is, however, only a limited pool of experts in any given area at any given time. Industry seeks their expertise during the development process for a new medicine and the MHRA benefits from their advice during the regulatory assessment. Consequently, it is essential to have in place a robust, transparent and effective system to avoid any potential conflicts of interest for experts in relation to a specific medicine. The MHRA operates just such a system, whereby committee members are subjected to a high level of transparency and rigorous declaration of personal interest, to ensure that their expert scientific opinion is independent and unbiased. Independent experts with a declared personal interest in a particular pharmaceutical company are excluded from assessments involving that company’s medicines.

**Financial Structure of the MHRA**

6.8 The Evans-Cunliffe report recommended that the full cost of the then Medicines Directorate should be charged to the pharmaceutical industry. Therefore, the Medicines Control Agency (the predecessor of the MHRA) was established as a Trading Fund that had to be self-sufficient and recoup its costs through fees charged to the industry for its assessment and control activities. The pharmaceutical industry has no choice but to pay the fees levied by Government.

6.9 The ABPI is supportive of the MHRA being properly funded so that it can operate efficiently and effectively as a centre of regulatory excellence in Europe. There are sufficient checks and balances in place to ensure independence from industry. Fee levels are set by the Treasury, following public consultation, and are detailed in the relevant UK statutory instruments. However, the pharmaceutical industry has asked for greater transparency from the MHRA on how income from fees is allocated. This is particularly

40 Medicines for Human Use (Marketing Authorisations, etc.) Regulations 1994.
important since the merger of the MCA and Medical Devices Agency, as most of MDA’s activities were previously funded by the Government. Fees for the control of medicines should not subsidise activities related to medical devices.

6.10 The industry would welcome any proposal to review the financing of the MHRA if this would help dispel any perception of undue influence.

Post Marketing Authorisation Phase

6.11 If a medicine is approved and obtains a licence to be marketed, this does not mean that the assessment of the medicine is finished. It marks the beginning for the applicant company of a legal obligation continuing throughout the lifetime of the medicine to provide the MHRA with information about the medicine both at regular intervals and on an ad hoc basis. The benefit/risk assessment of a medicine is a continuous process.

6.12 At the time of approval there will be extensive clinical data on the use of the medicine. However, companies have pharmacovigilance systems in place to monitor and assess the safe use of the medicine in the wider population after its launch and risk management plans to deal with any problems.

6.13 Newly approved medicines and significant changes to existing medicines are subject to intensive monitoring by the MHRA as part of the Committee on the Safety of Medicines (CSM) Yellow Card/Black Triangle scheme. This scheme allows rapid monitoring of potential new risks as medicines become more widely used in patients. The CSM is currently considering the introduction of direct reporting by patients of side effects through the Yellow Card scheme. Whilst the ABPI supports any improvements to strengthen the scheme, the reporting of side effects by patients without validation by a health professional could inundate the MHRA with reports of side effects that all require validation by the MHRA, and make accurate signal detection of actual ADRs difficult. Patient reporting has been introduced in the US, but required a significant increase in resource at the FDA in order to collect, analyse and validate the increased numbers of reported side effects.

6.14 Pharmaceutical companies and the MHRA continuously monitor Adverse Drug Reaction reports which companies submit expeditiously to the MHRA and also summarise regularly in Periodic Safety Update Reports (PSURs) submitted to the MHRA for in-depth review. Changes to the approved product information or labelling have to be based on evaluated scientific evidence, which involves open interaction between the relevant parties. The aim of this is to ensure that the medicines are used as safely as possible, without restricting access to patients who could benefit from the medicine. The requirement for pharmacovigilance is embodied in the pharmaceutical legislation and there are severe penalties for non-compliance. MHRA also conducts regular inspections and has enforcement powers if serious non-compliance is found.

Communication between Industry and Regulatory Authorities throughout the Lifecycle of a Medicine

6.15 There are clearly defined legislative requirements, which necessitate communication, dialogue and the submission of data from industry to the MHRA during the life-cycle of a medicine. Such regular dialogue is in the public interest to ensure that effective and safe new medicines reach the patient as quickly as possible. It is essential that this integral part of the regulatory framework is continued throughout the various regulatory processes, including pharmacovigilance.

6.16 It takes an average of 12 years to develop a new medicine and various issues of a technical or scientific nature might arise during this process where written guidance is not available. It is important to ensure that the right development programme is carried out to enable registration of safe and effective new medicines in the most efficient way and avoid unnecessary clinical trials or delays in getting new medicines to the patients.

6.17 During the regulatory review of a new medicine, or a change to an existing medicine, there is an ongoing dialogue between the applicant company and the MHRA. The applicant company explains the data, provides clarifications and answers questions based on the scientific evidence provided. Through such dialogue, the MHRA is able to make decisions on the safety, quality and efficacy of the medicine based on the totality of the evidence available and the proposed usage.

6.18 Good communication channels between the MHRA and the company are also essential when the MHRA requires information from companies, often at very short notice (eg the safety review on TSE41).

6.19 Input from the industry and other stakeholders during the drafting of guidelines on issues such as clinical trials and manufacturing standards is essential to highlight the practical implications of such guidance particularly given industry’s knowledge of future likely scientific developments.

41 Review of all medicines to minimise the risk of transmission of Transmissible Spongiform Encephalopathies.
Future improvements

6.20 Not only is a strong, efficient and effective UK regulatory agency necessary for ensuring the safety of public health, it is also fundamental to drive a competitive UK-based pharmaceutical industry that will develop innovative medicines for the benefit of patients. The impact of the establishment of the European Medicines Evaluation Agency on the EU regulatory environment has been significant. Companies now have the possibility to select any one of the 25 Member States to assess their medicines. Experience shows that companies select European regulatory agencies that not only provide high scientific excellence, but also consider customer service and efficient performance. In order to be selected by companies the MHRA must promote their specialist expertise in particular therapeutic areas in order to distinguish themselves from the other leading regulatory agencies.

6.21 The MHRA is considered to be one of the top five leading regulatory agencies in Europe. Findings in the National Audit Office Report on the MCA42 (the MHRA’s predecessor) indicated that the Agency would be looking to improve the quality of the services it provides to industry in order to attract more business. The ABPI strongly supports the ongoing development of the MHRA as the leading regulatory agency in Europe but this will require dedicated high-quality staff who are sufficiently senior and experienced to chair key European scientific committees.

6.22 The Medicines Commission has appointed individuals to its membership who have expertise in the pharmaceutical industry since it was formed in 1968 and the industry has also provided advice to the previous MCA Executive Board on the Agency’s performance through representation on the Ministerial Advisory Board. The ABPI believes that the presence of such persons on these advisory bodies has been essential in providing information about the practical implications of medicines regulation policy and feedback on the Agency’s performance from one of its major stakeholders. The continued presence of people with industry expertise on the MHRA’s Board and the Medicines Commission, or its replacement, is recommended.

7. Product Evaluation, Including Assessments of Value for Money

— Industry’s participation in NICE health technology assessments are vital in developing effective guidance for the NHS.
— NICE has itself sought the participation of industry in various consultative groups.
— Lack of implementation of NICE recommendations remains a major issue.
— Faster patient access to clinically and cost-effective technologies would be promoted by a number of initiatives.
— Industry should be engaged as a full partner both in these initiatives and in implementation activities more generally.
— Varying processes in England, Scotland and Wales need to avoid duplication to achieve best outcome for patients.

Introduction

7.1 The pharmaceutical industry is committed to ensuring equitable access to clinical and cost-effective treatments and to achieving faster uptake of new technologies. Through partnership and constructive engagement and with appropriate probity, the contribution of the pharmaceutical industry to Health Technology Assessment (HTA) is vital to the production and dissemination of robust, evidence-based guidance for the benefit of both patients and the NHS. The following comments relate principally to NICE but separate sections have been included on industry engagement with HTA bodies in Scotland and Wales.

The pharmaceutical industry as a NICE stakeholder

Submission of evidence

7.2 The ABPI welcomes NICE’s collaborative approach towards HTA. Company submissions are considered by the independent Appraisal Committees of NICE alongside those of patient/carer groups, health professional groups and NHS organisations.

7.3 NICE itself recognises the value of the industry submission in the appraisal process. NICE has declined to adopt the WHO’s recommendation43 that NICE should be presented with a single set of analyses (incorporating manufacturers’ input via consultation rather than separate submissions).

Partnership

7.4 The pharmaceutical industry is represented on the group which helps to develop NICE’s work programme (the Advisory Committee on Topic Selection). Industry contributes specialist knowledge and expertise helping to ensure that the most appropriate, suitable and relevant topics are referred.

7.5 NICE welcomes the contribution of pharmaceutical industry consultees on the Appraisal Committees, as they share experience which enhances the depth and quality of the appraisal. The probity of industry representation on both of these committees is assured by the Department of Health’s procedures with regard to conflicts of interest.

Constructive engagement

7.6 Industry has worked with NICE to achieve a more efficient, fair and transparent appraisals process, through regular dialogue between NICE and the ABPI’s National Health Technology Assessment/Clinical Guidelines (NHTA/CG) User group.

7.7 A good example of this constructive engagement has been the development of a framework on the use of confidential data, in response to the Health Select Committee’s concerns in 2002 about the transparency of the appraisal process. The framework sets out guidelines on what company data should be made public during a technology appraisal.

Further improvements

Ensuring quality and maintaining standards

7.8 The Health Select Committee’s 2002 report raised the issue of the quality of the work undertaken by the independent academic groups which produce the Health Technology Assessment (HTA) reports. This remains an issue, with variability in performance between the groups, and one on which the ABPI will collaborate further with NICE and the National Coordinating Centre for Health Technology Assessment.

7.9 There is a need for a common framework to improve consistency and quality control. The industry shares the Health Select Committee’s concerns with regard to the resourcing of the HTA centres.

7.10 There is also a need for the appeals process to be independent, robust and transparent. In particular by the nomination of an independent share of the appeals committee (which is currently chaired by the chairman of NICE). The appropriately constituted appeals committees are also restricted in the evidence they can consider by narrow and limiting criteria. This means that they cannot reach a fully informed decision on the issue at hand.

Clinical Guidelines

7.11 The development of NICE’s clinical guidelines programme, which industry supports, has helped to shift the focus in the direction recommended by the Health Select Committee. However, further clarity is necessary in the relationship between technology appraisals and clinical guidelines and the criteria for choosing between them.

7.12 The pharmaceutical industry has not been treated equitably by NICE in the development of NICE Clinical Guidelines. It is the only stakeholder that does not have access to or membership of the Guideline Development Groups which are responsible for compiling the guidelines. Approaches to NICE to improve this situation have been repeatedly rejected.

7.13 Increasingly, HTA guidance is being put into guidelines rather than going through the rigorous HTA development process which includes an opportunity for appeal. The process by which these decisions are made is opaque and of considerable concern to industry.

Implementation

7.14 The most important measure of the work of HTA bodies is their ultimate impact on patient access to new technologies. Industry has worked with patient groups and NICE to develop the evidence base which has identified inconsistent take-up of NICE guidance around the UK (see, for example, the relevant papers

linked to the NICE website), and has contributed to Professor Richards’s report on cancer services. A significant portion of this extensive evidence base was not available to the NHS without the contribution from the industry.

7.15 The UK still lags behind most other major countries in the adoption of new medicines. Industry looks forward to collaborating with NICE, the Health Care Commission, the Department of Health and NHS organisations to promote greater consistency between different parts of the country in patient access to clinically effective and cost effective technologies.

**HTA in Wales and Scotland**

All Wales Medicines Strategy Group (AWMSG)

7.16 The ABPI Cymru Wales Therapeutic Development Assessment (TDA) User Group has begun to meet regularly with the Welsh Medicines Partnership (WMP) in order to develop a more effective and workable assessment process. These changes in process are then considered by the All Wales Medicines Strategy Group (AWMSG)—Steering Committee “in camera”, before final public consideration by AWMSG.

Specifically the industry is working in Wales on the need:

— for early clarification of the scope of the assessment;
— to establish a means of treating “in confidence” material;
— to ensure retention of a transparent and robust appeals process; and
— for clearer timelines for the assessment process.

Scottish Medicines Consortium (SMC)

7.17 The SMC’s process for appraising new medicines has been developed in consultation with industry through constructive dialogue and active industry participation from its inception.

7.18 The SMC operates to the highest standards of probity, basing its policy on declaration of interests (in common with NICE) on that of the Medicines Commission, and publishes a register of interests for SMC members.

**Future developments**

7.19 Constructive engagement between industry and HTA agencies has helped to shape and establish fair and robust processes which are open to the sometimes conflicting views of a variety of stakeholders.

7.20 Faster patient access to clinically and cost effective technologies would be promoted by a number of initiatives:

— The Department of Health, in conjunction with NICE, the Health Care Commission, the NHS and industry, should actively promote NICE’s implementation support plan and act on the recommendations of Professor Richards’s report. Industry should be engaged as a full partner both in these initiatives and in implementation activities more generally.
— The Department of Health and local NHS organisations should work with industry to investigate instances of “NICE blight” and continue to develop mechanisms to address this issue in order to maintain and increase access to new medicines.
— The Department of Health and NICE, in conjunction with the National Coordinating Centre for Health Technology Assessment, should ensure that the HTA groups have sufficient professional capability to complete their work for NICE to the highest standard. Collaborative working between industry and the HTA groups should be promoted to ensure that NICE’s Appraisal Committees focus on the most important aspects of the decisions they are required to make.

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— Multiple technology appraisal processes have developed as a result of devolution. The Department of Health, Welsh Assembly Government and Health Department of the Scottish Executive should review these processes and devise a mechanism for sharing best practice across the three separate technology appraisal systems to avoid duplication of effort and achieve the best outcome for patients.
— The Department of Health should periodically review the operation of NICE, as recommended by the 2002 Health Select Committee report on NICE, at least every three years.
— Official documents referring to technology appraisals should highlight the value of industry submissions in assembling the evidence on which appraisals are based.

8. CONCLUSION

8.1 We trust this submission has highlighted to the Committee the indispensable nature of the partnership between the NHS and the pharmaceutical industry that serves it. Each needs the other. Interactions between the two are subject to stringent regulation in a wide variety of respects. However, it is critical for both the NHS’s effectiveness and the performance of this vital industry that the partnership be continuously enhanced to develop and deliver optimum treatment for the benefit of patients. We therefore look forward to discussing this with the Select Committee.

August 2004

Memorandum by the Bioindustry Association (PI 147)

I. INTRODUCTION

1. The BioIndustry Association (BIA) congratulates the Committee on this inquiry and is pleased to have the opportunity to submit evidence.
2. The BIA is the trade association for innovative enterprises in the UK bioscience sector. We represent over 350 members, the majority of which are involved in realising the human health benefits that bioscience promises.
3. The UK bioscience industry is the European leader and second globally only to the US. One third of Europe’s bioscience companies are in the UK.
4. At the end of 2002, the sector:
   — comprised 486 companies;
   — employed approximately 25,930 people;
   — had 225 new drugs in clinical development or awaiting approval; and
   — had 47 publicly quoted companies with a total market capitalisation of €9.7 billion.50
5. The BIA defines bioscience companies as those that are developing products or services that are derived from the study of living systems, or use living systems in their research, development and/or manufacturing activities. Such companies will typically be operating in the fields of human or animal healthcare, including diagnostics, therapeutics, vaccines and nutrition; environmental protection and remediation; or will be companies providing technical services to such companies.
6. The BIA, in conjunction with the DTI and the DH, last year led the Bioscience Innovation and Growth Team (BIGT), whose report, Bioscience 2015—Improving National Health, Increasing National Wealth,51 was published in November 2003.
7. Bioscience 2015 is the biggest policy review of the sector to date and follows months of consultation with more than 70 leading industry figures. The report, with a foreword by the Prime Minister, said the UK must act now to secure its leading position as other countries recognise the value of a vibrant bioscience sector. The recommendations in the report form the core of this written submission.
8. This response focuses on the following areas of the Committee’s inquiry:
   — drug innovation;
   — the conduct of medical research;
   — regulatory review of drug safety and efficacy; and
   — product evaluation.

50 All data from Critical I.
51 www.bioindustry.org/bigtreport
II. EXECUTIVE SUMMARY

9. The BIA makes the following points in this submission:

10. Unmet medical needs remain high and bioscience has the potential to address them, which would not only improve health but also the economics of preventative medicine and treatment of illness.

11. A supportive regulatory environment, both in the UK and EU, is critical to the ability of the UK bioscience sector to deliver human healthcare benefits. A growing number of regulatory decisions are made at EU level, many of which threaten to hamper the ability of the bioscience sector to develop medicines and to disincentive innovation.

12. Bioscience companies need adequate funding to ensure their ability to innovate and deliver new medicines and treatments.

13. Improving the UK’s clinical research infrastructure will help to deliver new treatments and cures for patients, give the UK the opportunity to become the world-leading location for clinical research, and attract industry, academia and investment to the UK.

14. Industry should work with NICE, MHRA and EMEA to improve transparency in order that MHRA, EMEA and industry engage early in the development process to discuss which patient outcomes will be important for subsequent acceptance.

15. More needs to be done to ensure early access to life-saving medicines for patients. The new EU pharmaceutical legislation (Regulation (EC) No 726/2004) is a helpful step towards introducing a system for provisional licensing of drugs, similar to the French Autorisations Temporaires d’Utilisation (ATU) de cohort system, which would make promising new treatments available to patients where a genuine public health need exists, often before the completion of Phase III clinical trials. However, it falls short of recognising that products supplied for compassionate use are equivalent to authorised products for the purpose of reimbursement.

16. A robust approval procedure for biosimilar medicines (please see definition in paragraph 65) is necessary not only to guarantee patient safety but also to protect the future of biotechnological innovation in the healthcare industry in the UK.

17. PPRS—price modulation across portfolios is a disincentive for innovative, emerging companies in the UK. If this and other bioscience-specific issues are to be fully discussed—for the benefit of patients, the NHS, and the taxpayer—representation of the bioscience sector needs to be ensured in future PPRS (or equivalent scheme) negotiations.

III. DRUG INNOVATION

(i) An innovative sector addressing unmet medical need

18. Biopharmaceutical drugs account for 8% of total global pharmaceutical market sales, and are the fastest growing part of the market. They will be an increasingly important part of the healthcare landscape over the next decade. One third of all drugs in development are now biologics. While non-chemical entity (NCE)-based pharmaceutical company growth is expected to slow, due to patent expirations and pipelines of incremental innovation, biopharmaceuticals are widely expected to deliver both improved R&D productivity and strong growth.

19. UK bioscience companies have produced 42 marketed biotech drugs with a further seven waiting for approval and at least 23 in phase III trials. The UK bioscience sector has the largest product pipeline in Europe, with 225 of the European total of 502 drugs in clinical development awaiting approval. UK companies have developed 43% of the products in late-stage clinical trials in Europe.

20. Unmet medical needs remain high and bioscience has the potential to address them, which would not only improve health but also the economics of preventative medicine and treatment of illness. New bioscience technologies, such as genomics, proteomics, and bioinformatics, have the potential to address many medical challenges. Although tests that enable early diagnosis and highly effective innovative treatments are expensive on a per unit basis, they can reduce the total cost of care and the economic burden of disease. A good example of this is seen with diabetes. Regranex, a recombinant treatment for diabetic foot ulcers, is expensive, with one 20-week treatment costing at least £550–825. However, combined with appropriate ulcer nursing, Regranex actually reduces the cost of care and improves health (providing more healthy months and fewer amputations) compared to the alternative of ulcer nursing on its own.

52 Biopharmaceutical drugs includes vaccines. all figures at ex-manufacturer prices. CAGR (compound annual growth rate) for biotech drugs 15% between 1997 and 2002 (Evaluate Pharma) vs 8% for total pharmaceutical market (IMS Health). Forecast biopharmaceutical drug growth: 17% CAGR 2002-07 (estimated from IMS Health 2003, Evaluate Pharma 2003, and analyst reports) www.evaluatepharma.com.

53 “In development” means Pre-clinical through Phase III. Source: Pharmaprojects, March 2003 www.pharmaprojects.co.uk.

54 PharmaProfiles2003.

55 Critical I.

56 E&Y 2003.

21. Bioscience has the potential to enable:
   — earlier identification of disease risk and disease diagnosis, through genetic screening and
diagnostics—eg as seen in breast cancer;
   — development of targeted drugs, with higher efficacy (because they focus on particular patient pools
or forms of disease), and improved safety (because they may reduce side effects);
   — faster and more precise detection of pathogens;
   — disease prevention through more effective and targeted vaccines;
   — new modes of treatment for previously untreatable conditions, eg engineered tissue, stem cell
therapies; and
   — Faster drug development, which will enable faster delivery to patients of critical treatments.

22. At the same time, it should be remembered that generally accepted pharmaceutical industry data
shows that it takes 10–15 years and in excess of $800 million to develop a drug launched in the US or
Europe and that less than half of these drugs ever repay their costs of development. Only one in nine drugs
entering clinical trials will ever be launched. Most UK bioscience companies are not yet profit-making. At
the start of 2003, there were 18 profitable bioscience companies in the UK.

(ii) Barriers to innovation

23. A supportive regulatory environment, both in the UK and EU, is critical to the ability of the UK
bioscience sector to deliver human healthcare benefits. The UK has been a leader in establishing
appropriate, science-based regulation in a number of areas, such as stem cell research. However, a growing
number of regulatory decisions are made at EU level many of which threaten to hamper the ability of the
bioscience sector to develop medicines. Often the real threat is from other EU Member States, which either
do not understand the potential benefits of bioscience or do not consider its continued development to be
a priority. This threat was highlighted by the Prime Minister in Prime Minister’s Question Time on
18 June 2003:

24. “The biotech industry in this country is immensely important, and it is important for its future that
decisions made by Government will be based on proper scientific evidence. It worries me that there are voices,
here and in the rest of Europe, that are not prepared to give enough consideration to the potential benefits as
well as the potential downsides.”

25. Bioscience 2015 recognised that “the increasing requirement of regulation, due to heightened concern
for the precautionary principle, threatens to stifle innovation.” The recently published Research for
Patient Benefit Working Party report also recognised that a review of the regulatory environment for
clinical research in the UK needs to take place.

26. Overly restrictive regulation reduces the incentive to investigate and develop innovative drug
therapies. It also lengthens the time, increases the cost, and constrains the market for innovative drugs,
usually without any increased patient safety. Bioscience companies have limited financial resources and are
producing innovative and expensive medicines, so these cumulative constraints weigh particularly heavily.

27. There is also a real risk that the health benefits of this regulatory tightening will be more than offset
by significant health costs, including:
   — loss of some drug development (due to lack of R&D);
   — delays in drugs reaching the market;
   — higher cost of new therapies leading to de facto rationing of supply; and
   — weakening of competition among suppliers through inhibition of new market entry.

28. An example of the increasing regulatory requirements from EU legislation is the recently
implemented Clinical Trials Directive, which tightens regulation, monitoring, and standards for early stage
clinical trials. Bioscience 2015 expressed serious concerns that the implementation of the Directive into
national legislation could have a negative impact on the attractiveness of the UK as a location for clinical
research, in terms of extra costs, and bureaucracy. The report also expressed real concerns, in particular,
about the requirement for all Investigative Medicinal Products (IMPs) to be Good Manufacturing Practice
(GMP) compliant, and the increase in statutory time periods for regulatory and Ethics Committee approval
of trials.

58 Tufts.
59 Critical I.
60 Bioscience 2015, p 50.
61 http://www.dh.gov.uk/assetRoot/04/08/26/75/04082675.PDF.
29. The MHRA’s commitment to appropriate implementation of the Directive was key; it took on board industry’s concerns about the possible crippling impact of the Directive on early stage research, in fact delaying implementation of the Directive to further examine these issues. The BIA believes that the implementing Regulations in the UK are as sensible as they could have been, although the impact of the Directive over time will need to be monitored.

30. Another recent example of EU over-regulation concerns the recent revision of the EU Technology Transfer Block Exemption Regulation (TTBER), which came into force in May 2004. The TTBER is a set of terms and principles that allows the drafting of commercially viable licensing agreements with reasonable certainty that they will not be found to be anti-competitive under competition law. The industry has operated successfully with the old TTBER but the new rules will mean that most licensing agreements—the life-blood of the bioscience industry—will lose the certainty of the TTBER regime.

31. To come within the new rules, companies working together must now not have a combined market share of more than 30% of either technology or products. The innovative nature of the bioscience sector means that companies can find themselves at times with a high, even a 100%, market share. Many bioscience licensing agreements will now fall outside the new Block Exemption, resulting in higher legal costs—an unnecessary and unhelpful burden for emerging, innovative companies. The BIA is monitoring the impact in practice of the revised Regulation on licensing agreements and would be happy to keep the Committee informed of results of this work.

32. Increased uncertainty and additional bureaucracy, of which the Clinical Trials Directive and the TTBER are but two examples, could reduce the ability of the industry to deliver new treatments for the many life-threatening and debilitating diseases that still have no cure. This flies in the face of the European Commission’s own Life Sciences and Biotechnology Strategy and its recently launched consultation, “Innovate for a competitive Europe”. If the regulatory environment continues to stifle innovation, the real losers will be the end-users—patients.

(iii) Innovation—the impact of consolidation

33. A key driver of innovation is the ability of companies to access sufficient capital to undertake the research and product development required in order to bring life-changing/life-enhancing or life-saving drugs to the user.

34. In the long term, there are benefits for both patients and the NHS if pioneering drug companies are able to innovate, grow and develop products and still remain UK-based, without automatically being acquired by other, larger companies once they reach a certain size.

35. Currently, there are many excellent UK bioscience companies with world-class science and management, whose ability to continue to innovate from the UK is hampered because of an unequal “equity playing field”. In simple terms, successful innovative UK biotech companies grow to a certain point when their capital requirements mean that they are nearly always obliged to access US capital markets in order to continue the drug innovation process, which itself often means being acquired by large companies.

36. We now need to ensure that UK bioscience companies are adequately funded so that innovation can benefit. We hope that the Committee will agree that we owe it to all those suffering from illness to ensure that the UK remains a world leader in bioscience. Specifically, Bioscience 2015 recommended:

- Amending the pre-emption Guidelines to permit UK-listed life science companies to issue up to at least 20% of their share capital on a non-pre-emptive basis.
- Strongly supporting efforts to create a more accessible and liquid capital market for technology companies, through harmonisation of listing rules and through a LSE-led pan-European technology exchange.

37. These measures would have a positive impact on innovation and bring direct benefits to patients and procuring public bodies.

IV. THE CONDUCT OF MEDICAL RESEARCH

(i) Building a mutually advantageous collaboration between the NHS and Industry for patient benefit

38. The BIA would like to bring to the Committee’s attention one of the key recommendations in the Bioscience 2015 report in which the BIA is closely involved in taking forward.

39. Improving the UK’s clinical research infrastructure will help to deliver new treatments and cures for patients, give the UK the opportunity to become the world-leading location for clinical research, and attract industry, academia and investment to the UK.

40. The report recognised the need to ensure that UK patients must not be left behind in their access to innovative treatments. Tapping the full potential of the NHS patient pool was seen as a way of building sustainable competitive advantage in clinical research, and in bioscience, for the future. The power of this asset will grow over the coming 10 years, as new technologies such as genetics, transcript profiling, proteomics and metabonomics start to be used more frequently in clinical development and practice.
41. Bioscience companies find it challenging to access patients for clinical trials in the NHS. There is a lack of transparency regarding trials capacity; lack of simple co-ordination mechanisms for dealing with multiple trusts or research centres; lack of standard practices when it comes to collaborating with industry—though progress is being made in this area; and lack of the business mentality required to conduct these trials swiftly and to high quality standards. Medical consultants in some of the existing trials units express frustration at the need (as they see it) to solicit business personally and assist NHS Trust R&D offices handling contract negotiations. There are also clear infrastructure constraints: particularly a lack of clinical research facilities and the necessary research staff to support high quality execution.

42. The EU Clinical Trials Directive, which came into force in May 2004, will substantially increase the managerial burden of conducting trials, as regulatory measures that previously applied only to late stage trials will now affect all clinical trials of investigated medical product including Phase I trials. Importantly, in an increasingly decentralised NHS, there is no single organisation to champion clinical research and address the challenges above. Bioscience 2015 recommended the creation of a new organisational entity to fund and lead clinical research in the UK, together with the creation of a national network for clinical trials.

43. The Government responded to this recommendation by setting up the Research for Patient Benefit Working Party (RPBWP), under the Chairmanship of Professor Sir John Pattison, then Director of Research and Development at the Department of Health. The BIA welcomed the recommendation in the RPBWP’s Report that a UK Clinical Research Collaboration (UKCRC) be established, and the Secretary of State for Health’s subsequent announcement during the health budget debate on 22 March 2004 of the Government’s plan to implement this, involving the NHS, patients, the Medical Research Council, the Wellcome Trust, the medical charities and industry. The Secretary of State has also announced that a network of paediatric centres is to be established, that the mental health research network be expanded, and an infrastructure is to be developed to facilitate research into diabetes, Alzheimer’s and stroke.

44. The BIA represents the bioscience sector on the UKCRC Steering Group and values this opportunity to work with Government and other stakeholders to develop the opportunity presented by the creation of the UKCRC, current and future research networks for the benefit of patients. Industry involvement in the Steering Group is important in order to reflect the position of industry as a leader in research and a prime sponsor of high quality research.

45. It was also very positive that the Budget earlier this year explicitly recognised this recommendation to strengthen clinical research in the UK, and that funding has been earmarked to take this forward. In direct recognition of the Bioscience 2015 recommendation, the Chancellor announced that NHS funding for R&D will be increased by £100 million by 2008 and the combined budget for medical research and for R&D within the NHS will rise to around £1.2 billion a year by 2007–08.

(ii) Access to information on clinical trials

46. In order to ensure safety, efficacy and quality of licensed medicines, it is reasonable that all clinical trial data should be made available to the licensing authorities.

47. In addition, the BIA’s Code of Best Practice (please see next page for further details) points out that Companies must establish their own formal procedures for handling unpublished information which, if it were made public, would be likely to have a significant effect on the price of its listed or publicly traded shares or securities.

48. It is essential for the management of these companies to build and maintain the confidence of investors who rely upon projections and information about potential future revenues from the research and development pipeline in valuing the companies. Investors rely heavily upon these companies to communicate information in a way that they can understand. Investors also rely on analysts who interpret information emanating from companies. It is therefore of the utmost importance that companies constantly seek to apply best practice in their communications policies and activities.

49. It is very important, however, that the obligations a company has to release “financially sensitive” information is handled in confidence where it arises. It is also important that legal rights of companies are protected if misrepresentation of data via the Internet or the media has taken place.

(iii) The BIA Code of Best Practice

50. The BIA’s Code of Best Practice is mainly concerned with how companies publish and communicate information, particularly in relation to the development and commercialisation of products, technologies and services. The Code applies to bioscience companies that are members of the BIA.
51. The Code does not attempt to prescribe in detail how companies should operate and it would be impractical to try to do so. The Code contains general principles that BIA members should observe. Member companies that are expected to comply with the Code must report in the Directors’ Report in their annual report and accounts on how the principles have been applied. They must also report on compliance with the provisions of the Code and provide the reasons for any non-compliance.

52. The BIA wishes to act as a forum for establishing and developing best practice. The Code does not replace or override legal or regulatory requirements. It is designed to supplement and reinforce the London Stock Exchange’s rules and guidance—the Continuing Obligations Guide and the Guidance on the Dissemination of Price Sensitive Information.

V. REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY

(i) Making the case for innovation

53. The impact of overly restrictive regulation has been covered already in this submission. There is a real risk that this could adversely affect the health benefits that bioscience products have the potential to deliver.

54. The introduction of novel therapeutic approaches can lead to improved outcomes as well as reduced cost of patient care for healthcare providers such as the NHS. Newly launched products penetrate the UK market slowly relative to other countries slowly as it is—in 2000, only 16% of expenditure on medicines in the UK was on new medicines (of those launched between 1996 and 2000), compared with 25% in Germany, and over 33% in the US. The UK ranks above only Japan on this innovation index. It also lags Italy, France, Australia, Switzerland, Spain, and Canada.

55. Bioscience 2015 stressed that the case for innovation needs to be made, to signal the UK’s receptiveness to innovation and more assertively promote the advantages of technological research and scientific progress. The report highlighted the weakness of the precautionary principle that it does not allow account to be taken of what constitutes an acceptable risk. Society is generally poor at calibrating risk, eg patients suffering from acute disease usually have a different view of safety thresholds than healthy people. While innovation inevitably involves risk and cost, it also offers huge potential benefit.

(ii) Creating a collaborative relationship

56. Bioscience 2015 highlighted the need to create a collaborative relationship between the EU and UK drug approval regulators and the bioscience and biopharmaceutical industry.

57. The report recommended that industry should work with NICE, MHRA and EMEA to improve transparency in order that MHRA, EMEA and industry engage early in the development process to discuss which patient outcomes will be important for subsequent acceptance. This should take place along the lines of FDA-industry interaction.

58. It went on to recommend that MHRA and EMEA should seek to at least match the FDA’s target of reducing drug approval times by 10%, and that the FDA, EMEA and MHRA should also be encouraged to work closely together to ensure shared process and protocols.

(iii) Research Ethics Committee approval

59. A thorough but efficient ethics review process is central to the competitiveness in attracting clinical research. The new system was simplified on 1 March 2004, but is still slow.

60. A review is needed to look into actions that could be taken to improve NHS Trust approval. Delays caused by the R&D offices within NHS Trusts are probably the single cause for most of the delays and the reason why industry conducts trials abroad.

(iv) Making promising new treatments available

61. Drugs take 10–15 years to progress from initial research through to on-market sale, and spend at least three years in Phase III clinical trials and pre-registration. In some markets, pricing and reimbursement decisions further lengthen those timelines. Getting safe, innovative drugs to the patients who need them, quickly, is a shared objective of both industry and Government. However, more needs to be done to ensure early access to life-saving medicines for patients.

62. The BIA would like to bring to the Committee’s attention a key BIGT recommendation to introduce a system for provisional licensing of drugs, similar to the French Autorisations Temporaires d’Utilisation (ATU) de cohort system. This would make promising new treatments available to patients where a genuine public health need exists, often before the completion of Phase III clinical trials.

63. The system was introduced under the French Social Security Code in 1994. It is an exceptional measure for compassionate use of medicines, allowing the sale of drugs that have not yet been granted a marketing authorisation. The aim of ATUs is to provide early access to new promising treatments where a genuine public health need exists—where there is no alternative available. The diseases most frequently concerned are cancers, infectious diseases such as AIDS, and neurological disorders. ATUs are typically granted for drugs where there is a strong presumption of efficacy against an acceptable safety profile. This typically occurs at an advanced stage of clinical development when, for example, a marketing authorisation application is in the course of production or registration.

64. Drugs that received ATU status from the French regulatory authority AFSSAPS are included in the list of medicinal products approved for hospital use, thus permitting reimbursement. Pharmacies of healthcare establishment are authorised to purchase the ATU approved products.

65. The new EU pharmaceutical legislation (Regulation (EC) No 726/2004) is a helpful step towards this, laying the foundation for an EU-wide framework for compassionate use of medicinal products in advance of authorisation and providing the opportunity for Member States to implement a fast-track registration procedure, conditional marketing authorisations. However, it falls short of recognising that products supplied for compassionate use are equivalent to authorised products for the purpose of reimbursement; pricing and reimbursement fall within the national competence.

(v) Regulation of biosimilar medicines

66. A biologic is a medicine that can be made only by using a living system/organism. Biologics have large, complex, inherently diverse molecular structures. A so-called similar biological medicinal product (a “biosimilar”) is a product that purports to be similar to a reference biological medicinal product manufactured by an innovative biopharmaceutical company.

67. Since biological medicinal products are inherently different and more complex than small chemical molecules, they must be approved under strict conditions to guarantee patient safety. With the adoption of the EU pharmaceutical review package earlier this year, the EU has established a regulatory and legislative pathway for the approval of such medicines, together with other, earlier adopted Directives and supporting EMEA guidelines. In short this pathway states that contrary to what is required for generics, the application for a marketing authorisation for a biosimilar medicine must include appropriate pre-clinical and clinical data, to establish safety and efficacy, on a case-by-case basis.

68. Biosimilar medicines are not identical or “substitutable” to the original product the way generic drugs can be substituted, because they are not made from the same parent cell or via the same manufacturing process, and thus cannot be an exact copy or “generic”.

69. Small differences in the production process of biological medicines can yield vastly different products. A faulty or imprecise “copy” of a biologic might appear to be the same as the original product, but can cause extreme side effects in patients and could raise serious safety concerns. It is therefore right that the legitimate attempts to make and market biosimilars should not compromise patient safety. The field of biopharmaceuticals is a very new one. The first biopharmaceuticals will be coming off patent very soon, paving the way for other companies to copy these products and sell them. Now is the time to get the definitions and the conditions right to ensure that the products offered to patients are as safe, as efficacious and of as high quality as the original products.

70. The system needs to ensure that what the patients are getting is safe, but it also needs to ensure that the emerging biopharmaceutical sector can develop. Safety issues that might arise due to inadequate approval regulations for biosimilars would damage the development of bioscience in the UK and Europe. We therefore believe that a strict approval procedure is necessary not only to guarantee patient safety but also to protect the future of biotechnological innovation in the healthcare industry in the UK.

VI. PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY

(i) NICE

71. As outlined in Bioscience 2015, there are concerns about how quickly drugs can be effectively marketed in the UK after approval. Particular difficulties are foreseen with new bioscience products. NICE has an emphasis on mainstream drugs, whereas the bioscience industry often has niche products where the patient numbers involved falls below NICE’s economic threshold. As a review by NICE of a new drug comes after approval of that drug through the MHRA or EMEA and before its availability to the NHS, it can be a barrier to diffusion. In addition, nothing has been done so far to rectify the “postcode prescribing”, which is widely publicised, especially in the oncology area.

72. Bioscience 2015 recommended that: industry should work with NICE, MHRA and EMEA to improve transparency in order that NICE is aware of clinical trials data at the earliest appropriate moment for each individual company. NICE and industry should engage in mutual education—about, for example,
which drugs NICE will look at, NICE criteria for niche medicines/therapies, and the best framework for evaluating total cost of care. In addition, NICE should take full account of the wider economics of health and social care when making decisions about the cost-effectiveness of therapies.

(ii) PPRS

73. The PPRS is an agreement for the purposes of Section 33 of the Health Act 1999. The objectives for the scheme are that it should continue to:

— secure the provision of safe and effective medicines for the NHS at reasonable prices; and
— promote a strong and profitable pharmaceutical industry capable of such sustained research and development expenditure as should lead to the future availability of new and improved medicines.

74. An issue that has been raised with the BIA by several bioscience companies in the context of the PPRS is that of price modulation across portfolios. This related to a mechanism whereby companies with portfolios are able to maintain prices on individual products, providing that sufficient price cuts are made on other products in the portfolio. The problem that this presents for bioscience companies is that they are likely to have a small portfolio—often one or two products.

75. Consequently, the option of making price cuts across the portfolio is not open to them, putting them at a significant disadvantage to larger companies with larger portfolios. This is a definite disincentive for innovative, emerging companies in the UK.

76. Moving forward, as more bioscience products reach the market, not only will this issue affect a greater number of bioscience companies, it is also likely that more issues specific to the bioscience sector will become pertinent to the PPRS negotiations. If these issues are to be fully discussed—for the benefit of patients, the NHS, and the taxpayer—representation of the bioscience sector needs to be ensured in future PPRS (or equivalent scheme) negotiations.

Memorandum by the British Generic Manufacturers Association (PI 148)

I. SUMMARY

1. The role of the generic pharmaceutical industry within the NHS is:

— To provide low-cost high-quality versions of older medicines once the patent protection on those products lapses, thus reducing the medicines bill and allowing the NHS to pay higher prices for branded medicines, ensuring that originator pharmaceutical companies have the funds to research and develop truly new innovative products (the “headroom” principle).

— To provide competition for older medicines produced by originator pharmaceutical companies, thus offering a commercial impetus for them to research truly innovative new chemical entities against which generic medicines cannot compete during the period of patent protection.

2. These principles have been adopted and endorsed both by the European Commission, and the UK Government. However, the launch of generic equivalents to branded products does not always take place immediately following expiry of the patent protection enjoyed by the brand. In some cases, this may be due to technical or scientific issues.

3. In others, however, it can be due to a failure of the policy and legislative framework within which the generic pharmaceutical industry must rightly operate, and this failure may be subject to influence exerted by the originator branded pharmaceutical industry. Clearly, if originators are able to delay the launch of generic versions of their products, they extend the commercial life of them.

4. We believe that the Government should be more alert to activity undertaken to produce this “evergreening”, and act in a more concerted and joined up way to prevent it happening. Only in that way will the Government ensure that the NHS fully benefits from the reduction in the prices of medicines brought about by generic competition.

II. THE BRITISH GENERIC MANUFACTURERS ASSOCIATION (BGMA)

5. The BGMA is the representative trade body of the manufacturers and suppliers of generic medicines in the United Kingdom. Our members are: APS/Berk (Teva), Alpharma, Crescent Pharma, Dr Reddy’s Laboratories, Generics UK (Merck), Genus Pharmaceuticals (Stada), IVAX, Kent Pharmaceuticals, Ranbaxy, ratiopharm, Rosemont, Sandoz and Sterwin (Sanofi).

6. We believe that our membership accounts for more than 80% of the supply of generic medicines in the UK.
III. GENERIC MEDICINES

7. A generic medicine is one that contains the same active ingredient as an original branded product. It is subject to the same regulatory standards of safety, quality and efficacy as the original brand; and, before being marketed in the UK, must similarly receive a marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA).

8. However, rather than having unnecessarily to reproduce data relating to preclinical and clinical trials as with an originator product, a generic manufacturer instead needs to demonstrate that the generic product is essentially similar to the original brand in terms of its effect on the patient. This not only avoids the need for unnecessary trials on animals and humans, but reduces the research and development costs involved in bringing a generic medicine to the marketplace.

9. Under current UK legislation, a generic manufacturer may make a so-called abridged application for a marketing authorisation to the MHRA, based on demonstrating “essential similarity” 10 years after the commercial launch of the original product. Once the MHRA has issued a marketing authorisation, the generic medicine may be launched, so long as any relevant patents on the original brand have expired. It may take two years or more to develop a generic version of an original brand.

10. Thus, after the expiry of the patent or patents covering an original branded medicine, there are a number of versions of that medicine in the marketplace: the original brand, and any number of generics, depending upon the number of generic manufacturers that chose to launch the product. Under a community pharmacist’s terms of service, the pharmacist must dispense the brand if the GP writes a prescription for the brand; but a prescription written generically may be met by the generic or the brand (since the two are equivalent and thus interchangeable). In the latter case, however, the community pharmacist is reimbursed at the lower generic price, even if the brand is dispensed.

11. The reimbursement price of a branded medicine under the NHS is directly related, and can be close to its market price. Market prices are only indirectly regulated by the Department of Health under the Pharmaceutical Pricing Regulation Scheme (PPRS), which sets a limit on the overall profit that members of the Scheme are able to make. The PPRS takes account of the very significant research costs borne by the branded sector and also provides allowances for promotional and advertising activities.

12. Because there are typically a number of suppliers of most generic medicines, the market price paid by community pharmacists and wholesalers is set by competition between generic manufacturers. Different generic manufacturers compete largely, but not wholly, on the basis of the price of their products. The reimbursement price paid to community pharmacists by the NHS (the Drug Tariff price) is determined on a monthly basis by the Department of Health and is based upon a weighted average of the list prices of five suppliers (three generic manufacturers and two wholesalers, the latter contribution being weighted double: ie, manufacturers provide three sevenths of the prices taken into account, and wholesalers four sevenths).

13. Competition naturally drives down prices and, according to the latest published Department of Health statistics, generic medicines account for 55% of prescriptions dispensed, at a cost of only 24% of the drugs budget. On this basis, if there were no generics available, and all medicines paid for by the NHS were priced at the average cost of brands today, the drugs bill would increase by over £5 billion.

14. [In fact, we believe that the savings due to generics could be significantly greater than this because the current reimbursement price does not fully reflect discounts from list prices that are offered by generic manufacturers. With others, we have been working with the Department of Health to agree a more realistic reimbursement scheme which will ensure that the NHS fully benefits from the savings due to generic medicines.]

IV. DELAY IN THE LAUNCH OF GENERICS

15. It is clear, therefore, that any delay in the launch of a new generic after expiry of the patent or patents on an original brand is potentially very expensive for the NHS. We set out below some recent examples of where delay has been caused, at least in part due to the influence or actions of the originator branded pharmaceutical industry.

16. In many cases, the delay is due to the brand originator changing the active ingredient, formulation or pharmaceutical form shortly before patent expiry. Generic manufacturers will already be well down the road of developing generic versions of the original product. Launch of the changed version of the brand often leads to GPs prescribing the new version—particularly if the originator has withdrawn the first version from the market—and thus there is no market for the generic under development.

63 Changes to the detail but not the principle are due to be implemented next year.
64 It is open to a generic manufacturer to make a different form of application before the expiry of this ten-year period of “data exclusivity” by undertaking its own preclinical and clinical trials; but an abridged application under which the MHRA compares the similarity of the generic with the data submitted by the brand originator in support of its application is the normal way of bringing a generic to the market.
65 Other competitive factors include quality of service, range of products available, customer loyalty schemes, etc.
17. Developing the revised version may take another two years or more, delaying generic launch by that period. Alternatively, the brand originator may claim data exclusivity on the revised form, delaying generic launch by 10 years (though the recently adopted revised EU pharmaceutical legislation limits the scope for this in future).66

18. In making these points, we must make clear that we do not seek to undermine the legitimate rights of the originator sector, nor criticise them for making the most of available opportunities to extend the commercial life of their products, especially where real benefits are given to patients and are cost-effective. However, it is crucial for everyone concerned in the NHS, not least patients, that the creative energies of the originator pharmaceutical companies are directed to researching and developing new medicines, which will become generic medicines in due time, rather than working to extend the commercial life of their older products and reducing the headroom created to pay for true innovation.

(i) **Chiral switching (Example: Omeprazole/Esomeprazole)**

19. Most commonly used drugs are administered as 50:50 mixtures (also known as racemic) of enantiomers, a type of optical or stereoisomers. These are left-handed and right-handed 3-D forms of the same molecule. The originator company usually first markets its product as a racemic mixture.

20. With a view to evergreening or extending the return on the originator product and delaying generic competition, it has become a common strategy for originator companies to develop and market different mixtures of, or single isomer forms of the original product, and gain extra patent and other intellectual property protection on the new product. These invariably have no or only marginal therapeutic benefit to patients over the first originator product. Where these new products are introduced, changes to prescribing habits are promoted further restricting the market for the previously available form.

21. In this case, the originator sought to establish a distinct identity for the single isomer version by obtaining a marketing authorisation for it to be used at twice the strength of the original product (40mg for indications where 20mg was traditionally used and 20mg where 10mg was used).

22. Marketing to GPs to prescribe the single isomer version undermined the market for generic versions of the original form which had been developed ready for launch.

23. Issues surrounding the introduction of esomeprazole are currently the subject of a competition inquiry by the European Commission.

(ii) **Switching to active metabolite (Example: Loratadine)**

24. Originators can also switch the active metabolite, potentially to the more active isomer.

25. The withdrawal of loratadine and its replacement with desloratadine prior to patent expiry similarly meant that there was no market for generic loratadine once it became available since GPs had changed to prescribing the new form, desloratadine.

(iii) **Different formulations (Examples: Doxazosin and Mirtazapine)**

26. In this case, different formulations are marketed, usually based on sustained release technologies. Historically, they were marketed alongside the original brand but increasingly they are replacing the original product.

27. Just before patent expiry the originator marketed a sustained release version of doxazosin and discontinued the corresponding strength of the conventional product.

28. Just before patent expiry the originator marketed a soluble version of Mirtazapine (Soltab) and discontinued their tablet form.

29. In each case, prescribing patterns changed so that there was a reduced market for the generic.

(iv) **Different presentations (Example: Ramipril)**

30. Ramipril was licensed and sold in the UK as a capsule. Elsewhere in Europe, it was presented as a tablet. The patent expired on 9 January 2004, at which point generic manufacturers were ready to launch Ramipril capsules.

31. The originator attempted to withdraw the capsule form in the UK, intending to replace it with the tablet form, to be sold at the same price as the capsule. The originator contacted all major wholesalers and retail suppliers informing them that capsules would be replaced by tablets with effect from 3 November 2004. A large number of GP prescribing computer systems were also changed to list and print prescriptions for the tablet form and not for capsules. Pharmacists would be required to dispense tablets if that form was specified on the prescription.

66 See footnote 2 for an explanation of “data exclusivity”.
32. If action had not been taken there would have been very little or no market for Ramipril in the capsule form, when patent expiry took place in January 2004, if the majority of prescriptions had required the tablet to be dispensed. It would have taken generic manufacturers two or three years to undertake from scratch the development work for the tablet form, and gain authorisation from the MHRA.

(v) Different salts (Example: Amlodipine)

33. Medicinally active chemical entities are commonly insoluble in water and are therefore manufactured in salt form to increase solubility. One of the decisions of the recent European Pharmaceutical Review was that a generic may be based upon a different salt than that of the brand if the products can be shown to have the same safety and efficacy profile. This is logical given that it is the medicinally active chemical entity that provides therapeutic benefit to patients.

34. The Amlodipine base is not water soluble, and must therefore be manufactured in salt form. The brand is manufactured as amlodipine besilate. Other salt forms include amlodipine maleate and amlodipine mesilate. Generic versions are based upon these latter two salts since, although the patent on the amlodipine base expired on 7 March 2004, there is a further patent on amlodipine besilate which does not expire until 25 March 2007.

35. The originator company wrote to GPs, in March 2004, advising that alternative salt forms were not identical to the brand (amlodipine besilate), despite the European Medicines Evaluation Agency having confirmed that the two salts were equivalent in adjudicating upon two arbitrations. In parallel, many of the GP prescribing software packages automatically produced apparently “generic” prescriptions for amlodipine besilate (ie, the brand) due to the generic description entered in the product’s Summary of Product Characteristics by the originator.

36. We are still working to ensure that GPs’ software produces a generic descriptor when desired by the GP that is salt neutral and allows all forms of amlodipine to be supplied by a pharmacist.

(vi) Costs of delays

37. We have calculated below the potential cost over one year to the NHS should these circumstances lead to a delay in the onset of generic competition. In doing so, we have used two hypotheses: first, that the generic would take 50% of the market, and reduce market prices by 50%; and, secondly, that the generic would take 75% of the market and reduce market prices by 75% (the latter being more normal).

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<th>NHS annual saving</th>
<th>75% becomes generic and 75% price drop</th>
<th>NHS annual saving</th>
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V. Patent Law

38. The generic industry is facing growing difficulties in launching new products due to the increasing number of patents on very minor or marginal changes to pharmaceutical products. There is evidence that this could become the principal obstacle facing the industry. As an example, in the year 2000, the US Patent Office granted 6,730 pharmaceutical patents whilst the US Food and Drug Administration only registered 27 new chemical entities.
39. This growing global trend has the effect of delaying the entry of new generic products, and allows the originator industry to reap continuing benefit from its older products. This not only keeps the cost of medicines unnecessary high, but reduces the incentive on the originator sector to develop truly innovative new chemical entities.

40. We believe that more should be done to simplify current patent structures, and to ensure that the growing trend of establishing numerous patents on superfluous aspects of medicines for the sake of prolonging market exclusivity should not be allowed to become common practice in the UK and the EU. This is particularly important in the light of the newly adopted EU legislation on the enforcement of intellectual property protection.

VI. BRAND EQUALISATION

41. We are also concerned about the way in which branded and generic medicines are treated under the Government’s approach to reimbursement. This allows the branded sector to use the flexibility it enjoys under the PPRS to compete with generics in the post-patent market in a way that is unfair and which lessens the cost savings that the NHS would otherwise enjoy as a result of generic competition.

42. Under so-called “brand equalisation”, the brand originator sells a proportion of his product at the generic market price, thus allowing pharmacists to dispense a branded product against a prescription written and reimbursed generically without suffering any commercial disadvantage. Branded companies may similarly be able to “balance” prices across their patented and non-patented portfolio to gain a greater market share in segments of the market where they face the greatest competition, such as primary care. Notwithstanding the restrictions placed on modulation in the current PPRS, branded companies are able to manage the pricing of the portfolios in this way.

43. We believe that this form of competition acts against the interests of the taxpayer and patients, as well as those of the generic pharmaceutical industry. At a time when the Government intends to change the way in which generic medicines are reimbursed, we believe that it is crucial to ensure that the current competitive balance between true generics and off-patent brands is not tilted in favour of brands.

44. Indeed, we believe that it is essential that the Government ensures that the impact on this competition is properly assessed in the light of its proposals to amend the generic reimbursement scheme, and as part of its consideration of changes to the PPRS. This is apparently not being done.

45. We believe that the current scope of PPRS does not reflect the operation of the marketplace, and is thus wrong. As we have commented above, off-patent brands and generics compete in the marketplace to meet prescriptions written generically. Broadly, the PPRS applies to brands and the generic reimbursement system to generics. These are not, however, two distinct markets. Rather, there is an on-patent market and an off-patent market. The Government’s schemes for managing the price of medicines to the NHS should reflect this market reality.

46. For on-patent markets, competition takes place in the doctor’s surgery. Brand originator companies market their products to encourage doctors to prescribe their brand. (Even if doctors prescribe an on-patent medicine generically, only the brand will be available.) For products still under patent, therefore, there is no competition outside of the doctor’s surgery: once the prescribing decision has been taken, they enjoy a monopoly in the marketplace.

47. Once a product’s patent has expired, however, the scope of competition normally increases dramatically. If the product is prescribed generically, the prescription can be met by a generic medicine, typically manufactured and marketed by a number of competing companies, or by a brand. There is, therefore, usually very considerable competition at pharmacy (and wholesale) level. However, if the brand originator succeeds in persuading doctors to continue to prescribe the brand after patent expiry, no price competition exists at pharmacy or wholesale level.

48. We believe that these features of the marketplace under the current twin systems of price regulation (the PPRS and the generic pricing in the Drug Tariff) act against the interests of the NHS and the taxpayer. We believe that the market would be more competitive and more dynamic, and more closely meet the public policy principle of “headroom”, if one form of price regulation—the PPRS or its successor—were to apply to the on-patent market, and another—the proposed revised generic reimbursement scheme—to the off-patent market.

49. We have urged the Department of Health to seek to renegotiate the PPRS along these lines.

VII. CONCLUSION

50. The Department of Health has from time to time intervened to ensure that the launch of generics, and the benefit that that brings for the NHS, is not delayed and is fully realised. That intervention has, however, been sporadic and ad hoc. There has, further, been little co-ordination between the different government agencies involved, and external suppliers to the NHS.
51. We believe that, if the NHS is to achieve the maximum benefit from generic competition, the Department needs to take a more holistic approach. We have raised these issues with them and are confident that they will respond positively. We should, however, very much welcome the Committee’s endorsement of this view.

16 August 2004

Witnesses: Dr Richard Barker, Director General, and Mr Vincent Lawton, President, Association of the British Pharmaceutical Industry, Dr David Chiswell, Chairman, BioIndustry Association, and Mr Simon Clark, Chairman, British Generic Manufacturers Association, were examined.

Q720 Chairman: Could I ask you each to introduce yourselves briefly to the Committee.

Dr Barker: Richard Barker, the Director General of the ABPI. It is post I have held for only four months. Before that I was involved in the biotechnology industry, in the United States principally.

Mr Lawton: I am Vincent Lawton. I am the current President of the ABPI and managing director of Merck Sharp and Dohme a pharmaceutical company.

Mr Clark: Simon Clark. I am Chairman of the British Generic Manufacturers Association. If I could just clarify a slight difference from the branded sector: the branded sector is focused on promoting to physicians to influence the type of medicine that they choose, but as far as the generic sector is concerned we focus our promotion on pharmacists to influence which company they may choose to purchase the off-patent product from.

Dr Chiswell: I am David Chiswell. I am currently Chairman BioIndustry Association, which is a trade company for the emerging companies in the sector. Previously I was founder of CAO (Cambridge Antibody Technology).

Q721 Chairman: Could I ask a brief overall question along the lines I asked at the start of the previous session—and I think you were here, so you heard broadly the discussion that we had—about the issue that is at the core of this inquiry, it is okay as it is. If we look at the position where in 10 years’ time we have overall an environment which is the same as it is today, we will be quite happy, I think there are some improvements we could see. I think there has been a trend over the years for longer clinical trials, for example, and longer regulatory review periods. I am not sure that is wholly to the benefit of anyone and often it is because of bureaucracy rather than real safety or real efficacy. I think if we could roll that back a little bit, and find mechanisms, if a new drug comes along which really meets a pressing medical need, where that can get into the patients more quickly, that would be to the benefit of everyone.

Mr Lawton: I think the answers given in the previous session and also by Vincent are absolutely appropriate, that it is all with the focus on the patient. We are all patients, or we all will be, and, if we focus on something which is good for the patient, that is good for the industry and it is good for the public health. We also have to recognise that we, as patients, change. Patients change and, particularly with reference to the last session, patients are going to know more about their conditions, real or imagined. I think that is the world we have to live in as professionals. Wherever you are in the medical world, the patient should know more. That is going to be to the benefit of us all in the long run.

Q722 Chairman: Your organisation, you have said, represents the emerging companies. Are the regulatory mechanisms that we have now a problem? Do we have the balance right in terms of those mechanisms from their perspective? Or are you faced with concerns being expressed by some of these people you represent over the current arrangements for regulation?

Dr Chiswell: We live in an industry which needs to be regulated. I think that within the UK generally it is okay as it is. If we look at the position where in 10 years’ time we have overall an environment which is the same as it is today, we will be quite happy, I think there are some improvements we could see. I think there has been a trend over the years for longer clinical trials, for example, and longer regulatory review periods. I am not sure that is wholly to the benefit of anyone and often it is because of bureaucracy rather than real safety or real efficacy. I think if we could roll that back a little bit, and find mechanisms, if a new drug comes along which really meets a pressing medical need, where that can get into the patients more quickly, that would be to the benefit of everyone.

Mr Clark: If I could build on the comments that have been made and look at the latter stage of the lifecycle of a drug, the relationship between the branded original drug and the generic drug is symbiotic in a lot of respects, in that, for the first in excess of 10 years, the branded drug enjoys a period of a monopoly market place. That is imperative in order that the R&D investment is recuperated. However, at the end of that period it is also imperative we see a thriving generic market, because that delivers three principal benefits. The
first benefit is that on the launch of a generic to the market place we see a reduction in the price of that drug. That is a direct saving to the NHS to allow investment into other areas. One of those areas could be—which is the second benefit—investment into new and more innovative medicine. The third benefit that comes along from that is that then becomes an incentive on the originator company to invest further into new drugs which deliver real patient benefits and real clinical benefits to the patients and the needs of the NHS.

Q724 Mr Bradley: One or two questions about the maintenance of a successful UK industry, first of all, to the ABPI. In your evidence you regularly refer to the need to have the UK industry to be competitive. What should the Committee understand by that term? How do you think government, regulators, researchers, prescribers can help in that process of competitiveness as you describe it?

Mr Lawton: You will recall that there was a group set up in 1999 which is the Pharmaceutical Industry Competitiveness Task Force. This was an attempt to look at not so much the competitiveness of our industry but more the competitiveness of the UK as a place for our industry to invest. Over a year, working in conjunction with various departments, the Treasury, the Department of Trade and Industry, the Department of Health and so on, we established a series of benchmarks for things like clinical research, for the economic conditions, whether it was the tax or incentives or whatever, to do particular types of research and so forth, the infrastructure available. We update those benchmarks annually and look at ourselves against them. If I take clinical research, for example, which is critically important to furthering health care, the three components were quality, timeliness and cost. The quality in the UK is extremely high in general. It can be better and I think the royal Colleges have acknowledged the need for those who conduct clinical trials in general practice, for example, to have more training in how to do it, to be skilled in how to do this properly. In terms of the speed, we had a system of local and national ethics committees' approval of clinical trials, which used to run in series and now we have adjusted it so that they can run in parallel so that we can actually save time and be more competitive or as competitive as the best countries in Europe and the rest of the world. Then there is the issue of cost: How much does it cost to conduct a clinical trial in the UK compared to anywhere else? I think this is still where we have a difficulty. There is a lack of transparency as to why a particular cost is established. The price, for running a trial in one part of the UK can be significantly different from other parts of the UK. The UK is in fact the second most expensive place to conduct clinical trials after the United States in the world.

Mr Lawton: I can submit those to the Committee, Chairman. They are really quite dramatic differences of 100–200%. Because of no transparency in the way the price structure is established, it has been very difficult to break that open to see whether it related to real added value. But, having said that, the Chemical Clinical Research Group in the NHS, which includes the industry as participants, is looking at that and I think a tremendous amount of progress has been made. I am co-Chair of that particular group with Professor Sally Davis of the NHS.

Mr Lawton: If I may add another point, Chairman, the training of general practitioners, undergraduate training and postgraduate training, has something like—Dr Taylor is probably going to contradict me now but I hope not—five or six weeks only of clinical pharmacology. When you consider how long a doctor has to spend evaluating medicines, making decisions which really should include quite a reasonable in-depth knowledge of clinical pharmacology, that really is not enough. I think that should be another recommendation that early on in the education process of general practitioners this should happen. I have addressed the deans of the medical colleges about this. I think it is an extremely important point.

Q725 Chairman: Could you give me an example to illustrate that particular point of the costs in different parts of the UK?

Q726 Mr Bradley: You have touched on the next question. In your evidence you also say that it is inevitable that the industry will have a beneficial effect on the provision of health in the NHS. Would you all agree that that is inevitable?

Mr Lawton: The inevitability is bound by the quality of the research, the development and the medicines which we produce, and the relationship of those medicines to the clinical needs which pertain. Nearly half of the research and development which takes place in the UK is concentrated on the top four priorities of the NHS, so, in that sense, with those caveats of quality and real need, yes, I think it is inevitable.

Dr Chiswell: Whether at the emerging end of the industry or the more mature end of the industry, if you do not produce the goods that people want to buy, you are going to go out of business. Unless
your produce something which is good for patients somewhere, then your business is going to be limited. So I think there is an inevitability.

Q727 Mr Bradley: How would you describe good in that sense?

Dr Barker: I think it gets back a little bit to the point on which the Chairman started: where is the balance and why has the industry come under criticism? The phenomenon here is that we tend to consolidate the positives and focus on the negatives. Over the last five years we have seen breakthrough therapies on cancer, on age-related blindness, HIV, hepatitis. Many, many diseases have been successfully addressed, and in the pipeline we have new therapies on Alzheimer's disease and other forms of cancer, heart disease, osteoporosis, but we tend to say, “Thank you very much,” and forget rather quickly when these new medicines come forward. But they really only will have an inevitable benefit if the medicines are taken up. Just to reinforce the point that came up in the earlier session, we still use somewhere between only a quarter and a half the level of advanced cancer medicines than others countries in Western Europe. We still have the worse survival rate in breast cancer. These are not things to be proud of and we will only get the inevitable benefits that you are talking about if we do in fact create a culture which is very receptive to new medicines.

Q728 Mr Bradley: Dr Chiswell, in your evidence you underline the need to ensure that your bioscience industries are adequately funded and you refer to the inequalities in the playing field which force companies to go to capital markets in the US rather than the UK. Could you briefly explain why that is and what remedies you might want to bring forward that are realistic to tackle that problem?

Dr Chiswell: Before I do that, I would support the remedies that we have already talked about here, about access to medicines, getting them into the market place, because in the end that pulls everything through. Our companies are younger, they have no products on the market yet, as some of them do, we do not have the profitability yet as individual companies to drive the R&D that is required within this industry, so we need to fund that stage of the work for quite a long time, using investors and either private capital markets or venture capital funds all in the public equity markets. In this country, and in Europe in general, we have not been as successful in tapping those markets as they have been in the States. The States got going a little bit earlier than us: they obviously have a more entrepreneurial capitalism culture and it has proved easier in the past for the companies on the US markets, US-based companies, to raise the very significant amounts of capital required to build a new generation of pharmaceutical companies. Where we have been successful here, it has been in building companies like Amersham, where I used to work. They have built a model of health care but actually slowly and surely and not acquiring huge capital investments. So we are lacking some of the systems for pure capital investments and a lot of our competitive issues come along with, “What can we do to adjust this?” Obviously what we could do would be to think more European. If we look at the UK, we have been talking about the UK as being 3% of the pharmaceutical market. In our industry, say, the biotech industry, on some measures it is like San Diego. The number of companies we have, for example, you would not expect San Diego to succeed in investment of its own industry if it did not have a sort of US-based industry. Here we seem to think we can build our own UK industry without looking European. When the day comes that a successful Swiss company can be used in the London markets as a good model for a UK-based company, I think we will have turned a big corner. In the meantime, if we can support setting up a pan-European capital market, we can do things like the Government are doing by reviewing pre-emption rights—which actually is a technical limit on how we can raise cash on the public markets; we can make sure the research environment is good, well funded and free of pressure from extremists in the animal rights area. I think there is a lot of things that can be done around the areas where we need it.

Q729 Dr Taylor: Could I pick up on a point Dr Barker made, because you have suddenly made me realise that the slow up-take of new medicines really we have to divide into two groups. There are certain medicines where the slow up-take would be a jolly good thing (for example, things like Vioxx and some of the antidepressants) whereas the slow up-take of the real advances in the anti-cancer drugs is a very bad thing. Can you comment on that? How could you as an industry, instead of promoting a new NSAID, for example—and I do not accuse any of you of this—as a major breakthrough, you somehow let people and doctors know that the real advances are these anti-cancer drugs is a very bad thing. Can you comment on that? How could you as an industry, instead of promoting a new NSAID, for example—and I do not accuse any of you of this—as a major breakthrough, you somehow let people and doctors know that the real advances are these anti-cancer drugs, for example, which our PCTs probably have a huge amount of difficulty in affording?

Dr Barker: I think there is something of a false dichotomy there because some of the COX-2 inhibitors, for example, address issues that the non-steroidal previous generation of non-steroidal drugs do not. I was with a friend a few days ago whose knee pain is only dealt with by a COX-2 inhibitor. If it is a matter of mobility for individuals, as it is here, these things can be really quite important. The generations of medicines that you are talking about, unfortunately you have to get them out to a significant number of patients before you know that there are problems, therefore holding back the use of medicines, such as medicines for arthritis and pain, would not actually do us any good. We would see the side effects later and only be able to take action later. It is certainly true, however, that whatever your recommendations can do to ease the pressure on primary care trusts, which sometimes results in them putting pressure on doctors not to use these...
anti-cancer medicines—and cystic fibrosis is another example where we are well behind the rest of Europe in the use of therapies—would be good. The final point I would make is that NICE was set up to engage with the very issues you are talking about and has done a lot of very professional work, but the implementation of NICE recommendations in some of the areas that you have just mentioned we think lags, so anything you can come up with to reinforce the implementation of NICE recommendations we would support.

Mr Clark: I would like to build on your question but in a slightly different way. You asked a question about the slow up-take and you referred to it at the earlier end of the market, and I would like to jump us towards the importance of a fast up-take of generics within the market place as well. One of the things we found within the generic market is that you get the every rapid change in the pharmaceutical market. You will have a situation where you will have one branded product being marketed and then the following day the same product could be marketed by 10 or 20 different companies. That causes quite a bit of change within the department and the NHS, and one of the first areas that affects is obviously on the Mhra. It is one of the reasons why individual submissions come mostly from the generics’ area. One of the areas that they have struggled with is being able to resource the number of submissions coming through. We have seen over the last number of years actually the length of time in terms of approvals lengthening as they have coped with those submissions coming through. That leads to a delay in a generic coming on the market and savings being taken by the NHS. One way of rectifying that—and it is something we have already shared in a meeting with the Mhra—is to give more visibility up front to the number of generic products that are going off patent and allowing them to know the number of applications—because as yet they do not get that visibility. That goes further forward, and in terms of launching a generic on the market place there is a number of various departments at the Department of Health that are affected by this, everything from getting the price for the Ppa, right the way through to the department itself and getting the reimbursement mechanisms, so a Gp knows that when he is prescribing generically the pharmacist is able to dispense that product. Again, that visibility has not really been there in the past and is something I believe we need to improve upon, to get that tighter communication between departments so that change can be implemented more quickly.

Q730 Dr Taylor: Would the major companies agree with that or approve of that or support the rapid changeover to generics?

Mr Lawton: Where the therapeutic benefits of a product which is a generic are proven, absolutely. The appropriate use of generics does allow headroom for use of more innovative products. I think that should certainly have a hard endorsement, and it does: the ABPI. If I may go back to the point about the access to medicines and the therapeutic conservatism which is traditional in the British physician: it is not just in cancer treatments, which it is critically important that we address, but in lots of others as well. If NICE makes the recommendation, its implementation is patchy. I think anything the Committee can do to make recommendations in terms of giving that implementation some real force, then I think that would be most welcome. But in terms of bringing new medicines on to the market, whichever therapeutic area they are in, I think it is less a question of restricting it and it is more a question of finding out the efficacy and the outcomes—the positive outcomes, and the negative maybe—of particular treatments by very good follow-up and control mechanisms. General practitioners have 2,000–2,500 patients and it is really very difficult to follow up every single patient as rigorously as is needed, particularly during the early stages of the entry of a new medicine. But it is critical that it happens. I think it is a question of follow-up and control. Maybe sharing of databases within PCTs is a way of doing this. I do not think doing nothing solves a problem. I think it is a question of doing it rigorously but following up patients very carefully that is important.

Q731 Dr Taylor: We have been told that when electronic prescribing really comes in the whole matter of monitoring will become much easier.

Mr Lawton: Yes, it will facilitate better progress. But I think the important thing is the time which the GP is able to give to following up individual patients or patients who are on particular medicines. The GP contract goes to some extent to address this by giving the incentive to follow up to general practice, but I think a lot more needs to be done.

Q732 Chairman: I want to come back to Dr Barker’s point. You said that you felt that young people were not attracted to chemistry. Did I get the right impression from the answer you gave?

Dr Barker: I am speaking as a chemist, so I obviously have a built-in incentive to see people trained in chemistry. We have seen major universities close their chemistry departments in recent months. That is a very worrying trend. It is clearly not the only discipline that is necessary, and, of course, the closer you get to employment in a pharmaceutical company the more specialised you would become, so medicinal chemistry, the ability to recognise and design drugs that will be effective, is very important, and I mentioned some of the other disciplines too. But, yes, you understood me correctly.

Q733 Chairman: Is that a problem for the industry, as such, the fact that youngsters are not as attracted perhaps as they were when you were at school?
Dr Barker: Chemists go into several different industries, as you can imagine, but we are going to be dependent on the broad flow of people trained in these disciplines. So, yes, it will become a significant problem and we are concerned about it.

Mr Lawton: One of the reasons for companies, including my own, to invest quite significantly in the UK was the presence of a very good chemistry base because it forms part of our basic research as a critically important part of our science. The closure of Swansea University’s chemistry department is very sad. What is happening at King’s College in London, which is associated with its medical school, is very sad as well. It is going to make the UK less competitive on one really critical area of science. That is the concern.

Dr Barker: We do, yes.

Q738 Dr Naysmith: Is that the best way to encourage innovation, particularly in terms of benefits to the patient?

Mr Lawton: The effect of the PPRS in encouraging innovation is certainly there but it is not the only reason that we would spend money on innovation. I think we would spend money on innovation for the last reason—for the benefit of patient care—and the allowance we get within the PPRS, which is a really highly complex system, is welcome but it is not a critical determinant of whether or not we do research. Mostly it is the quality of the science and the ability of that science to be translated into results.

Q739 Dr Naysmith: What I am trying to get at is what the benefit is of this mechanism to you in terms of patient care or is it just a little economic industrial encouragement?

Mr Lawton: It is economic and industrial encouragement. You cannot translate it specifically into a particular benefit to a patient, I think, but you can translate the research and development.

Dr Barker: Perhaps I can just add a comment, as a scientist, that the scientists do not always get paid as much as the lawyers and accountants and senior executives.

Mr Lawton: I do not know quite when he said that but I think the scientists, the chemists, are competitively rewarded now. Of the top calibre that we need in our industry, there are a number of them competing for a post. That is fine now, but, as they close chemistry departments, it is going to make them more scarce. and perhaps then, perversely, the salary will go higher.

Q735 Dr Naysmith: I am not in favour of getting rid of chemists. All I am saying is if industry regarded the chemists a bit more highly and paid them on the same scale as they pay other people. I am not comparing one chemist against another.

Mr Lawton: It is very competitive now because we want to avoid a brain drain to other parts of the world as well.

Q736 Dr Naysmith: Under the Pharmaceutical Price Regulation Scheme, companies are rewarded in rather a complicated way for being innovative. I just wonder if you could tell us what you think innovation means in this context and whether innovation necessarily translates into improvements in patients’ health.

Mr Lawton: The innovation referred to is essentially the research and development activity which takes place. It is the search for new molecules, the development of new molecules into medicines.

Dr Barker: It is approximately £10 million per day across the industry and £3.5 billion a year. The other factor, which I think it would be worth the Committee knowing, is that the promotional efforts of the industry represent about 11 minutes a week of a GP’s time, so the impression that some people would give you that GPs are overrun with promotional efforts is very misleading.
Q741 Dr Naysmith: We heard in the previous session that there are something like between 4:1 and 5:1 personnel employed in marketing as compared with research. It is quite a lot of personnel.

Dr Barker: I do not think that is representative at all of the UK.

Q742 Dr Naysmith: I have a question for Simon Clark in the BGMA but first of all can I take up something you said way back in your initial remarks. You talked about you were different from the branded companies in that you promoted to pharmacists rather than to GPs?

Mr Clark: Correct.

Q743 Dr Naysmith: Have you given up persuading GPs to prescribe without naming a brand name or is that just a decision you have made?

Mr Clark: One thing we are fortunate about within the UK market is that we have seen, as was alluded to earlier, about 78% of products being written generically by the INNA, and that is something that we would continue to encourage for the rest of those products that are appropriate to be written generically. As a result of that, doctors are putting through prescriptions to the pharmacists with a generic descriptor, therefore the role of the generic members and also competing against the brand is to offer the pharmacist various product prices, the lowest price being the one that the pharmacist will choose to meet the needs of that script.

Mr Lawton: If I may add a point on that. One of my own company's drugs, simvastatin, when it went off patent was being prescribed 90% as generic simvastatin.

Q744 Dr Naysmith: That is interesting because that brings us on to the question I was going to ask Simon. Your submission makes reference to evergreening. Maybe you could explain this term to us and describe the tactics used by the industry to limit profit loss when a medicine approaches patent expiry.

In the absence of the Chairman, John Austin was called to the Chair.

Mr Clark: Evergreening is a term given where a company may use tactics to extend the commercial life of the original product at first patent expiry.

Q745 Dr Naysmith: And you would be against that?

Mr Clark: We would definitely be against that. What happens here is you will have a product that enjoys this market monopoly position for a period of in excess of 10 years and during that time there may be changes in the product or the product may evolve and that delivers real patient or clinical benefits to the NHS, and we would absolutely support that without a doubt. However, we have seen an increase over the last number of years in cases where one can be sceptical about some of the changes that are made, in some cases two or three months before the patent expires on the product. These changes could be a different form of the product being released, they could be different indications and a different type of product and, as you see, there are some examples there. The real issue is that the originating company would then promote strongly that product to move the position to start writing scripts in the new form of the product and not writing prescriptions in the old form, so when the generic comes to launch there are no generic prescriptions there to be met by the generic product, and the impact on the generic company is that it then has to do a new filing and go through a new licence with the MHRA so we could see a two-year delay before a generic comes out on the market-place to meet this new form. If you are dealing with a product that has worth of over £100 million (which a number of other products have) that are going off patent that is obviously a significant value to the originator company but it is also a loss of saving to the NHS. The examples we have put in the report are not specifically to pull out those or to dig into those in detail, they are just to illustrate the point. What we feel the focus should be on is looking forward to make sure that there is a healthy generic environment. To achieve that, a number of changes that have been made in the EU Pharma Regulation that went through recently are helping us on that progress, but what the recommendation would be is that the Department has existing powers to make sure it puts in place a strong generic industry and has started using those, and we saw some pay-back 12 months ago with one particular product.

Q746 Dr Naysmith: Is this a fairly widespread practice? Do all companies do it?

Mr Clark: No, all companies do not do it. I would not say it is widespread on every single product but we are seeing a recurring instance of it and we are making sure that we are sharing that information where we see it with the various departments as well.

Q747 Dr Naysmith: I am sure Dr Barker will have something to say about that.

Dr Barker: The process by which companies bring new variants of products to the market is obviously one that is controlled by the same regulatory process that we have heard described in detail before. In other words, the product has to provide advantages and has to be approved by the regulator. The advantages could be efficacy advantages. For example, sustained release formulation could provide control of the use of that medicine over the day, it could be the ability to take therefore a medicine once a day rather than twice a day, and so there has to be a therapeutic benefit for this process to operate and therefore we do not think there is anything reprehensible about the fact that a company does that through the life of the patented product.

Q748 Dr Naysmith: Yet in the process of giving market authorisation the regulatory authority is barred from considering whether the product holds
any clinical advantage over other established products. Do you think this favours the industry to the detriment of prescribers and patients?

Mr Clark: No, I do not believe it does. To set the context here, the UK has been pretty successful in stimulating a generic industry. As we have heard before, generic prescribing is widespread through the life of the branded product and the turnover to generics is really pretty rapid. If you look at it, as Professor Lawton said in the case of one of his own products, there was 90% generic writing by the end of the prescription period. So I think of the problems we have this may not be the greatest. There is a pretty significant creation of this headroom for innovation through the use of generics.

Q749 Dr Naysmith: Does anyone else want to say anything?

Mr Lawton: The product has to have a therapeutic benefit. If there is an attempt to change the form it is usually because there is a perceived need for that form.

Q750 Dr Naysmith: Mr Clark is suggesting that sometimes this happens just because a drug is getting towards the end of its patent.

Mr Lawton: I do not know if that is the case. He has more information than I do about it and certainly not widespread. The adjustment and development of molecules, whether it is single molecules or whole classes, is a gradually evolving thing. This is what we would call “incremental innovation”. If you take the birth pill from 1961 when it first appeared up until current day, there have been about 18 different developments either in form, in strength, in tolerability and so on, as a result of which the medicine now is much more effective, it is much more tolerable and safer to take than it was when it originally came out, and there is now less active ingredient in a whole packet of these medicines than there was in one pill when they first came out in 1961, so I think these incremental changes do have a critical role, but I agree that they do need to have a role and they do need to have proven benefit. Doctors really need to be able to assess that.

Q751 John Austin: One of the other issues that has been suggested in evergreening is cosy relationships between a manufacturer and a generic manufacturer prior to the expiry of the patent to extend the profitability. It has also been suggested that some manufacturers may buy up some generic companies in order to eliminate competition. Is this widespread and would you regard either of those practices as anti-competitive?

Mr Lawton: Having had a number of products go off patent over the last five years—and very large products including simvastatin—I do not know that cosiness would be a word I would use in terms of the relationship. I think we respect very much the high-quality generics manufacturers. A number of pharmaceutical companies used to own their own generics manufacturers, some still do, but in fact fewer and fewer (rather than going the other way) own generics companies than was previously the case.

Mr Clark: Just to build on your question and answer directly in terms of buying up companies whether there is a reduction in the number of generic companies in the UK—no, there is not and in fact the generic market now is more aggressive than it has been, and what you get with the generic market is a situation where each individual product is a commodity market in its own right. We see products such as pravastatin which went off patent during the summer and within 48 hours it was down 60–70% and amlodipine after three or four months was down to 98% off the original price of the product. So that is not the case; in fact, the reverse is the case. To build on that, we are seeing an increase in the number of Indian companies that are entering the UK generic market because of the attractiveness of the generic market in itself.

Mr Lawton: During the renegotiation of the PPRS before last we were looking very carefully at the competitiveness of various sectors and we observed that the UK generics market was seen as one of the most efficient in the world.

Q752 Dr Taylor: Turning to the provision of information, I think it was Professor Lawton who talked about the inadequacy of clinical training of pharmacology students and now Dr Barker says 11 minutes a week is the GP’s contact with the drug representatives. In the ABPI evidence you have given us the result of the Taylor-Nelson study showing that of the GPs surveyed they rated their contact with representatives among their top three sources of information. This is really getting rather alarming and certainly we will get advice from our expert advisers on the degree of training that medical students are having, but talking about the work that you do in promoting, is it right that the discoverer, the developer and the supplier of the product should be the most important adviser?

Mr Lawton: I think that the people who know most about the medicine right from its inception are those who discover it and bring it to market. The information which we develop about it and how to use it and where not to use it, the benefits versus the risks, and so forth, is carefully studied and presented. They are subject to external scrutiny and we also have within our companies a medical legal control procedure so that all information—whether it is related to clinical papers or whether it is a smaller study—has to be approved by a medical doctor and legal expertise before it can go out.

Q753 Dr Taylor: Is that an independent medical doctor?

Mr Lawton: No, it is within the company, and externally there would be the Code of Practice of the ABPI which has to be adhered to as well and there are independent physicians on that and the complaints procedure is open to all medical practitioners if it is seen to be inappropriate.
Q754 Dr Taylor: With their very limited training in pharmacology do you think the GPs have enough information to view your information critically or do you think they just take it at its face value?

Mr Lawton: That is an extremely good question which I would hesitate to give a very simple answer to because it is a very complex issue. The GP is looking for clinical end points and benefits rather than the clinical pharmacology relating to how the medicine works, the molecule, the shape of the molecule, and the potential benefits of any chain in that molecule. I think they are less able to be critically evaluating the latter but on the former, in terms of the clinical benefits, they should be able to see whether or not those clinical benefits, as they are important to their patients, are properly represented in materials and also the quality of the discussions they are having with whether it is the company representative or external doctors.

Q755 Dr Taylor: Do representatives concentrate more on GPs than on consultants because they think they can influence them more?

Mr Lawton: There are 90,000 practitioners of one sort or another in the UK and general practitioners are the majority. A large amount of time is spent on general practitioners because they are the ones who are more likely to be in the prescribing area, but that is rarely done without consultation with the consultants who deal with those general practitioners, so that the consultants have to feel comfortable and they will ask very technical and difficult questions which we need to be able to answer and satisfy them on. They will be the advisers to the general practitioner within a primary care trust but we do visit general practice more.

Q756 Dr Taylor: Information direct to the public is obviously limited to the non-prescription drugs.

Mr Lawton: Yes.

Q757 Dr Taylor: We gathered at a week or two ago’s session that simvastatin was already being advertised pretty widely in the ordinary press. Does that come from the generics?

Mr Lawton: Simvastatin went over the counter last year and that was the only time it has been advertised in the press. It has not been advertised in the press before that.

Q758 Dr Taylor: No, but it has since then.

Mr Lawton: Simvastatin over-the-counter version.

Q759 Dr Taylor: Yes?

Mr Lawton: Yes.

Q760 Dr Taylor: Is that MSD advertising that or is it just the generic makers?

Mr Lawton: It is actually Johnson & Johnson MSD, which is a consumer part of our company.

Q761 Dr Taylor: So this is one of the occasions when you make the generic form of this drug?

Mr Lawton: Yes, we manufacturer it there.

Q762 Dr Taylor: How common is that?

Mr Lawton: We also have another one called Famotidine. There are other agents of that sort manufactured by other companies.

Q763 Dr Taylor: Do any of your manufacturers make simvastatin?

Mr Clark: Yes. We make our own simvastatin. The simvastatin that is advertised in the press is nothing to do with the generic prescribed simvastatin. It is purely the OTC version that is available.

Mr Lawton: It is the low dose one.

Q764 Mr Jones: Mr Lawton, you have spoken about the Code of Practice. In our earlier sessions we have heard a great deal of concern regarding the marketing activities of companies. This criticism that we have heard so far is particularly in relation to the time taken for complaints to be handled and that the sanctions appear to be weak. Do you think the system could be improved by addressing these issues?

Mr Lawton: Any system, including this Code of Practice, needs to be reviewed on a regular basis. Every year or two we do a periodic review and we are doing a fundamental review now and consulting stakeholders and it is looking at sanctions, it is looking at everything about the Code of Practice procedures. Whether or not the sanctions are adequate is something that I am aware has been raised several times. The sanctions are varied. They go from, first of all, having to withdraw the materials. When somebody may have contravened the Code they would have to stop that promotional activity, withdraw those materials, which can cost tens of thousands or hundreds of thousands of pounds in itself for that company and it stops them pursuing that particular promotional activity. Very often they have to publish a retraction of this and say what happened and why and this appears every quarter in our Code of Practice review bulletin which you may have seen.

Q765 Mr Jones: So you would not agree the sanctions are particularly weak, would you?

Mr Lawton: I do not think the sanctions are weak. The industry takes it extremely seriously.

Q766 Mr Jones: Dr Chiswell, in your written evidence you say that biological products slip through the NICE net, that NICE does not evaluate them because they are specialised products and not enough patients use them. Have you raised that point with NICE? Do you or they doubt that “therapeutic value for money” evaluations would be worthwhile?

Dr Chiswell: We are not saying that all of our products do not come through NICE. I am associated with a product called Humira which NICE reviewed for Rheumatoid Arthritis and recommended. NICE cannot get to everything. I think there has to be a limit from NICE’s point of view as to how much they can do. Maybe there is
another mechanism required whereby products which work for a few hundred people get into the system and people get reimbursed. We do have orphan drug regulations both from the UK and Europe and they will be reviewed in Europe this year. There are mechanisms where we could see more approvals of those sorts of products going through.

Q767 Mr Jones: Is there a case for those orphan products to be evaluated more at the multi-national level rather than at national level?

Dr Chiswell: Possibly, but in the end the way the system works is that somebody in a PCT is going to have to pay for it. Ultimately it is the reimbursement that counts.

Dr Barker: I wonder if I could add a point or two on Mr Jones’ first question because I think you raised the point about the speed of evaluation (under the PMCPA) which Professor Lawton did not address. The average time is about eight weeks for the Code to investigate the matter. If it goes to appeal, which is governed by a second panel that is headed by a QC, that adds a few more weeks to the time. I would say it is really a pretty rapid process based on my observation of this over the first few months of my time in the job. By the way, this is an arm’s length entity. It is not one that reports to me but I have had a chance to review the process based on my observation of this over the first few months of my time in the job. By the way, this is an arm’s length entity. It is not one that reports to me but I have had a chance to review the process based on my observation of this over the first few months of my time. So it is pretty rapid.

Mr Lawton: Yes.

Dr Barker: Yes.

Mr Lawton: Transparency is extremely important.

Dr Barker: Yes.

Mr Lawton: Transparency is extremely important to us. Where our image has been tarnished one way or another then clearly we have to address that very carefully. There is a lot of baggage which is hanging over from 15, 20, 30 years ago which keeps coming up. I think the rigours of the processes of regulation now are such that there are many fewer occurrences which would bring our industry into disrepute. As far as the public is concerned, there is not much of a perception of what the pharmaceutical industry is, we are unable to communicate directly to them and with them, so they find out through newspapers and they find out about hopeful stories about medicines which are being developed in the long term and medicines as they are released and so on and I think that is absolutely fine. They will find out from us sometimes because of the work we do in the community with education, with schools and science education and that sort of thing. I am not sure that we have one image. The regulators, the politicians, the health care professionals and so
on know us very well and by and large I think they know us because we are great contributors to the economy with a £3.6 billion positive balance of trade and we have 80,000 people employed and 240,000 others get jobs as a result of our presence in the UK. After 25 years in this industry I know that everybody that I know well and respect in this industry wants to do good for patients and I think the people who know us know that. The public really do not know us. I think we have a mixed image. Where we have perpetrated a negative image then we need to sort that out through transparency or whatever, but we will fix it. Where it is wrongly perpetrated, we will defend ourselves against that by asserting what our values are, which are values of ethics, of doing good for patients and trying to be more transparent and more open.

Dr Taylor: That is very clear. Thank you. Whatever other problems the pharmaceutical industry has it is not an orphan industry because within government at least it is sponsored by the Department of Health, but Sir Richard Sykes at the session we had with him told us he thought it should be transferred to the Department of Trade and Industry. Do you all agree with that?

Mr Lawton: I think we would say that we are generally well-regulated and well-sponsored but just like nearly everything else it could be better.

John Austin: If my colleagues have no other questions, could I thank all of our witnesses for a very informative session.
Thursday 20 January 2005

Members present:

Mr David Hinchliffe, in the Chair

John Austin
Mr Keith Bradley
Mr Simon Burns

Dr Doug Naysmith
Dr Richard Taylor

Witnesses: Professor Sir Alasdair Breckenridge CBE, Chairman, Professor Kent Woods, Chief Executive, and Dr June Raine, Director, Post-Licensing Division, Medicines and Healthcare products Regulatory Agency (MHRA), examined.

Q774 Chairman: Colleagues, good morning. Can I welcome you all to this session of the Committee and welcome our witnesses. Can I thank you for your cooperation and for your evidence to us; we are most grateful. Can I ask you briefly each to introduce yourselves to the Committee.

Dr Raine: Good morning. I am Dr June Raine. I am the Director of the Post-Licensing Division at the Medicines and Healthcare products Regulatory Agency and my responsibilities include all the issues that relate to medicines once they are authorised for use on the market.

Professor Sir Alasdair Breckenridge: I am Alasdair Breckenridge, I am the Chairman of the Board of the MHRA.

Professor Woods: Good morning. I am Kent Woods and I am the Chief Executive of the MHRA.

Q775 Chairman: Can I begin by asking you this, Sir Alasdair; you have been around for quite a long time in this whole area and obviously you have got some pretty detailed knowledge of many of the issues that we have been addressing during this inquiry. We are now towards the end of the inquiry and I have no doubt you will have been following some of the sessions and some of the evidence that we have had. What is our view, from your background, of the key issues that perhaps have been picked up in this inquiry in relation to the medicines regulatory system?

Professor Sir Alasdair Breckenridge: I think one of the impressions that I have gained is that a lot of the discussions which have taken place have referred to what happened many years ago in the old Medicines Control Agency and the one thing that I would like to stress is that since the MHRA came into being in April 2003, there have been many, many changes in the way in which the organisation works, partly because this is the aim of the organisation itself and partly because the climate in which medicines regulation takes place has changed totally.

Q776 Chairman: So what you are saying is that some of the evidence that we have had is outdated? Could you give examples in particular where you feel that the situation is being inappropriately represented?

Professor Sir Alasdair Breckenridge: Well, it is not misrepresented, but there was quite a lot of discussion about how the Agency did not release information, for example, on human albumen and on some of the other issues in the early 1990s. Well, we have changed that now and there are two big things which we are actually changing. One is the transparency under which we work and secondly is the communication skills which we have put into operation and for your evidence to us; we are most grateful. Can I ask you briefly each to introduce yourselves to the Committee.

Dr Raine: Good morning. I am Dr June Raine. I am the Director of the Post-Licensing Division at the Medicines and Healthcare products Regulatory Agency and my responsibilities include all the issues that relate to medicines once they are authorised for use on the market.

Professor Sir Alasdair Breckenridge: I am Alasdair Breckenridge, I am the Chairman of the Board of the MHRA.

Professor Woods: Good morning. I am Kent Woods and I am the Chief Executive of the MHRA.

Q777 Chairman: I think that was a good example which will probably be picked up by one of my colleagues later on, but in terms of the future, do you see, from the evidence that we have picked up, any particular key areas where you perhaps would suggest there is a need for change?

Professor Sir Alasdair Breckenridge: I think that the other area that I would pick up is that of the education of the public in terms of risk and benefit. A lot of the discussions which have taken place in the Select Committee have been about the safety of medicines and relatively little about this concept of risk and benefit. When we change a licence, we do not do this purely based on a safety profile of a drug. If we did this, there would be no anti-cancer drugs available and there would be no anti-HIV drugs because the adverse reactions to them are huge. They have got to be balanced against the benefits which these drugs have and the one thing which I would like to see you concentrating on, with all respect, is this concept of risk and benefit. We are going to be communicating that very strongly with our new communications set-up, but I would like to see that as one important aspect coming through from this Committee.

Q778 Chairman: You had in 2003 a report from the NAO which was somewhat critical about your external profile. We have got a rough idea of the main findings. Now, in terms of the way you suggest that the information we have received perhaps is a little dated from some of the witnesses that we have had and some of the representations we have...
received, in relation to those findings what steps have been taken to address them and perhaps what further steps might you take in the light of some of the issues that we have picked up?

Professor Sir Alasdair Breckenridge: The main thing which the Agency did when it received this report is that we commissioned a report on our communications strategy and this reported to us in June 2004 and there were many recommendations from that report which we took up. The main two which we have acted on are the two I have mentioned already, firstly, setting up communications, and this is absolutely critical for an agency like ours. In the past, the old Medicines Control Agency and Medical Devices Agency, working in a different time, did not see this as one of their main purposes. Now it is quite clear, and we are determined, that this is one of ours. The second one is the issue of increased transparency and I have already mentioned the example of SSRIs. The other thing which we have done is that as of the middle of this year, when we give a licence, we will be issuing what we call a “United Kingdom public assessment report” which will give data of all the clinical trials on which we made our decision, so the public will be able to see again the evidence on which a drug has been licensed. The third part of the transparency move which we have made is that we have reviewed the yellow card system. This was done independently and we might be coming back to that later, but in fact as of this week we have published on our website all the adverse reactions to every licensed drug and this is accessible to everyone, suitably “anonymised”. Therefore, we have taken concrete steps with respect to transparency, communication, and the other question which was raised by the National Audit Office was the question of interests and we have moved on that both with respect to the staff and with respect to the committee structure, and we can deal with that. The final one which I would mention is that we have increased greatly the patient voice in medicines regulation. We have been conscious for a long time that regulation was too inward-looking, not involving the public enough, and we can discuss again in some detail how we are actually increasing the patient voice in regulation.

Q779 Chairman: So taking account of the views we have had expressed about your external profile as an organisation, how would you describe it now?

Professor Sir Alasdair Breckenridge: We are moving very quickly from the time when we started business in April 2003 and if someone who worked in the Agency even in the early part of the 2000s came back and looked at the work that we are doing now, they would find huge changes.

Q780 John Austin: Can I raise the issue of Seroxat and your knowledge and involvement. In 1998, I believe you were on the advisory board of GlaxoSmithKline or SmithKline Beecham, as it was at the time.

Professor Sir Alasdair Breckenridge: No, let me just clarify that. From 1992 to 1997 I was a member of a scientific advisory committee of SmithKline. I resigned from that in 1997. This had been an extremely valuable exercise for my development in medicines regulation. We did not discuss specific products on that board; it was a matter of the larger picture of industry. I resigned from that in 1997 and this post had been taken up with the full cognisance of the then MCA. I discussed this with the MCA and I acted in a totally appropriate manner with respect to the decisions that I was party to there and in drugs and medicines regulation.

Q781 John Austin: I was not suggesting otherwise. My question was whether you were aware or whether the company made you aware at the time of any testing that they were doing in relation to Seroxat and the use of Seroxat for children.

Professor Sir Alasdair Breckenridge: We never discussed any medicines at all. That was never part of the remit of the scientific advisory board.

Q782 John Austin: It is clear now that the company were aware of some negative results, particularly in terms of withdrawal. Were those ever communicated to you either in your role with SmithKline Beecham or subsequently in your role with the Committee on Safety of Medicines or the MHRA?

Professor Sir Alasdair Breckenridge: With respect to me, as I have said already, certainly not and perhaps Dr Raine might like to answer the question about the communications to the Agency, if that is your wish.

Q783 John Austin: I also note that we do not have Dr Ian Hudson with us this morning, although he was listed as one of the witnesses. Is there a reason why not?

Professor Sir Alasdair Breckenridge: Yes, Dr Hudson is one of our delegates at the CHMP, the Committee on Human Medical Products at the EMEA and he is there today. He is fulfilling a different role for the Agency down there.

Q784 John Austin: Would he have been able to answer the questions and would he have been aware?

Professor Sir Alasdair Breckenridge: I cannot answer that on his behalf.

Q785 John Austin: What was his role at that time?

Professor Sir Alasdair Breckenridge: I cannot answer that question. I do not know that.

Q786 Chairman: He is a colleague in the Agency—

Professor Sir Alasdair Breckenridge: He is the head of licensing in the Agency.

Q787 Chairman: Obviously he played a very key role in this respect and you have no knowledge of what that role was? You have not discussed it with him at all?

Professor Sir Alasdair Breckenridge: No, I have not discussed it with him. He was appointed to the Agency in 2000 because he was the best candidate for the job to head up the Licensing Division.
Q788 Chairman: And in advance of today’s session, where no doubt you would have anticipated that this issue would have been raised, you have not discussed the possible involvement he may or may not have had?

Professor Sir Alasdair Breckenridge: I have not discussed that with Dr Hudson at all. I do not know whether any of my colleagues have, but I have not.

Q789 Dr Taylor: Would you be expected to be aware of everything that goes on in, for example, the expert working groups because we are told quite clearly that the expert working group on SSRIs was given evidence more than 18 months ago that withdrawal did cause suicidal hostility. Is it beyond the possibility of a job as large as yours to keep tabs on absolutely everything that goes on?

Professor Sir Alasdair Breckenridge: Well, it is, but I have an interest in the field, having served on the Committee on Safety of Medicines, and I am aware of the recommendations as they went through, but I was not a member of the working group and it was not my role to be at them.

Dr Taylor: So we really have not got anybody here who can answer that specific question?

Q790 John Austin: I think it would have been useful if Dr Hudson had been here because, as far as I understand, he was at SmithKline Beecham and his department was responsible for the collection of adverse reaction information such as there was with Seroxat.

Professor Sir Alasdair Breckenridge: Yes, I know that, but I—

Q791 John Austin: So he would have been a very key witness.

Professor Sir Alasdair Breckenridge: But I have not discussed that with Dr Hudson.

Q792 John Austin: So you must admit that it is very unfortunate he is not with us today?

Professor Sir Alasdair Breckenridge: Well, I apologise for that, but I think there was some confusion about who was going to attend and I think the Clerk was told that this was where Dr Hudson was going to be.

Q793 Chairman: It is a little bit strange then with an issue as sensitive as this that there appears to have been no discussion within the Agency. Does Professor Woods want to come in at this point?

Professor Woods: Yes. I would like to answer that because I do have some information which might be helpful to you. As Chief Executive, I have discussed with Dr Hudson his previous role within GSK in relation to the specific question of Seroxat and he assures me that he has had no direct personal involvement in those safety issues. However, because of his role within the company, we agreed, and have since scrupulously observed, that he should have no role within the Agency in any decision-making concerned with Seroxat.

Q794 Chairman: And this was not communicated to Sir Alasdair?

Professor Woods: I would regard it as an executive matter. I frequently do discuss issues with Sir Alasdair, but it is something I would consider, as Chief Executive, as my responsibility.

Q795 John Austin: Presumably, Sir Alasdair, you were aware that the CSM had an expert working group which we now know reported in December looking at some of these issues?

Professor Sir Alasdair Breckenridge: Yes.

Q796 John Austin: In October you appeared on a Panorama programme in which you said that SSRIs antidepressants did not cause suicidal behaviour in adults.

Professor Sir Alasdair Breckenridge: Yes.

Q797 John Austin: That statement at that time was completely at variance with the findings of the expert working group which reported two months later.

Professor Sir Alasdair Breckenridge: No, with all respect, what the expert working group reported were two things. Firstly, in May 2003, we said that with respect to children there was an increase in suicidal ideation in children and no benefits, and that was May 2003. In 2004, the results of the expert working group said that whilst the SSRIs were clearly beneficial in adults, there was no evidence of increased suicide or suicidal thoughts compared to the times before the patients took the medicines. This was highlighted by the large studies which had been undertaken, three large studies, using the GPRD database, comparing SSRIs with the tricyclic antidepressants and there was no increase in suicidal behaviour due to the SSRIs. My own belief is that clearly in depression suicide is a huge problem. When the patient starts to take SSRIs, there is a period of time before benefit takes place and in that time before benefit takes place the patient is at great risk of suicide and this is a time when there must be intense monitoring and great care taken of the patient.

Q798 John Austin: Could I also ask you in relation to this that after the report was published the MHRA informed doctors, following the report, that SSRIs were effective medicines in the treatment of depression and anxiety conditions. Now, nobody is disputing that, but do you not think that that required some qualification both in relation to the expert working group’s report and also into the lack of evidence of the efficacy of the products in treating mild depression?

Professor Sir Alasdair Breckenridge: Sorry, maybe I am not picking this up, but you have quoted the results of the expert working group quite rightly and this is the line which we have consistently followed. Perhaps there is something else in your question which I do not understand.
**Q799 John Austin:** Well, after the report, my understanding is that your information to doctors merely stated that these are effective medicines in the treatment of depression and anxiety and did not have any qualification to that.

**Professor Sir Alasdair Breckenridge:** Yes, it did, it had qualifications. What the expert working group did was to look at three issues about antidepressants: firstly, the question of withdrawal; secondly, the question of suicidal ideation; and, thirdly, the question of dose. The problem of withdrawal has been well known with antidepressants, especially Seroxat, and I happen to have before me the information sheet, the data sheet which we published, which the MCA published in 1990 when Seroxat was first licensed. If I can just read it to you, it says, “As with many psychoactive medicines, it may be advisable to discontinue therapy gradually as abrupt discontinuation may lead to symptoms, such as dizziness, sensory disturbances, sleep disturbances, agitation or anxiety, nausea, sweating and confusion”. That was in 1990. We returned to that in 1993 in our journal *Current Problems in Pharmacovigilance* and we published an article on this again in 2000, so this is an issue which we have worried about and kept under review for a long time. The second issue which came up at the expert working group was suicidal thoughts to which you have referred already and the third issue was that of dose. If I return to the data sheet in 1990, the data said that the recommended dose was 20 milligrams and in some patients if it was necessary to increase the dose, this should be done gradually and that is what the data sheet says today.

**Q800 Chairman:** So you are saying that there was a clear qualification?

**Professor Sir Alasdair Breckenridge:** There was additional, clear information for the patients and this was—

**Q801 Chairman:** And you say that was clear qualification?

**Professor Sir Alasdair Breckenridge:** Well, it is a matter of semantics whether that is clear qualification. I would say with what we are talking about, withdrawal, it is adding to information which was there already and with respect to dose, whether that is qualification or adding to the information which was there already is a matter of debate.

**Q802 John Austin:** But up until 2003, both the MHRA and the manufacturers were saying that the incidence of withdrawal reactions was rare and that has now been revised, so 10 years after, when all this surveillance has been going on, that estimate has been raised to 25 to 30%.

**Professor Sir Alasdair Breckenridge:** When a drug is licensed and for the first few years until there is good clinical trial data, one cannot say what the incidence of an adverse reaction is. You cannot tell that from yellow card reports. Yellow card reports give signals. You have got to rely either on clinical trials or patient databases. As that evidence became available, we were able to put a figure on the incidence of withdrawal which we had never been able to do before. Dr Raine was involved with this and perhaps she might like to take over on that, but that is the precise situation about monitoring the safety of medicines.

**Q803 John Austin:** With something like a hundredfold increase in the estimate?

**Professor Sir Alasdair Breckenridge:** Well, I do not know whether ever anyone said what the first instance was. I was not aware that there was.

**Q804 John Austin:** You said it was rare.

**Professor Sir Alasdair Breckenridge:** Well, you said it was rare.

**Q805 John Austin:** No, the MHRA said it was rare and so did GSK when they were before us.

**Dr Raine:** Clearly quantification of the incidence was very difficult based on spontaneous reporting and it was only with gradual better understanding, and I would say that the patient reports that we had when we set up the expert group were very valuable in this regard, plus additional data that we sought that we were able to put a much more real-life quantification on it. If I may turn to one other point which you mentioned, Chairman, which was advising on the efficacy of these medicines. The important step that we took was to ensure that the advice on risk was accompanied by clear guidance from NICE at the exact time on the place of these medicines in clinical use. That in a sense was going beyond the responsibility of the regulator but clearly the vital part of the jigsaw for those who are seeking to treat patients with this serious condition.

**Q806 John Austin:** Could I just go back to the question of when there was an awareness of the implications of withdrawal symptoms. I understand that in its original submission for marketing authorisation, which was submitted in 1990, SmithKline Beecham did provide an analysis of their clinical trial data which showed that the experience of adverse effects of withdrawal were much higher with the drug than the placebo, so in 1990 the company, when it applied for market authorisation, was aware of the severe problems of withdrawal and yet the MCA was then still saying that it was rare.

**Professor Sir Alasdair Breckenridge:** Well, I repeat again what we said then, and this was what was put into the data sheet from the information, and I have read it out to you already, and the word “rare” does not occur in that. It said that it can happen. It said, “As with many psychoactive drugs, it may be advisable to discontinue therapy gradually as abrupt discontinuation may lead to symptoms”, and it spells out the symptoms very, very clearly. There is no evidence and the word “rare” does not come into that.

**Q807 John Austin:** Well, we will leave that on one side. The company very clearly was continuing to argue that the incidence was rare when their clinical trial data suggested that it was not and that
Professor Sir Alasdair Breckenridge: There always has been.

Q808 John Austin:—why then, as the regulator, were you not requiring the expert working group actually to look for withdrawal problems in their examination? Although the expert working group has identified severe problems with withdrawal, their studies were not designed, nor required, to look actually at that. They discovered it, but it was not part of the design of the study. Was that a failing?

Professor Sir Alasdair Breckenridge: Well, we are looking back 15 years now and when the SSRIs were licensed from 1987 onwards, it was clear that this was an important group of drugs with many benefits over the previous agents, but with a different adverse reaction profile. That adverse reaction profile, as we have discussed already, was known, but the quantification and the importance of it was not clear.

Q809 John Austin: Would it not have been sensible to design the study to look at that and not find it by chance?

Professor Sir Alasdair Breckenridge: Well, the MCA, as it then was, was not in the business at that time of designing studies. It was a regulatory body at that time which did not design studies itself and set up investigations like that.

Q810 John Austin: Could I ask then whether any lessons have been learnt from the experience, in particular, how to improve scrutiny of drug licence applications?

Professor Sir Alasdair Breckenridge: Yes, there have been many lessons and the main lesson which has been learnt, as we have touched on already, the first lesson, is that the safety profile of a medicine, when it is licensed, is not very well known, the whole profile. Secondly, when yellow cards become available, they will put up signals, but these are signals and these signals must be tested in different ways. That is one of the main lessons that we have learnt.

John Austin: I think we will come on to yellow cards later.

Q811 Dr Taylor: Can I ask about another lesson, if perhaps you have learnt and changed it, because we gather in the past that you worked on company summaries of trial data rather than the raw data and we have been told that, particularly with Prozac, you or your preceding bodies chose just to take the trials or were given just the trials from America and not the trials from Europe and, therefore, you were relying on the choice of evidence given to you by the drug firm. Have you changed that? Are you now looking at raw data or are you making sure you trawl right across all the availability?

Professor Sir Alasdair Breckenridge: I think, Dr Taylor, there is a misconception about raw data and company summaries. Yes, we rely on company summaries. European medicine regulation says that we should and we do, but a company summary is for each trial that is done, and there may be 10 or 15 trials for each licence application, and what each company summary will contain is 80 to 100 pages of dialogue, several hundred pages of tables, and statistical analysis as well, so the submission for one agent will be many, many hundreds of volumes. This is what are commonly called “company summaries”. Raw data are the individual case reports on each individual patient and we routinely do not look at raw data. We have done on occasion, but this is not a routine practice. I have noticed on one or two occasions before in the transcripts that this topic has come up and I think there is a misconception as to what is meant by a “company summary”. When we get an application coming in to the MHRA, it is delivered in a pantechnicon there are so many volumes, and these are the company summaries which, as I have described, are very full and, if necessary, we go back to the company or the Agency can go back to the company and ask for the raw data and it does this on occasion.

Q812 Dr Taylor: And you have a method of making sure that you are getting all the data, the good data and the bad data?

Professor Sir Alasdair Breckenridge: The company signs an affidavit that they are delivering all the data. There has got to be trust in this. They sign that they are delivering all the data. When they come to a hearing, they are asked that and they are asked to give an undertaking. We also have the ability to send in inspectors to inspect the company for good clinical practice and pharmacovigilance should there be any suspicion that they are not producing all the data. I do not know whether Kent wants to add anything to that.

Professor Woods: No, I think that is a very clear account of the situation. The ability to inspect sites for good clinical practice has been recently strengthened by the provisions of the European Clinical Trials Directive which has been implemented in the UK with effect from 1 May last year, so there is at the level of the trial subject the opportunity, which we take, to carry out random audits to inspect that what we see in the records is actually representative of the data which has been gathered, so this adds another layer of security to the quality of data.

Q813 John Austin: Can I raise a question which I raised at the last session with AstraZeneca which related to the promotion, advertising and marketing of one of their products. I am wondering what the relationship with the MHRA is or what powers the regulator has. I raised the specific issue of Crestor and you were saying, Sir Alasdair, earlier that you were relying on the choice of evidence given to you by the drug firm. Have you changed that? Are you now looking at raw data or are you making sure you trawl right across all the availability?

Professor Sir Alasdair Breckenridge: I think, Dr Taylor, there is a misconception about raw data and company summaries. Yes, we rely on company summaries. European medicine regulation says that
any way in which the behaviour of pharmaceutical companies can be regulated in those circumstances? Would you comment on that?

Professor Sir Alasdair Breckenridge: Perhaps Dr Raine could answer that. She is in charge of that part of the Agency.

Dr Raine: The legal position is that as long as the company is advertising in line with their licence the summary of product characteristics, we do not have powers, say, to make them stay their hands while the new advice is adopted into clinical care and that is a fact.

Q814 Chairman: Do you think you should have those powers?

Dr Raine: I think it is something that we should consider. We are currently, having overhauled our advertising processes since 2003, consulting on how we interpret some of this guidance. Our guideline is out to consultation and clearly it puts into the current climate the capability to look to see how we would wish best to interpret these things nowadays and it is not just how actively and aggressively products are promoted, but matters such as inducements and hospitality.

Q815 Dr Taylor: I must just ask something about the Panorama programme because I think many of us who are doctors were desperately embarrassed and sorry for you with the way you were forced to come out. Now, you have made a much more robust defence of the situation to us today. Is that because some of your comments were edited out?

Professor Sir Alasdair Breckenridge: I was interviewed for 2½ hours without a break for Panorama and I was shown on the programme with 7½ minutes of what I said. The bits of my robust defence of the position of the Agency were not shown and I cringed from behind the sofa when I saw the bits which they did show of what I had said. It was very embarrassing.

Q816 Chairman: We have been through that process, don’t worry!

Professor Sir Alasdair Breckenridge: Well, I am reassured by that.

Q817 Dr Taylor: We certainly have. We have been told that there are recent changes in the safety standards in the International Conference on Harmonisation which perhaps could put patients at greater risks from new drugs. Any comments on that?

Dr Raine: I would be interested to know how Dr Taylor has, if you like, been alerted to this. Our take on the International Conference on Harmonisation is that it is a vehicle actually to raise standards, and our own strategy to improve standards of pharmacovigilance and to turn drug safety monitoring from a reactive to a proactive process has used ICH. We have recently adopted the guideline on pharmacovigilance planning and worked with the European legislature to achieve an amendment to the law this October 2005 to ensure that when a new medicine comes on to the market, we have a proactive plan to gather the safety data and to look for new risks rather than to wait until they come and hit us, so my take on ICH is that it is a tool for improvement rather than a danger to us.

Q818 Dr Taylor: If I may just quote from our brief because I am not an expert on this, our brief tells us that there appears to have been a certain amount of downgrading in standards relative to the higher standards practised at the time within ICH, that, most importantly for drugs for non-life-threatening illnesses, the requirement for expedited reporting of known serious adverse drug reactions has been dropped, and that periodic safety update reports from companies to regulators during the first three years post-launch have been reduced in frequency, those sort of concerns.

Dr Raine: These are actually not the true position at all. We have ratcheted up the frequency of periodic safety update reports. It is obviously six-monthly in the early stages, but they will now be coming in three-yearly rather than five-yearly and we are working with our colleagues in Europe to ensure that whilst every Member States has many thousands of these to look at, we can focus with different Member States taking the lead in different established products, so I would like to reassure you that this is not the case and we are pushing ahead with ICH.

Q819 Mr Bradley: Can we explore a bit further information and promotion. One of your stated objectives is to “provide authoritative and accessible information”. How successful do you think you are in achieving that and how would you say you compare with the information that is supplied by the industry itself?

Professor Sir Alasdair Breckenridge: Well, thank you for that question. There are several ways in which we do inform patients. The obvious ones are, firstly, the summary of product characteristics and the patient information leaflets which we have approved, and that is a very important bit of getting information about the medicine through to patients perhaps taking a specific drug. The second broad areas that we are involved in is disease awareness campaigns, the Ask About Medicines Week, the Medicines Information Project, and these are broader ways in which we inform patients as well. The other way in which we inform patients is when there is a safety issue. When a safety issue does come back and we are acting reactively, we have quite a good mechanism now for informing healthcare professionals and the media about the safety issue and this is picked up and usually well reported by the press, so the public do get to hear about safety issues as well. It comes back to something, Mr Bradley, that I was saying earlier on, that we believe it is important that we do more than that, that we have got to be far more on the front foot rather than on the back foot and the change which you will see in the Agency in the future is better communication about the issue of risk:benefit which I believe is terribly important and working with the press, with the media, putting our heads above the parapet and
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letting people know that there is no such thing as a drug which is a silver bullet, that there are risks and benefits everywhere that you look, and that is a change which you will see coming from the Agency in the future.

Q820 Mr Bradley: Can I take from that that to date you do not think that your information has been as good as that put out by the industry and the public are more likely to take that information and promotion rather than yours, accepting the point you are making that you will try and do better in the future?

Professor Sir Alasdair Breckenridge: Well, we have suffered as an agency for not being professional enough in our communications. That is the bottom line and we are determined, as I have said once or twice already, to change that. It seems strange that a regulatory organisation did not think that communication was important, but since 2003 it is quite clear, the importance that it has, and we are acting very greatly on it. I do not know, Kent, whether you want to add something to that.

Professor Woods: I would just add a word because it is a very important area of our business. We had an independent external review of our communications activities which reported some months ago earlier last year and, as a consequence of that, we are forming within the Agency the Communications Division. That will bring together some 26–27 people, many of whom are already in the organisation, but we are drawing this together as a focus of activity. We have appointed a Director of Communications, who will take up post in about 10 days’ time and we are also investing about £1 million in our website over the next six months, so this is a very substantial investment, as an organisation, in our ability to communicate information not only to the general public, but also to health professionals. We have quite a complex external environment who require communications from us and I think that one of the difficulties we have had in the past has been that because we did not make an explicit task of communicating in that way, others have done it perhaps with less disinterest and, therefore, I feel that we do, as regulators, have an important function in ensuring that we are a source of authoritative, independent and trusted advice on matters of drug safety, efficacy and quality.

Q821 Mr Bradley: In that review, did they comment on the fact that your independent review panel on advertising and on breaches of advertising did not meet at all in 2002 and has it met since?

Professor Woods: I cannot answer that specific question. Dr Raine may be able to shed some light on that.

Dr Raine: You are absolutely right, it has not met and, for that reason, and it is an appeal mechanism which industry may choose to follow, we are adopting different strategies and the main one has been to publish the complaints that we have. I think you will find on our website that there are 17 correct statements out there now. It is adopting one of the successful strategies which the FDA has used which is naming and shaming. If we cannot get the appeal forum used as a way to get a rigorous result, then we will adopt other measures and, as I have said, we are consulting on how we interpret the law at the moment.

Q822 Chairman: When I opened up, talking about the changes you are bringing about, one of the issues which was mentioned was openness and, in particular, your view that the public should be much more engaged and more aware of some of the difficulties and some of the implications of the work you do. I think a theme which has come through our discussions in this inquiry and, in particular, with the companies themselves has been their understanding of the need to be much more open and transparent, but of course at the end of the day in an area of quite vigorous competition you have got commercial confidentiality and I wonder whether you feel you can go further on openness and engagement where you have inevitably at the end of the day got the problem of this commercial confidentiality. Would you, for example, like to publish some of the data that you have referred to which you receive and which currently you cannot? Could we reach a situation where we could at some point achieve that possibility which will engage more with the public and inform the public possibly?

Professor Sir Alasdair Breckenridge: Yes, I think, Mr Chairman, there are two changes which are taking place. Firstly, although we are bound, as you say, by the laws of commercial confidentiality, if an issue does come up of public health importance, we will publish that data irrespective of the commercial confidentiality and we have done this on several occasions. The second thing which is happening, and I know that you have discussed this as well, is that there are these proposals which are going ahead incredibly quickly now about the registration and the making public of clinical trials, so however these are worked out, and we are a party to these discussions obviously, once the public know that a trial has been registered and they will be able to access the results at some time, it will be impossible for companies who are starting bits of work to hide that away. We welcomed this move both to register and to publish clinical trials and that will make our job much easier, although we still recognise that there are issues of commercial confidentiality with which we will have to deal.

Q823 Dr Taylor: Can I go back to Dr Raine and the problem with the particular drug that I think Mr Austin raised. Is there a likelihood when patients are used in market research that this can indirectly sort of turn into a promotional campaign? Certainly with this particular drug, we have had evidence that their campaign was actually to target consumers and patients. Now, are you aware of that? Could you expand on what you said to Mr Austin before? What methods would you have of controlling that sort of activity?
Dr Raine: Would you like to name the medicine?

Q824 Dr Taylor: It is AstraZeneca and Crestor.

Dr Raine: Yes, of course. No, our controls on promotion do not extend to the activities and these would fall under the general controls on clinical trials and the nature of the consent that needs to be obtained and full explanation. It would not be within my domain in advertising to look to see the information that is provided to subjects in trials of this nature.

Q825 Dr Taylor: So would anybody be aware of promotional campaigns taken on, which could target the consumers directly?

Dr Raine: The issue of direct-to-consumer promotion of a prescription medicine is prohibited very clearly. The grey area which Professor Breckenridge referred to where we do have obviously a policeman role is what is called “disease awareness”. Now, the law prevents us from getting involved so long as specific medicines, specific licensed products are not mentioned, but clearly, by implication, if there is a new medicine in a particular area, one can construe that a campaign might be referring, by implication, to Viagra, for example, if that is the only medicine in that area. Certainly we would take very careful advice, including legal advice, if we thought a disease awareness campaign was effectively promoting a medicine.

Q826 Dr Taylor: Promoting a particular drug?

Dr Raine: Yes.

Q827 Dr Taylor: So you would be able to do that?

Dr Raine: Yes.

Professor Sir Alasdair Breckenridge: Yes.

Q828 Dr Naysmith: Perhaps we can turn to an area really which you have mentioned already two or three times, which is this question of balance between safety and efficacy, and of course we have spent quite a lot of time talking about safety so far. Could I ask you if it concerns you that there are pretty reliable figures suggesting that under 50% of new drugs which get on to the market offer any significant advance?

Professor Sir Alasdair Breckenridge: Thank you for asking that question. It is a very interesting question because when you see a drug being developed, it will be 10 or 12 years before it comes to the market. It is based on a pharmacological idea and many companies will light on this idea and start to develop the medicines. Now, the precise route which they go down differs and the drugs may well come to the market 10 or 12 years later at about the same time and there are several very interesting examples of where the company, which was first in the field, in fact did not finish up the best and it was the second in the field which had a better efficacy profile or fewer dangers. The other thing which does happen of course is that as drugs are developed, they very often develop indications for efficacy in areas for which they were not intended, so whilst the drugs which are developed down the line from the leaders may not have obvious advantages in one area, they may well be incredibly important in other areas. There are many examples of that going back to the 1960s with beta-blockers and more recently with angiotensin-converting enzyme inhibitors where it was the second and third drugs in the line where people began to notice an effect in heart failure and not in hypertension and these are the mainstays of heart failure treatment now, so it is a very interesting debate as to what a me-too drug really means.

Q829 Dr Naysmith: What I am really interested in is finding out what you can do to encourage less concentration on need-to drugs. For instance, the FDA in the States categorise new molecular entity drug applications according to significant therapeutic advance and what they do with them then is prioritise them for peer review and moving into the system. Now, do you operate anything similar to that?

Professor Sir Alasdair Breckenridge: No, we do not.

Q830 Dr Naysmith: Why not?

Professor Sir Alasdair Breckenridge: Well, the law says that we will consider a drug for safety, quality and efficacy. That is the law under which we operate. There are certain other countries which do, I am aware, operate policies which you describe, but the European law, as far as I am aware, under which we operate cannot categorise medicines in that way.

Q831 Dr Naysmith: Are you saying that it would prohibit you from doing it in that way?

Professor Sir Alasdair Breckenridge: I think it would. I think that if a submission came to us for a new chemical entity and its safety, efficacy and quality were sufficient, we would license it.

Q832 Dr Naysmith: But there is a backlog, is there not? There is a queue to get things through.

Professor Sir Alasdair Breckenridge: Well, the queue is much less than it was. You may care to ask Sir Michael Rawlins in the next session that question because that is very relevant to his role.

Q833 Dr Naysmith: I realise that, but it is also relevant to your role.

Professor Sir Alasdair Breckenridge: Well, with all respect, it is not because we are regulators. We do not say how people should use drugs and whether the National Health Service—

Q834 Dr Naysmith: So you are criticising the FDA’s policy?

Professor Sir Alasdair Breckenridge: I am not criticising it. Who am I to criticise the FDA? I am just saying that they operate under a different legal system than we do.

Q835 Dr Naysmith: But maybe if we thought it was a good idea here, we could start beginning to change the legal system here, if people thought it was a good idea. I am trying to find out what your views are on it and whether your Agency, in doing what you do, could be helpful in this.
Professor Sir Alasdair Breckenridge: For all the reasons I have just discussed with you about looking into the future as to what the role of an individual agency may be, I think it would be a very brave thing for an agency to say, “Look, this is just a me-to drug. We are not going to license it”. I think that is not how I see the role of the Agency.

Q836 Dr Naysmith: I do not think people are saying that they are not going to license it, but they are saying that if there is competition for resources, they will maybe try to go for something which offers more advance potentially. Professor Woods looks as if he wants to have a go at this one.

Professor Woods: A couple of thoughts might be helpful. Firstly, the assessment times for new products have been very substantially shortened over the years and I do not think there is a queue such that one would need to prioritise in the way you suggest. The second thing is that although it would be nice if each innovative drug broke into a new therapeutic territory, in reality we do not actually fully understand what the utility of a drug will be at the point it reaches the market. We know about its safety, its efficacy and its quality to a degree sufficient to grant the product licence, but its actual utility and use will become clear. I think the distinction between safety and efficacy on the one hand and practical utility on the other is an important one. Speaking as a prescriber, and I spent 30 years prescribing drugs as a physician, it is certainly valuable to the prescriber to have a range of options available to suit the needs of the individual patient. Although you can say that drug A is not as good as drug B in large trials, when it comes to the individual patient if drug A does not work, you may want to try drug B and, therefore, there is that, if you like, redundancy in the system, but in reality it is the flexibility which allows patients to be better treated. The other point I would make is that if you were to consider legislating in a way which inhibited the development of what seemed like need-to drugs, there is a risk that we would lose things. For instance, if you take the antibiotic area, there is a multitude of antibiotics which might treat a particular infection, but we need all of them because patterns of resistance change and the likelihood that we might actually discard or obstruct the development of a drug which five years down the line is actually the antibiotic that we need because the first four antibiotics are no longer working. I think that is the kind of practical implication one would have to think through before considering new legislation.

Q837 Dr Naysmith: Some of the things you have said are really very interesting because we have had views expressed here, and I know from my own experience and background in various aspects of medicine and so on, that we need more, better, more efficacious new drugs and whilst I accept what you say about altering the odd molecule here and there can make quite a difference, there is a concentration, and I am sure many people agree with this, on diseases which are sort of easy to crack, easy to treat rather than looking at some of the very difficult ones. For instance, on a worldwide scale, it is ridiculous that malaria still kills so many people, but it has been suggested that because there is not a particularly good market for it in developing countries, maybe there is not nearly enough concentration. That is a very extreme example, but the same applies to lots of other drugs, I think.

Professor Woods: I think that is absolutely right.

Q838 Dr Naysmith: Witnesses have told us this.

Professor Woods: Indeed.

Q839 Dr Naysmith: All I am asking is if there is anything you can do as an agency to sort of encourage firms to do the right thing. Of course if you are saying you cannot do it because of legal constraints, then maybe we need to look at that.

Professor Woods: Well, I think there are limited things which regulators can do to ameliorate this situation. It is a problem, I do not dispute that and I think you are absolutely right, but the drivers which encourage or inhibit useful innovation in the pharmaceutical area are quite complex and regulation is only one of them. It can act negatively. If one creates a climate where innovation generally is made more risky, more expensive, if one over-regulates, if you like, it means that the available investment will go towards the safer products, safer in the commercial sense. To produce another beta-blocker is not going to be quite as much of a blockbuster as to produce a completely new treatment for something untreatable, but, on the other hand, it has a degree of commercial sense about it and, therefore, it is important to recognise that although regulators cannot do a great deal to stimulate innovation, and there are some things we can do which I will come back to, if we can certainly do things to inhibit innovation and we must be careful that we do not inadvertently do that. The ways in which we can simulate innovation are actually to engage with innovating companies at an early stage of product development to provide scientific and regulatory advice, that is to say to help the company understand the hurdles that will have to be cleared, perhaps a different mechanism of action, perhaps breaking new ground, to satisfy us as regulators that it is worthy of a product licence. I think that scientific advice is something which we have really only been doing over the last year or two and the number of scientific advice meetings we hold is going up really quite steeply. I think that is something very positive that we can do and the only constraining factors on us really is firstly industry’s uptake of that option which they are very keen to do and the second thing is our resources, our scientific resources within the Agency, to provide that degree of assistance. The FDA, to whom you referred, I think have taken this even further and they have produced a very thought-provoking document recently called Innovation or Stagnation? which asks the question and delves more deeply into the matter of, what can regulators do to foster innovation? The areas they see as a difficulty are the growth of regulatory science, if you like. Are there better ways
of predicting clinical hazards at an early stage of development in order that companies do not waste money on drugs which ultimately are going to fall down? Are there other surrogate markers which will detect potential hazards at an early stage and, if so, can the regulators introduce those into the assessment process? Are there therapeutic markers that we can pick up earlier in order that the process of development can be more accurately targeted on those things which are going to work and have an acceptable safety profile than those things which are doomed to fail at a late stage of development? Regulators around the world are thinking about this and both the FDA and ourselves have discussed it internally at length.

**Professor Sir Alasdair Breckenridge:** The other thing is that the picture for malaria, which is an area in which I am closely involved, may not be as gloomy as you are saying. There are some very interesting things happening in that area now, thank goodness.

**Q840 Chairman:** Professor Woods, can I just clarify in the treatment of individual patients. It seems that after your answer on “me-toos” because you appear to be questioning the entire concept of “me-toos” that has been raised with us on numerous occasions during this inquiry. Do you accept that there are “me-toos” or are you saying that there are subtleties between different products that perhaps we ought to be aware of and that “me-toos” do not exist and there are distinctions that are important?

**Professor Woods:** Yes. From practical experience as a clinical pharmacologist, there are no two drugs in a class which are identical in terms of their duration of action, in terms of their handling in the body and how they are eliminated. For instance, you might have a patient with impaired renal function. You would select a drug within the class that was not really excreted, you would choose one that was metabolised. Therefore, if you know the drugs and you know their individual characteristics, you can select in a way which maximises efficacy and minimises toxicity. So, I think the concept of a “me-too” is a rather blanket description which does conceal some more fundamental facts.

**Q841 Chairman:** Are you saying that there are not any “me-toos”?

**Professor Woods:** There are groups of drugs which contain an awful lot of agents which have rather similar actions.

**Q842 Chairman:** But “me-too” is not a concept that you would use? I just want to be clear what your views are.

**Professor Woods:** One uses it as a kind of shorthand, but I think we probably have enough beta-blockers: last time I counted I think there were about 15 and I think that is enough. The point is that if one took the opposite approach and said that, in each therapeutic class, there will be one or two agents, we would actually lose.

**Q843 John Austin:** I accept your point that the “me-too” might be efficacious with a particular patient, but in terms of the overall therapeutic benefit compared with the cost of the research and all that goes into it, it surely cannot be the best way to go, can it?

**Professor Woods:** It comes back to what I said earlier about the distinction between efficacy, safety and so forth and utility. The NHS now has—and you will be hearing later evidence this morning about the work of the National Institute for Clinical Excellence—a mechanism for providing guidance to practitioners as to which within a class are the most useful drugs and I think there is a difference there, a very important difference, between therapeutic utility, which can actually change over time, and the criteria of safety, efficacy and quality which allow a drug into the marketplace, and I think it comes to this question of the intelligent consumer and, by “the consumer”, it might be the NHS as the purchaser, it might be the prescriber or it might be the patient who is actually taking the drug. I think that one needs to give those end users the information to allow them to make judgments about the actual place of a drug in the treatment of individual patients. It seems a little extravagant, it seems a waste of scarce R&D resources to develop a drug which is rather like a drug which is already there but, on the other hand, it is not something that one should legislate against because commercially it is not the most attractive option either.

**Q844 John Austin:** We have had a great deal of evidence or argument before us about the importance of accelerating patients’ access to the drugs. I think one of the witnesses last week said that we were just behind Croatia in terms of new drugs, but we have also had discussion—and we have had some discussion this morning—about the slowness of the regulators in responding to safety problems with some drugs on the markets. One could draw from that a conclusion that, when it comes to early licensing of medicines, the regulators are willing to live with a very large amount of uncertainty but, when it comes to restricting or withdrawing drugs which are on the market, the regulators are demanding compelling evidence of injury and harm before taking any decisive action. Would it be fair to say that you give the benefit of the scientific doubt to the drug manufacturer, both at the pre-market review stage and the post-market decision making?

**Professor Sir Alasdair Breckenridge:** No, that is not true. The question of early marketing of medicines is an important one in that one does not want to withhold effective medicines from getting to patients. On the other hand, one is very aware that, as we have said already, the amount of safety evidence which is available for a new medicine once it is licensed, even under a normal route, is limited. It is going to be even less if there is going to be early licensing of a drug and what does happen under the situation is that the company who does ask for early licensing of the drug is given very strict tasks which it must fulfil by a certain time—and this is reviewed within fixed time limits—or the licence will be
withdrawn. There are risks attached to it. It comes back to my theme again of risk and benefit. If there is overwhelming benefit of the drug, for example in the treatment of AIDS or a new drug for cancer which one may be prepared to take, but if it were yet, coming back to our previous discussion with “me-too” drugs, another beta-blocker or something like that, it is not an area that one would want to follow.

**Q845 John Austin:** What would the policy of the MHRA be if there was scientific doubt about the safety of a drug which appeared to offer no significant therapeutic advantages over other therapies? Would it be left on the market?

**Professor Sir Alasdair Breckenridge:** It would depend on what the indication was. As I say, if this were a drug which had the promise of curing cancer or curing HIV disease, then the risk to benefit decision would be different from if it were a drug which was going to treat nasal blockage. That is the answer.

**Q846 John Austin:** Dr Taylor may want to come on to the recording of adverse incidents and whether it is an effective system at the moment but, in evidence to us earlier, the Medicines Commission made the point about the amount of research being carried out into adverse effects of medicines and I think they said in their evidence that funding for research into adverse drug reactions was an extremely important aspect of drug therapy but that it has been impossible to find in the current research climate the resources and the funding to do that and they went on to say that the pharmaceutical companies themselves provide little funding for such research because they do not perceive it as being in their interests to do so.

**Professor Sir Alasdair Breckenridge:** Can I address that by telling you a little about how the Agency is funded now. The Agency is funded essentially, since 1988, by the industry, by licensing fees and that was recommended, and that had the result of accelerating the new drugs which were coming through, the backlog fell quite dramatically. The second thing relevant to your question, Mr Austin, is that, in 1991, the decision was reached that a fee would be charged for every medicine which had a product licence which was on the market and that annual fee brings in now 40% of the income of the medicine sector. That is used for pharmacovigilance studies, for safety studies and for enforcement studies. So, we are in the position within the Agency of having a sizeable budget, 40% of our income, which is used for pharmacovigilance studies and for enforcement. Many other agencies do not have this.

**Q847 John Austin:** Is it usual for you, as regulator, to request companies to carry out further studies of adverse events?

**Professor Sir Alasdair Breckenridge:** Yes that does happen and the other thing is that we do commission studies as well. For example, the Agency commissioned a study in fact from Liverpool, from where I originate, on the whole effect of adverse reactions on the morbidity and mortality of patients and this was published in the *British Medical Journal* last year, that 6% of patients admitted to hospital suffered from adverse effects was due to adverse effects. This had a financial effect of about £400 million a year. This was the first study which had been done in the United Kingdom for 15 years to look at the financial significance of adverse effects and the Agency does fund studies like that as well.

**Q848 Dr Taylor:** Can we move on to drug safety monitoring in more detail and the yellow card system. You have already mentioned the yellow card system saying that you are going to put things on to the web. We have also heard that the yellow card system is going to be widened to allow patients to fill in yellow cards.

**Professor Sir Alasdair Breckenridge:** Yes.

**Q849 Dr Taylor:** Are you going to have a method of selection before things go on the web? How are you going to play this? Do you have any idea of how to make it more effective, more all-embracing than it is at the moment?

**Professor Sir Alasdair Breckenridge:** Dr Raine is in charge of this and she could answer but I would be very happy to start off. In fact, as of yesterday or two days ago, the adverse reactions/yellow card reports for every licensed medicine are available on the web. If you go to the website, yellowcard.gov.uk, you can call up the adverse reaction profile, all the anonymised yellow cards for every adverse reaction to every drug which is licensed in the United Kingdom.

**Q850 Dr Taylor:** So, you are putting on any card you get from Mrs Bloggs down the road without vetting it sort of thing?

**Dr Raine:** Yes, but there is very clear guidance about annual fee brings in now 40% of the income of the how the data can be... and look at the data. We are learning as we go and we have a patient reporting expert group which is chaired and largely constituted from patients and those with an expertise in consumer interests and they are helping us move forward with what are essentially some very important first steps to truly engage and inform in the way that patients want.

**Q851 Dr Taylor:** So, whatever it is, however unlikely it might be, it would go on?

**Dr Raine:** Yes, but there is very clear guidance about how the data can be interpreted and how far it can be interpreted. Clearly, it cannot give any idea of the incidence of an adverse reaction and, as with many websites, you have to read all this and say that you have and you understand, if you like, the health warnings before you go further and look at the data. We are learning as we go and we have a patient reporting expert group which is chaired and largely constituted from patients and those with an expertise in consumer interests and they are helping us move forward with what are essentially some very important first steps to truly engage and inform in the way that patients want.

**Q852 Dr Taylor:** How can you get the medical profession to fill in more yellow cards?
**Professor Sir Alasdair Breckenridge:** Thank you for asking that question! I hoped you would ask that question because this has come up several times, Dr Taylor, we are very clear in the instructions which we give that we want reports of drugs which have a black triangle and serious adverse reactions. That is what we want. We are very keen to encourage yellow card reporting but what we do not want is a lot more reports of rashes on penicillin and bleeding on warfarin. The yellow card system is not there to give an incidence of adverse reactions. It cannot do that. It is there to give—and this is a terribly important question—that you have asked—a signal where we can take that signal and explore it in other ways. So, while we do want more adverse reaction reports and yellow cards, the main thing is that we want better ones and the interesting thing, coming back to what June was saying, is that, when we have patient reporting, what kind of profile of adverse reactions will this give us? How will this add to our information on the safety of medicines? That is a very interesting thing which we are going to explore with the new way in which we are doing things.

**Q853 Dr Taylor:** Can you just explain the black triangle in case people do not know.

**Professor Sir Alasdair Breckenridge:** Every new drug and every drug which has, for example, a change in indication has a black triangle put opposite its name in the British National Formulary, in advertising and in our publication Current Problems; every month or two we indicate to people who read that what a black triangle means. Perhaps we have not been as successful as we might have been in informing the health professions about this. This is what a black triangle means, it means report any adverse reaction which does occur with this drug.

**Dr Taylor:** Are there any incentives for doctors who fill in more of these?

**Chairman:** What do you have in mind?

**Q854 Dr Taylor:** I have to remember that I probably did not fill in more than a fraction of the number of yellow cards that I should have done and it is so important that I am just trying to explore . . .

**Professor Sir Alasdair Breckenridge:** There is an apocryphal story that one of our fellow countries which is slightly to the west of us decided several years ago that they would give incentives to doctors to fill in yellow cards and the apocryphal story is that the number of yellow card reports went up a hundred fold by doing that but the therapeutic value of it did not rise commensurately.

**Q855 Dr Taylor:** What other major sources of information on adverse reactions are there?

**Dr Raine:** A broad range. We look at the published literature and we have studies that are commissioned post-authorisation and a very, very broad range. Internally, we have the General Practice Research Database (GPRD) which has information on 35 million years of patient data in primary care and we are trying to develop tools to use the data there to help detect signals. So, it is a very broad range. Probably about 40% of our new signals come from the yellow card scheme and others come from the published literature and so forth.

**Q856 Dr Taylor:** We get very worried when prescription drugs that have been licensed and released are withdrawn relatively soon after they have been marketed. How could we better prevent that? When we put that to the drug firms, they feel that the only way you are going to pick up side effects relatively quickly is if drugs are marketed on a big bang sort of approach. I would like to have thought that drugs that offer a very real advantage—and I do not just mean one of the minor developments that have been called “me-toos”—should be released more on a limited basis, perhaps consultant-only prescribing which inevitably goes for the drugs with high risk like the anti-TNFs and the anti-cancer drugs. If the COX-2s had been liberated on a more limited fashion because they did potentially have a real advantage, would that have just delayed the declaration of all these side effects or would it have been beneficial in the long run?

**Professor Sir Alasdair Breckenridge:** That is a debate which is very active at the present time. As you are aware, when the COX-2 inhibitors were launched in the late 1990s, because of a knowledge of the pharmacology, it was predicted that these drugs would firstly have a beneficial effect on gastrointestinal bleeding, but secondly they would not prevent cardiovascular disease as the old non-steroidals did. My understanding is—and I have probably read the same literature as you have—that the company that marketed the first of these did in fact set up studies at that time, at that very time, to explore the possibility that there might be adverse cardiovascular effects and it is these studies now which are coming through, which have shown that there was this increased incidence of cardiovascular disease. So, I think there are some adverse effects which are immediately apparent, there are some other adverse effects which take a long time to become apparent and of course, coming back to our discussions about yellow cards with respect to problems like cardiovascular disease, the yellow card is a very poor system of picking up adverse reactions which mimic a disease which is common in the population. So, as June was saying, you have to rely on either patient databases or clinical trials like I am describing to you with respect to the COX-2s.

**Dr Raine:** I do think that our new legislation which is coming through in October which gives us the powers to demand risk management plans at the time of authorisation, so studies will begin in a very prosactive way to test these questions, will actually prevent the shock of a medicine being withdrawn in quite the way that happened with so many people exposed to risk. It will never prevent a medicine ever being withdrawn again, but it gives us a much better tool to be on top of the safety as it unfolds.

**Dr Taylor:** That is encouraging.

**Q857 Chairman:** Before we move on from adverse reactions, obviously you have talked about our system and you will be aware of different approaches
in different parts of the world and we have looked at one or two. Do you have any thoughts of other systems that might have any merits to recommend them to this country or do you feel that, with the qualification you have just mentioned and the changes you have described, we are broadly in the right direction?

Dr Raine: I think we are moving in the right direction and I think that the world is moving in that direction too. We have to use better sources, more robust sources of evidence that are at our disposal. I think we actually do have to make a very active attempt to include the patient perspective. There are areas of our so-called “Excellence” strategy such as decision analysis that need careful testing as to whether they are applicable. They are applicable in other fields but are they applicable here? I am not aware of another regulatory system that is really delivering a better and more prompt identification and action on risk than we are at the moment. We must keep returning to transparency. Once the evidence for risk decisions is made public as a matter of course, then I think the whole discipline will move forward worldwide.

Q858 Mr Bradley: You mentioned the clinical trials register earlier and you said that you were in discussions about it. What form do you think such a register should take?

Professor Sir Alasdair Breckenridge: There are several proposals around just now. Let me start from where we are just now. With respect to the European Clinical Trials Directive, every trial which is started within Europe must be registered with the Agency in the country where the trial is being done and this will be collected on a European-wide basis and that information will be available to regulators. Broadening it from there, if the studies are being done in different environments to that, I think it very much depends on the willingness of the companies, because they are the people who do most of the studies, to conform to a single system and the companies are having these debates just now. Whether or not that will be sufficient or against some other discussions which are taking place just now that this should be made compulsory is, I think, an interesting decision.

Q859 Mr Bradley: Do you have a view on that yourself?

Professor Sir Alasdair Breckenridge: I would hope that, in the current climate, a voluntary system will be able to work combined with the European—

Q860 Mr Bradley: Do you think the public will have confidence in a voluntary system?

Professor Sir Alasdair Breckenridge: I would hope so, combined with the European Clinical Trial directive. Kent, you have had experience with the Clinical Trial directive and I wonder if you would come in on that.

Professor Woods: There are of course these two separate issues which have been referred to before. One is the registration of the fact that a trial has been started and the second is the availability of the results of that trial when the study has been completed. From the point of view of the regulator, the first part is important in terms of enabling us to ensure, as we are still here, that we have everything. In terms of the general public, it is the availability of clinical trial results in an accessible place which is perhaps more fundamentally important. The voluntary system which the global pharmaceutical industry has come up with in the last week or two offers a promise of how that might work but it is early days and, as we say, there must be public confidence that it will be actually implemented. Secondly, there are some technical questions to be sorted. Where do you put the trials data in a site which can actually be accessed by people? Thirdly, what should those records contain? Are they intended to be totally comprehensive, in which case they will be almost inaccessible to the general public, or are they in some way summarised data? I think there are some very important practical issues and issues of trust too which do need to be clarified. I think the default position would have to be some form of legislative requirement if that voluntary system does not work. We will know, I think, quite soon.

Professor Sir Alasdair Breckenridge: As I have said already, we hold out great hope for the European Clinical Trial directive registering trials on that system and this will teach us a lot which may well help to inform the other systems which Kent was describing.

Q861 Mr Bradley: Do you think there are any anomalies in the situation where clinical trials information is voluntary given by the companies but you may feel that you have to protect that same information because of commercial confidentiality? Do you think there are potential conflicts within that?

Professor Woods: Of course, the Freedom of Information Act which came into effect at the beginning of this month does substantially shift the rules of the game in effect that the default position is disclosure whereas the tradition, the legal position in UK medicines regulation going back to the 1968 Medicines Act, was very much that the presumption was that data submitted for licensing purposes were confidential data and indeed, under section 118 of the 1968 Medicines Act, it was an offence to release information unless, in the course of one’s duty, it was necessary to do so. The Freedom of Information Act is shifting that towards the presumption of disclosure and therefore it is no longer the case that information submitted to us as a public body is protected from the Freedom of Information Act and any exemptions from disclosure, that is relevant exemptions, are conditional on a test of the public interest of disclosure versus the public interest of non-disclosure. So, I think that does quite fundamentally shift the accessibility of trials data and we welcome this. We, as an agency, would sooner have information out in the public domain provided, from the company’s point of view, there will be occasions when the exclusions built into the act will be necessary, but the default has changed.
Q862 Mr Burns: Sir Alasdair, you slightly dealt with my first question in answer to my colleague Mr Austin, but, on your funding, as we know, it is from fees from industry and you have to compete with other European regulatory agencies for business. Do you think this creates a situation in which drug companies are your customers whom your organisation is competing to please and thereby perverting the priorities of your Agency away from the protection of public health and more to the advancement of new and effective drugs and, if your answer is “no” which I suspect it will be, why?

Professor Sir Alasdair Breckenridge: There are several parts to that question and let me start it off. We are part of Europe. There are three ways in which medicines in Europe can be licensed. Firstly, they can be licensed nationally and the companies will come to us for a licence and that is quite clear and I think you understand that. Secondly, there is the centralised programme—and this is increasing all the time—where a medicine is licensed within the whole of the EU and what happens there is that the company will approach the EU and their Scientific Advisory Committee will decide which of the countries are going to act as the assessors, as the rapporteurs and the co-rapporteurs, and that carries money with it, and that accounts for a sizeable amount of the funding of our Agency. We are one of the biggest gainers from that system because of the stature which our Agency does have. So, this contributes quite a lot to the funding that we do have. The third process by which a drug can be licensed is the so-called decentralised or mutual recognition process whereby a company will come to, let us say, the MHRA, to the United Kingdom, and, if we give it a licence, then it will go into Europe from there once it has been recognised in one country and mutually recognised and clearly that is financially beneficial again. So, you have to balance each of these three systems of funding which we do have against the incentives which you are talking about and it is clearly terribly important that we retain and advance our position in Europe not only from a UK plc point of view but also from the funding point of view of our Agency.

Q863 Mr Burns: Do you think you have adequate resources, both financial resorts and in terms of personnel, to be able to provide the high quality service to which you aspire?

Professor Sir Alasdair Breckenridge: The funding of the Agency comes from two sources. Firstly, there is the medicines part which we were talking about just now and we have discussed the ways in which we fund that and, in many respects, if we get more user fees, we will get that because of the excellence of the Agency and the excellence of the service which we provide. The second part of the Agency—and perhaps this is not the concern of this Committee—is for medical devices and medical devices are funded by Government. The very interesting areas which are now arising as we speak are that there is a huge interface between medicines and medical devices and how these are going to be licensed and how these are going to be regulated. We are in an advantageous position because of the actions that were taken two years ago to join the Medical Devices Agency and the Medicines Control Agency and this is an area in which we are very active just now and we want to make our imprint in Europe that we are an agency which is looking towards that possibility and thereby gaining more funding for the Agency in that way.

Q864 Mr Burns: You have dealt with funding, what about personnel?

Professor Sir Alasdair Breckenridge: Let me ask the Chief Executive about personnel.

Professor Woods: We are one of the larger regulatory agencies worldwide. I think that there are specific areas within the Agency where we will need to recruit additional expertise because science marches forward and we need to ensure that we have the most up-to-date skills and science base within the Agency. I see that as an incremental process. I do not think that there are any major shortfalls in our resources but we will need, over the years, to ensure that, as we recruit and develop our staff, we are able to handle new technologies, we are able to keep abreast of developments and we are able, also in the safety area, to use the latest techniques in epidemiology to study adverse effects of drugs and devices in the population.

Q865 Mr Burns: Do you think Mr Jim Thompson’s comments from Depression Alliance where it says that the regulatory body is woefully under-resourced is wrong?

Professor Woods: I think it is certainly not the case that we are woefully under-resourced. Perhaps that is a rather rash statement to make but I think that statement is wrong. Clearly, there are issues that we would wish to pursue in greater depth, but I think those are within the scope of that current funding mechanism and, as much as anything, it is a shifting of resources rather than an absolute shortfall. I really do not think that we are woefully under-funded and I think that we have some world-class scientific resources within the Agency, not just in terms of people but in terms of databases. We have databases that are absolutely unique in the world and our task over the next year or two will be to ensure that we have those additional very rare skills which enable us to exploit them fully.

Q866 Mr Burns: If you look at your own website say on 1 December 2004, you will see that there are currently delays in processing certain applications. Why is that the case if your financial resources and your personnel resources are fine and would it not have been predicted that there was going to be a problem and should the necessary measures to seek to minimise those delays not have been taken? Also, what impact are those delays having on the overall work and performance of the Agency?

Professor Woods: That is the one area where we have of late been falling short of our own demanding performance targets and the history of it is this. There was a change in the paperwork/documentation required for particular types of
licence application. Before the change came in—and this related to abridged applications—there was a rush of applicants wishing to get their applications in before the paperwork changed, before the common technical document came in. That meant that there was a short surge in demand which we could have predicted though in fact it is rather difficult to handle a short surge in demand because, if you recruit more staff and the demand goes away again, you have a slight problem. So, there was that initial surge of demand which knocked us off course. The other factor which we had not allowed for was that actually the number of applications coming in year on year is rising too. So, this is not simply a transient—

Q867 Mr Burns: I am sorry, can I just pick you up on one point before you carry on. You said—and there is a logic to your argument—that it would not necessarily be wise to take on extra staff to deal with a short-term surge, but why are you taking on more staff?

Professor Woods: If it were a simple matter of a surge where applications we were expecting to be spread across a year all turned up in January, then if we recruited to handle January, we would be overprovided with staff in February onwards. There is this more complex question that actually the number of applications coming in has shown a sustained rise. I have discussed this with the industry associations, firstly why has it happened and, secondly, can they give us more precise information about their commercial plans. I think the answer to your question as to how we cope with this is that, if we can better understand the commercial drivers from the industry which influences the timing and the number of applications, we can start to deal with that but, if we have these rather unpredictable fluctuations, we have a problem.

Q868 Mr Burns: Finally, we are told that it takes longer to process applications for generic products rather than for new chemical entities. Is that factually correct and, if it is, can you explain that?

Professor Woods: It is predominantly in that area that this particular difficulty of surges in demand arises. There is another factor which is that generic products will suddenly appear on the market when a branded product goes out of patent. Therefore, there is a starting point when every company which is going to start producing a generic produces a generic. So, intrinsically, it is a rather lumpy line of activity to cater for but, as I say, there is discussion which has been. I think, productive with the industry association for them to do work among their own members to give us a forward view of what those peaks and troughs are likely to be and, if we can map on to that internally, we can make sure that the absolute number of scientific staff is right and, on a micro basis, we can actually move scientific staff from one form of licensing to another as the demand arises.

Chairman: As you know, we have a shorter session—hopefully it will be a shorter session though we are not sure yet—with NICE following on. We have a couple of brief questions before we conclude.

Q869 Dr Taylor: Do you have a set scale of fees for licensing pre-marketing trials?

Professor Woods: Yes, we do have a set scale of fees. All our statutory fees are subject to external consultation and scrutiny by the Treasury and final agreement by ministers. It is a set scale. We do provide quite a range of regulatory activities which have their own fee structures but they are all, as I say, approved by that process.

Q870 Dr Taylor: So, a huge firm like Pfizer would be charged the same as a very small firm working on a specific vaccine, for example?

Professor Woods: Yes, we do have a set scale of fees. The details of that are a little more complicated. The service fee which we charge, as it were, for the post-marketing surveillance of products is influenced by the size of the company, the number of products and their volume of sales. So, the actual calculation of the fee does have that variable in it. It is quite a complex fee structure.

Q871 Dr Taylor: That is post-marketing but not pre-marketing?

Professor Woods: That is right, yes.

Professor Sir Alasdair Breckenridge: We could let you have details of the fee structure.

Chairman: That would be helpful.

Q872 Dr Naysmith: My question is a little similar to Richard’s but it was triggered off by what you said, Sir Alasdair, about the three different routes that materials can be passed through your Agency depending on whether it is for UK or it is for Europe or it is for a company which will start here and then . . .

Professor Sir Alasdair Breckenridge: Yes, mutual recognition.

Q873 Dr Naysmith: Are they all treated in exactly the same way?

Professor Sir Alasdair Breckenridge: Yes.

Q874 Dr Naysmith: The standards are exactly the same?

Professor Sir Alasdair Breckenridge: Yes, absolutely. The standards are exactly the same.

Q875 Dr Naysmith: So, it is not easier for a company to go one route rather than another?

Professor Sir Alasdair Breckenridge: That is very often a commercial decision for the company. Is it going to go and get a licence very quickly over the whole of Europe? The centralised procedure does specify certain areas where they must go for a centralised procedure such as high-tech products: anti-cancer drugs, HIV drugs and drugs for diabetes must go centrally. However, it is still up to the company. If they decide that they want to try for a licence over the whole of Europe, they can apply on the centralised procedure.
Q876 Dr Naysmith: It is not that the European standard imposes higher standards or lower standards than—
Professor Sir Alasdair Breckenridge: No because, for a centralised procedure, if we are the rapporteur or co-rapporteur or even an interested Member State, we will apply exactly the same standards to assessment and our opinion as we would to a national licence.

Q877 Dr Naysmith: What do you think it is that makes a company choose one route rather than the other?
Professor Sir Alasdair Breckenridge: I wish I knew. I have no idea. I think there are forces within industry which must make that decision. I guess it may well be if they are first in the field or if they are, using our vernacular again, a “me-too” drug. I suspect that these are influences which may affect them, but I think you would have to ask industry that rather than us.
Chairman: If there are no further questions from colleagues, can I thank you for a very interesting session. We are most grateful to you. If you wish to remain for the subsequent session, you are very welcome to stay. Thank you very much.

Memorandum submitted by the National Institute for Clinical Excellence (PI 32)

HEALTH POLICY, RESEARCH, PRESCRIBING PRACTICE AND PATIENT USE

1. Introduction

1.1 The National Institute for Clinical Excellence (NICE) involves a wide range of stakeholders in the development of its guidance including NHS staff, healthcare professionals, patients and carers, the academic world and the pharmaceutical and medical devices industries. The pharmaceutical industry has the same rights and responsibilities as any other stakeholder.

1.2 We take a structured approach to our engagement with the pharmaceutical industry that enables companies to make an appropriate contribution to the development of guidance and encourages them to work transparently, alongside other stakeholders.

1.3 The purpose of this memorandum is to describe the role of the Institute, to outline the way we work with our stakeholders, and to set the contribution made by the pharmaceutical industry within this context.

2. The Institute

2.1 NICE was established as a special health authority in 1999. Our role is to provide advice to the NHS in England and Wales on the clinical and cost effectiveness of drugs and other treatments. Our advice is for people who rely on the NHS for their care and for health professionals. Further information about the work of the Institute can be found at www.nice.org.uk.

2.2 A summary of the four main types of NICE guidance is set out below.

2.2.1 Technology appraisals: recommendations on the use of new and existing medicines and other treatments (devices, surgical and other procedures, diagnostic techniques and health promotion methods).

2.2.2 Clinical guidelines: recommendations on the appropriate treatment and care of patients with specific diseases and conditions, such as diabetes and schizophrenia.

2.2.3 Cancer service guidance: recommendations on arrangements for the organisation and delivery of services for people with cancer.

2.2.4 Interventional procedures: guidance about whether interventional procedures used for diagnosis and treatment are safe enough and work well enough for routine use. An interventional procedure is one used for diagnosis or treatment that involves making a cut or hole in the body, entry into a body cavity or using electromagnetic radiation (including X-rays or lasers) and ultrasound.

2.3 We publish around 25 technology appraisals, 12 clinical guidelines and 60 pieces of interventional procedures guidance each year.

2.4 NICE guidance is a key component of the national standards to which the NHS is now expected to work. Technology appraisals and interventional procedures guidance are “core” standards, which require immediate implementation, and clinical guidelines are regarded as “developmental” standards, the implementation of which will take place over a longer period.
2.5 The Institute is based in offices in central London. It has a budget of nearly £20 million, which is largely provided by the Department of Health but also includes a contribution from the Welsh Assembly Government, to which the Institute is jointly accountable. The Institute directly employs around 100 people.

3. Working with stakeholders

3.1 Since its inception, the Institute has taken the approach that those whom its decisions affect are entitled to express their views on how we go about our work and on the development of individual pieces of guidance. We define these groups as including, but not necessarily limited to:

3.1.1 patients, carers and the public, and those who speak for them;
3.1.2 healthcare professionals;
3.1.3 NHS management;
3.1.4 healthcare industries;
3.1.5 the Government.

We recognise these constituencies as key stakeholders in our work alongside a much larger group including, for example, other NHS agencies with related functions, research organisations and trade unions.

3.2 We make sure that our stakeholders (sometimes called consultees) have clear and reasonable opportunities to engage with us when we are developing guidance on a particular topic. The arrangements we have put in place have evolved as our experience of working with a diverse community of interested parties has grown. The main elements of these arrangements are summarised below.

3.2.1 Our processes and methods are developed in consultation with our stakeholders and with the independent experts who sit on our advisory committees. Drafts of our process and methods documents are exposed to public consultation and the comments received, together with the final versions of the documents, are approved by the Board in public session.

3.2.2 We consult with stakeholders on our interpretation (the “scope”) of the topics referred to NICE by the Department of Health and Welsh Assembly Government. These scopes form the basis of each guidance development project.

3.2.3 All draft guidance is subject to consultation with stakeholders and the wider public through the Institute’s website.

3.2.4 All documentation associated with the development of guidance, other than where we have agreed to restrictions for reasons of commercial or academic confidence (see Section 4.5), is released into the public domain.

3.2.5 Comments submitted to the Institute by stakeholders are made publicly available along with the Institute’s response.

3.3 We take the view that those who rely on our guidance should be able to understand how it has been developed; in effect, they should be able to see an “audit trail” from the evidence to the recommendations. It should be clear why our advisory committees reached their conclusions, where any changes—from the draft to the final conclusions—have been made and why. To this end each of our programmes displays a common set of characteristics, which are summarised below.

3.3.1 Use of the best available evidence: each programme secures a comprehensive evidence base, by contracting the work to an independent body or by undertaking the work in-house, and stakeholders are invited to check that all relevant evidence has been considered.

3.3.2 Involvement of clinical and patient experts: ensuring that our advisory bodies have access to clinical expertise and patient and carer perspectives as they interpret the evidence is crucial both to the relevance of the recommendations and to their credibility.

3.3.3 Independent advisory bodies: the guidance that NICE publishes is prepared by independent standing committees (for technology appraisals and interventional procedures) and individual development groups (for clinical guidelines). All our advisory bodies include healthcare professionals working in the NHS and people who are familiar with the issues affecting patients and carers. The standing advisory committees also include people who have current experience working in the healthcare industries. Under the Institute’s policy on declaration of interests, the members of our independent advisory bodies, who are mainly unpaid advisors, are required to register their interests and declare any interests they may have in the specific topic under discussion at the start of each meeting. If a conflict of interest is identified, the individuals are required to stand down and do not take part in the relevant decision-making process for that project.

3.3.4 Genuine consultation: all NICE guidance undergoes widespread consultation with stakeholders and the public. “Genuine” means that our advisory bodies will respond to reasoned argument that can stand up to independent scrutiny and, if necessary, change their original thinking.

3.3.5 Regular review: technology appraisal guidance and clinical guidelines are reviewed at regular intervals to ensure that they remain current. Review dates are set on the basis of the advisory body’s understanding of the anticipated pace of change in the evidence base.
4. Engaging with the pharmaceutical industry

4.1 We regard the pharmaceutical industry as a stakeholder in our work. As such, they have the same rights and responsibilities as any other stakeholder. Organisations developing health technologies on which patients rely have knowledge about disease areas and the therapeutic value of their own technology. They also have access to important clinical data that the advisory bodies need to access. The pharmaceutical industry employs staff who are skilled in the interpretation of clinical trial data and the outputs of economic analysis and they make a valuable contribution to the development of high quality guidance.

4.2 However, the Institute is conscious of the conflict of interest that manufacturers of health technologies have when engaging with us—that their desire, ultimately, is to ensure a market for their products and a return for their shareholders. Our structured arrangements for engaging with companies ensure that this conflict does not inappropriately influence the development of guidance.

4.3 The pharmaceutical industry mainly engages with the Institute in the development of the technology appraisals guidance and clinical guidelines, and it is on this basis that the following details are provided. Our structured approach to engaging with the pharmaceutical industry in these programmes (as with all our other stakeholders) is summarised below.

4.3.1 NICE drafts a written consultation on the scope for a technology appraisal or a clinical guideline.

4.3.2 NICE invites relevant members of the pharmaceutical industry, alongside the other stakeholders, to a meeting at the start of the development of a piece of guidance to discuss the scope, the approach to assembling the evidence base, and the key issues that will be addressed during the development of the guidance.

4.3.3 NICE consults on the evidence to be used by the advisory body and all stakeholders are given the opportunity to supplement the evidence base. Ultimately, the evidence that is taken account of is a matter for the advisory body, which sets out the rationale for the use or otherwise of the evidence submitted by all stakeholders.

4.3.4 The advisory body prepares a written consultation on the draft recommendations, on two occasions during the development of a clinical guideline (where there is no appeal stage), and on one occasion during the development of technology appraisal guidance (where there is an appeal stage). Comments received from the pharmaceutical industry on draft documents, in common with responses from other stakeholders, are posted on the Institute’s website.

4.3.5 In the technology appraisal programme the relevant pharmaceutical company, alongside other stakeholders, has the opportunity to submit an appeal on the grounds that the Institute has exceeded its powers or has failed to follow its process, or that the guidance is perverse.

4.4 One aspect of the way in which we engage with the healthcare industries which does differ from other stakeholders is that manufacturers do not attend meetings of the technology appraisals advisory committee, whereas patient and carer groups and healthcare professionals do attend these meetings. In our view this an important part of minimising the risks associated with the potential conflict of interest referred to in Section 4.2.

4.5 Guidelines on the release of company data into the public domain during a technology appraisal were agreed between NICE and the Association of the British Pharmaceutical Industry (ABPI) in May 2004. This agreement acknowledges the importance of putting relevant information into the public domain to ensure the credibility of NICE guidance. These guidelines are helpful in achieving consistency of approach by the pharmaceutical industry, and they are a step towards our long-term goal of achieving unrestricted access to and publication of all relevant data for the development of our guidance (see attachment).

4.6 The pharmaceutical industry has an interest in monitoring the implementation of the Institute’s guidance. Where individual companies or trade bodies have monitored the uptake of medicines or medical devices and have agreed to make this information publicly available, the Institute has published this information on its website alongside studies commissioned by the Institute itself and those provided by patient organisations.

4.7 We believe that this structured and transparent approach to our engagement with pharmaceutical companies enables us to take advantage of the knowledge and expertise of these companies and access to their data while shielding those who are formulating recommendations on behalf of the Institute from the potential distorting effect of an over-enthusiastic presentation of the benefit of a product.

5. Supplemental evidence

5.1 A copy of the agreement made between NICE and the ABPI on the release of company data into the public domain and referred to in 4.5 is attached at Appendix A for information.

5.2 Members of the Health Select Committee are also invited to review the detail of our arrangements for engaging with the pharmaceutical industry and other stakeholders in the process documents for the technology appraisals and clinical guidelines programmes, which are enclosed as Appendix B and C for information.
6. Conclusion

6.1 The pharmaceutical industry, alongside other stakeholders, contributes to the development of high quality, credible guidance that supports healthcare professionals and patients and their carers in making decisions about treatment and care.

6.2 The Institute takes a structured approach to the involvement of the pharmaceutical industry in the development of its guidance in order to manage appropriately the conflict of interest that the industry may have when dealing with NICE.

6.3 The Institute works with the pharmaceutical industry to encourage a consistent approach to placing relevant data in the public domain in order to support the transparency and credibility of guidance recommendations and enhance public knowledge.

National Institute for Clinical Excellence

August 2004

APPENDIX A

Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the National Institute for Clinical Excellence (NICE) on guidelines for the release of company data into the public domain during a health technology appraisal.

PRINCIPLES

1. NICE and ABPI acknowledge that it is in the interests of patients and health professionals for all relevant information about products being appraised to be put into the public domain. Both accept, however, that the legal rights of the owners of the data must be respected.

2. NICE has made a commitment not to place in the public domain any information provided to it as commercial-in-confidence during a technology appraisal prior to the launch of the product(s) into the UK market.

3. Any reference in this Agreement to abstracts shall assume the adoption of the CONSORT rules for the reporting of clinical trials, and an equivalent standard for reporting economic models.

4. In circumstances that warrant publication of data regarded by the data owner as confidential, or the non-publication of data normally available for publication in accordance with these guidelines, both parties will negotiate in good faith to seek to find a mutually acceptable solution, recognising the need for NICE to support its recommendations with evidence and the data owner’s right to determine a global publication strategy.

5. It is recognised that in all cases the data owner retains the right to make a final decision in relation to the release of information into the public domain.

6. It is acknowledged that the principles in this document apply to licence extensions as well as new chemical entities.

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<tr>
<th>Data</th>
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<tr>
<td>Clinical trial evidence</td>
<td>Any information, once published even in abstract form, can no longer be regarded as commercial in confidence (C in C).</td>
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<tr>
<td>— published</td>
<td>ABPI policy encourages voluntary registration of specified information relating to the protocols of phase III trials involving patients in the UK and the current publication status three months after marketing in the first major market and prospective registration of phase IV and SAMM studies relating to the product.</td>
</tr>
<tr>
<td>— unpublished</td>
<td>Companies will authorise NICE to quote publicly from either a full report, or an unpublished abstract, where the date of release, by NICE, of such data is not less than 12 months after the “sign-off” by the relevant company. This 12 month restriction shall be the subject of negotiation in good faith between NICE and the company in the event that the licensing authority “fast track” an application leading to NICE requiring earlier publication.</td>
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<tr>
<td>— design</td>
<td>Pricing information will not be released, by NICE, into the public domain before product launch in the UK. In cases where NICE commissions an independent economic model companies will normally provide—in confidence—the price (or range of prices) expected. It is acknowledged that the final price of a product is often only determined immediately prior to launch.</td>
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Draft SmPC and EPAR | Whilst both the SmPCs and EPARs are public documents, draft versions cannot be published as changes may take place even for the indications right up to the last minute.

Final SmPC and EPAR | Public documents

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Economic analysis  |

— published | Any information, once published even in abstract form, can no longer be regarded as C in C but only to the extent of the data in the public domain.

— unpublished | Companies will authorise NICE to quote publicly from either a full report or an unpublished abstract, where the date of release, by NICE, of such data is not less than 12 months after the sign-off by the relevant company. This 12 month restriction shall be the subject of negotiation in good faith between NICE and the company in the event that the licensing authority “fast track” an application leading to NICE requiring earlier publication.

— model | Companies shall normally agree to their economic models being available to an independent academic group, in electronic form, for the purposes of a NICE technology appraisal. The model will be supplied in confidence and subject to suitable intellectual property protection. The terms of Principle 4 above shall specifically apply to any decision about availability of economic models.

Similar arrangements apply to models produced as part of a NICE health technology assessment.

Budget/resource impact (including marketing/sales forecasts) | Companies are encouraged to supply data from any projections they have prepared of uptake of their products in the NHS, at their own discretion, indicating which data should remain as commercial in confidence.

Witnesses: Professor Sir Michael Rawlins, Chairman, and Mr Andrew Dillon CBE, Chief Executive, National Institute for Clinical Excellence, examined.

Q878 Chairman: Colleagues, can I welcome you to this second session this morning and particularly welcome our witnesses. We are very pleased to see you again and thank you for your attendance. Would you briefly introduce yourselves?

Professor Sir Michael Rawlins: I am Michael Rawlins and I am Chairman of NICE.

Mr Dillon: I am Andrew Dillon and I am Chief Executive of NICE.

Q879 Chairman: Before I begin, I think it is appropriate to say on behalf of the Committee that we do appreciate your response to the recommendations in our report some time ago. It is not always that we can say to agencies, “Thank you for listening to what we had to say and for doing something about it.” I think generally we have been very pleased with the response and I wanted to place that on the record. Before we get into some of the detailed questions, could I ask a similar opening question to the one that I asked at the start of the last session at which I think you were present which is, what lessons do you feel are the issues that perhaps we as a committee, in moving towards the conclusion of this inquiry, ought to be particularly concentrating on? You have a unique insight into many of the areas that we have talked about. As a starter, I would be very interested, Sir Michael, in what your thoughts are on that.

Professor Sir Michael Rawlins: Yes and Andrew may have some additional ones. As far as I am concerned, the part that particularly concerns me, partly as a physician—they still let me practise a little—and partly from NICE’s point of view is the public availability of all clinical trials. It does not just apply to the industry, it applies to people in academia who do clinical trials too because sometimes they do not get published or do not get made publicly available and there is overwhelming evidence to show that it is the negative trials that tend not to get published and I think you heard from Dr Kendal a few weeks again of his paper in The Lancet comparing the published and unpublished trials of SSRIs. That paper incidentally, since he saw you, has been awarded the “Paper of the Year” by The Lancet, which is pretty remarkable. So, it is the public accessibility of the results of all clinical trials. I know that sometimes people talk about intellectual property rights—and I am sure in legal terms that is right—but I am also very struck by the fact that it is patients who take part in these studies and we have an obligation to them to learn from what they have done because being a patient in a trial is inconvenient and sometimes can be hazardous and we owe it to them to make sure that their efforts and their discomfort has not been in vain.

Q880 Chairman: We have actually had that point made by patients.

Professor Sir Michael Rawlins: I think they are absolutely right.
Q881  Chairman: Do you have anything to add to that, Mr Dillon?

Mr Dillon: Just a thought that those who produce and those who use our technologies have some strong common interests, that ultimately the benefits of what is produced have to go through to patients, but they also have some different interests too. They help to produce health technologies and have a need to make a return on their investment and to keep the businesses that they are responsible for viable in order that they can produce good things in the future for example, and those who, like NICE to some extent, value those products have a different set of responsibilities. Because of that, I think it is really important that when those different interests engage, there is actually a structured and open and transparent process that recognises the reality of those different drivers and makes sure that they can be reconciled in a way that enables those who look at how decisions are taken to understand how they are taken and to be satisfied that they are taken objectively.

Q882  John Austin: In your submission, you acknowledge that there is a potential conflict of interest with the pharmaceutical industry’s involvement in NICE’s processes given their key responsibility to their shareholders to secure markets for their products and you have given a detailed description of the processes you follow to minimise this risk. The industry is also involved in selecting the topics that NICE addresses in its advisory programme.

Professor Sir Michael Rawlins: It is ministers who fall responsible. The industry can comment on it. No companies have refused to take part in an appraisal or a guideline but it is not them who decide whether their product will go forward, it is actually ultimately ministers.

Q883  John Austin: So, they do not have an independent involvement in determining—?

Professor Sir Michael Rawlins: They are present in ACTS, the Advisory Committee on Technology Selection.

Mr Dillon: There is an advisory committee within the Department of Health and the industry has seats on that quite large committee, but ultimately decisions are taken by ministers.

Q884  John Austin: Do you see any benefits or disbenefits of the industry being involved at that stage?

Mr Dillon: For us, the really important thing is that we pick up emerging technologies as early as possible in order that we can start work on evaluating them so that we can provide advice to the NHS as quickly as possible after they introduce them to the UK market. The people who know earliest and most about those emerging technologies are those who manufacture them. So, an understanding of how products are developed and the ways in which information can be obtained about developing products properly through publicly available data is quite important and I think one of the benefits of industry participation in that selection process is to provide that sort of perspective.

Q885  John Austin: You will be aware from our previous inquiry that we know your position and how you share our view on the importance of involving patients with patient organisations. It has been suggested now that some patient organisations might be very closely in bed with the pharmaceutical companies and many of them are funded by them. Do you think there are risks there and what is your view towards patient involvement where there is a clear link with the pharmaceutical industry?

Professor Sir Michael Rawlins: We do not exclude patient organisations or professional organisations because they have some relationship with a pharmaceutical company but we do formally ask them when they come to give evidence at the present committee meetings if they know what those interests are and we record them and they are placed in our minutes and the minutes of the meetings are placed on the website and I have a copy here of the guide which indicates the approach that is taken. We do not exclude them because they have an interest, I think that would be wrong, but we make sure that we know about the interest and we make sure that the members of the committee know about the interest and take that into account as part of the judgment.

Q886  John Austin: Can I ask an unrelated question arising out of the exchange between myself and Sir Alasdair in the earlier session when we were talking about SSRIs. I put a question to Sir Alasdair following the report of the Expert Working Group when the MHRA put out a statement following the report saying that SSRIs are effective medicines in the treatment of depression and anxiety conditions and I asked Sir Alasdair if that should have had some qualification to it. Could I ascertain the position of NICE because I asked specifically about the use of antidepressants in the treatment of mild depression. Could you confirm that NICE does not recommend the use of drug treatment in mild depression.

Professor Sir Michael Rawlins: I think it depends on the circumstances. We have recently produced a guideline on the management of depressive illness and that guideline indicates that, in mild depression, it may not be appropriate to go for pharmacological treatments but other sorts of therapy too. It is a very difficult decision if you are a general practitioner or psychiatrist as to the circumstances when you think that drug therapy is appropriate and circumstances when it is not. It is not all that easy to tell in the real world. We did want to shift a little bit away from automatically prescribing and availability of other forms of treatment. We were also very conscious that clinical psychologists are in short supply in the Health Service and those sorts of techniques, what someone would pejoratively call talking therapies, are important and that is one of the reasons why we have actually done an appraisal of computer behavioural therapy and they are at an early stage.
but they are another alternative route to that sort of form of treatment. Andrew, do you want to come in there?

**Mr Dillon:** No, that is a good summary.

**Q887 John Austin:** Would you acknowledge that there appears to be a difference of view between NICE and what the MHRA were saying?

**Professor Sir Michael Rawlins:** I do not think so really. Having been Chairman of the Committee on Safety of Medicines for six years and Vice-Chairman for six years, I am well versed in the archaic rites of it all although it is six years since I was involved but it is slightly different. The regulatory authority is primarily there to regulate the industry, that is what the Medicines Act is set up to do, and previous chairmen used to shout at me when I was a raw young youth on the committee with Alasdair, they used to shout at both of us, that we were the Committee on Safety of Medicines and not Medicine and our role was regulating the industry and not regulating the profession. It is a difficult thing to balance and do; it was difficult when I was chairing the CSM and I am not sure it is not easier now. I think there has been a shift over the years to being more engaged with the professions, more helping them to prescribe appropriately and so on, which was not the original intention but I think that is the right direction to go in.

**Q888 Dr Taylor:** Could you remind the Committee about the selection of drugs for evaluation, how you do it or who does it.

**Professor Sir Michael Rawlins:** The topic selection is formally made by ministers. There is a somewhat complicated process which Andrew is much more well versed in because he goes to the committee meetings.

**Q889 Dr Taylor:** So, you do have some influence in guiding the minister on what to select?

**Professor Sir Michael Rawlins:** Yes.

**Mr Dillon:** Very briefly, there is a whole series of sources of information about the kind of pharmaceuticals that NICE might look at and bear in mind that we only ever look at a small proportion of the total of new drugs introduced into the UK market at any one period of time. All that is looked at by a group called the Advisory Committee on Topic Selection, which is a Department of Health Committee with a whole range of membership from inside and outside the NHS. That creates a shortlist which is reviewed by a joint planning group that has NICE and Department of Health membership on it and that group makes final recommendations through civil servants to the minister.

**Q890 Dr Taylor:** Would you tend to try and concentrate on drugs that offer a real advantage but fill a real gap?

**Mr Dillon:** Yes. There are actually published criteria for selecting pharmaceuticals, those where there is the potential for real therapeutic gain, and another criteria might be where there is potential for very substantial resource impact on the NHS, and another would be where there is already considerable uncertainty in the Health Service about the therapeutic value of the drug and therefore NICE can add value by perhaps reducing some of that uncertainty.

**Q891 Dr Taylor:** How are you getting on weeding out some of the things that do not provide particular advantages or particularly good value?

**Mr Dillon:** Not well enough because we have not done enough on that, we have not had enough topics fed through to us and it is something that we, the ministers and the NHS think should change. In fact, the Department of Health is about to launch a series of workshops or seminars with the NHS to identify those topics in order that they can be fed through to the Institute.

**Q892 Dr Taylor:** Can you not seed them in yourselves and say, “This needs looking at. We want to get rid of it”?

**Professor Sir Michael Rawlins:** We could do but actually the Formulary does not have many totally inactive things in, I would be ashamed if it did since I was on the CSM for so long, and some of the very old things that you and I used to have to learn about in our youth are in the Formulary but are hardly ever used and to go through the whole . . .

**Q893 Dr Taylor:** So, it is not much of a problem?

**Professor Sir Michael Rawlins:** I think it is but I think it is more subtle. I think it is much more in areas like diagnostics. The pathologists have made proposals about the sorts of things which should not be done any more. The radiologists displaying films of the skull say this should not be done any more. I think it is those sorts of areas that offer opportunities that we really need to explore to a greater extent, even complementary and alternative therapy.

**Q894 Dr Naysmith:** I want to explore this concept of substantial therapeutic advance just a little further and ask if there are any other implications for NICE in this. Some of the witnesses have suggested that it would be good if NICE could set criteria about what does and what does not constitute a therapeutic advance. Would that be something you would be interested in doing or is it so bound about by circumstances and depends on this, that and the other that it is not worth trying?

**Professor Sir Michael Rawlins:** There have been discussions across the world about, what is innovation? I think the first group is where there is a substantial health gain in areas that have been previously untreated and those. I think, are the ones that we, as a society, would like to encourage. There is a very interesting report from the WHO commissioned by the Dutch Government on priority medicines making some really fundamental points about areas of great need, not just the sort of diseases of the third world like malaria but many other conditions which are common both in developing countries and in developed countries for which there is virtually no really effective form of treatment and for which there is great, great medical
need. Somehow, we need to encourage those areas of researches and I think there are a number of moves in that direction. Professor Woods was just talking a few minutes ago about the regulatory part of that. One of the very interesting things and I think a very important thing is that there is much more pluralism in drug discovery nowadays. University departments and so on are much more actively involved. The National Institute of Health is setting up its own chemical library for academics in the United States—I do not know if others will have access to it—to be exploring drugs. I do not think that is regarded as a failure of the pharmaceutical industry, I think it is a good thing that others are involved in an area which for 50 years pharmacologists have not been in universities.

Q895 Dr Naysmith: But it is not an area in which you see much role for NICE?

Mr Dillon: In a way, NICE has done because all the decisions that we make together act as a kind of case law. Those who want to understand in a sense what it takes to obtain support for innovative interventions or want to identify what it takes in a sense to get NICE’s support and endorse for real therapeutic value, just take a look at the decisions and indeed how the decisions have been taken. You can look at the standard methodology that we have published on evaluating the clinical and cost effectiveness of interventions and look at how that methodology has been translated into specific decisions and there is a story really over the last five years or so which is, as I say, a kind of case law which could be used by those who want to understand how innovation is interpreted, at least in the UK.

Professor Sir Michael Rawlins: Just to finally follow on from that, I have often used this example but Riluzole for Motor Neurone Disease which prolongs life by up to a year, we felt that was an important innovation for a disease that had previously never had anything at all specific. It was expensive at £38,000 per QALY. Relenza for influenza which you give to everybody also comes in at £38,000 per QALY and reduces your symptoms by a day and we said no to Relenza for everybody and yes to Riluzole. So, I think that demonstrates how we interpret it anyway.

Q896 Dr Naysmith: Can we move on to something different. What, in your view, are the factors that contribute to the time lag between the launch for a new drug and the publication of NICE guidance on new technologies?

Professor Sir Michael Rawlins: The processes—and Andrew will go into some of the detail—involves a very careful scrutiny of the relevant literature, full systematic review. That takes quite a considerable amount of time. Many hundreds, sometimes thousands, of references have to be looked at. We also have a very liberal, I believe liberal in the best sense of the word, approach to engaging our stakeholders and they have opportunity to comment and even to appeal against decisions. All that takes time. If we curtail it in any way we will do either a less robust job or we will end up disenfranchising some of our stakeholders. I believe the route we should be taking is to start with the appraisals around the same time as the licensing process and then complete the appraisal once we know the outcome of the licensing process. We have been doing this for the last couple of years. One of the difficulties, which happened, is that halfway through the licensing process and halfway through our appraisal the gentleman behind me finds there is a problem in the licensing, so it gets held up for a perfectly good reason I am sure, which means then we get held up in our appraisal process and have to stick that on hold.

Q897 Dr Naysmith: You are trying to get to the stage where the appraisal will be published about the same time as the drug’s launch?

Mr Dillon: We have to wait about three months, I think, but we need to know the precise indications the MHRA are granting.

Q898 Dr Naysmith: Are there any lessons to be learned from the drug licensing process for you in this in speeding things up? It used to take far longer 20 years ago than it does now for licensing.

Professor Sir Michael Rawlins: I think we are fortunate, unlike the licensing process where they have to react to demand and the problems of surges and so on. I remember it from years back, it was always happening. For example, when they introduced a fee in 1988, there were huge surges the week before it came into force, which might have been predicted. We do not have that problem, we can control the rate at which things come in, which is an advantage to us.

Q899 Dr Taylor: Are you working more closely with the MHRA than we got the impression you were when we did the short inquiry in 2002, I think?

Professor Sir Michael Rawlins: I think we are and we have developed very good relationships. When we launched our depression guideline, we did it, as it were, as a joint enterprise with the MHRA because of the licensing issues which came up at the same time. I think that is a way we would wish to work, but nevertheless, we have separate functions.

Q900 Dr Taylor: I think one of our ideas and hopes was that this might give you better access to some of the commercially confidential details which you did not have. Has that happened?

Professor Sir Michael Rawlins: Not to that extent. That is not necessarily the duty of the MHRA, they are circumscribed by the European route. I have to say it was to the eternal credit of the MHRA that Tim Kendall and his colleagues discovered the basis of the SSRI problem in children because they published the data on the website. That is something which would never have happened when I was chairman, you were not allowed to think about such things. Those sorts of things have been very important in helping us. I am sure it is the intention of the MHRA to carry that forward.
Q901 Dr Taylor: After our inquiry you got the WHO to do a report. One thing it advised was to make public the basis of any of the advice you published. Have you been doing that more?

Professor Sir Michael Rawlins: We have been discussing with the pharmaceutical industry in relation to commercial and confidential data. Andrew will comment on that. The WHO did admit they wanted to use us as stalking horse for getting more clinical trials out into the open.

Mr Dillon: We never had a problem in being able to publish enough information to justify, we believe, the decisions of taking the recommendations we made. Sometimes we had to negotiate hard with individual companies to obtain agreement on the release of particular pieces of data to allow that to happen, but we have always felt confident that we have been able to say enough. Following our last appearance before the Committee, the ABPI and NICE sat down and reached agreement on formalising what up until then had been informal episodic arrangements with individual companies in the form of a recommendation to all the associations’ members. That is now in a protocol which is operated both by NICE and the industry.

Q902 Dr Taylor: My memory is before the last inquiry we did get a lot of comments from people who felt you were working in a slightly obscure, less than open way. Do you think you have changed that?

Professor Sir Michael Rawlins: I think they were under a misapprehension and after the WHO report—which we were very grateful to you for suggesting in the first instance because it was not something we had contemplated—I think they recognised that it was more transparent than any other process in the world in that sense.

Q903 Dr Taylor: Can we turn to implementation. I am sure this is a fairly sore issue for most of us because certainly I get constituents writing to say: “This has been passed by NICE and I cannot have it, why not?” Have you any idea of the rate of implementation?

Professor Sir Michael Rawlins: The best information we have is probably from a survey we commissioned 15 months ago by Abacus who looked at 28 pieces of guidance which had been produced in the previous two or three years. They estimated there had been full uptake of 12 of those 28. There had been over-implementation of four—we will come back to that—and under-implementation of another 12. It was not a catastrophe but it was not nearly as good as it ought to be and in fact, we are setting up an implementation programme within NICE. The over-implementation was sort of curious. For example, we did an appraisal of metal on metal hips, instead of having the whole thing put in you can just put a bit of metal on the two surfaces. We estimated there were about 5,000 people a year who would warrant this type of thing, particularly young people. In fact, within a year 14,000 had been done. We may have got the wrong estimate, the epidemiological data might not have been that reliable. That is what I mean by over-implementation.

Dr Naysmith: There could be other explanations for it.

Q904 Dr Taylor: Were you able to tie down the implementation and the degree of it to any particular areas of the country, any strategic health authorities or specific PCTs?

Professor Sir Michael Rawlins: We have not done that but we have some data on it.

Mr Dillon: Yes, particularly with cancer drugs. We have data which shows the uptake of specific drugs, probably about eight or nine, by Cancer Network, which is probably the right geographical unit given the nature of those drugs. That shows the distribution before and the abuse of those drugs against an assumed appropriate target, given the nature and size of the population for each cancer network, both before NICE guidance was issued and after NICE guidance was issued.

Q905 Dr Taylor: Have you been able to relate that to whether the particular area is struggling with its finances or not?

Mr Dillon: Most of the NHS struggles with its finances most of the time.

Q906 Dr Taylor: The Government tries to deny this.

Mr Dillon: It is all relative.

Q907 Chairman: It is a good job Mr Burns has left.

Mr Dillon: Of course all organisations struggle with their finances in order to make the best use of available resources. What is interesting about the data is it shows that high performing cancer networks and strategic health authorities, where other data is analysed in that way, tend to improve their performance. Generally, all parts of the NHS improve after NICE guidance has been issued. The rate of improvement is greater in those that were already doing well, which is an interesting phenomenon.

Q908 Dr Taylor: Can you tell us where we can find the details of this data?

Mr Dillon: On the NICE website.

Q909 Dr Taylor: Again, when we were doing the previous inquiry we did have some worries that perhaps the selection of drugs for NICE guidelines did have an impact on other services and got preferential prescribing for these things against things which are time-honored and terribly useful, but did not have NICE guidelines. Have you had any further comments or thoughts on that?

Mr Dillon: When we go, as we do regularly, around the NHS and ask questions about the impact of NICE guidance, it is still an issue which comes up, but the reality is with or without the NICE guidance these interventions are going to be available to the NHS. Decisions are going to have to be taken relative to other desirable improvements in the service and funding interventions and practices.
which have been available for some time. The benefit of NICE guidance is that at least it informs those decisions in a way which quite often in the past simply did not happen. It reduces the variation in the way those difficulties are handled. In the end, the NHS and all the healthcare systems will always be presented in a way with more than they can consume, therefore, there is a need to make decisions, critical things to make sure they are evidence based.

**Mr Dillon:** In the end, probably not because they are guidelines and not every single patient presenting with a particular condition will benefit necessarily in the way we have described, so no it is not likely that is the case.

**Professor Sir Michael Rawlins:** We estimated that about 80% of patients would fit into a conventional guideline and, for all sorts of very good reasons, 20% would not.

**Dr Taylor:** I am very glad you said that because one gets the feeling that some people feel it has got to be 100%. I am grateful for that.

**Chairman:** Thank you very much, gentlemen. We are grateful for your help.

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**Letter from the Chairman, Medicines and Healthcare Products Regulatory Agency, to the Clerk of the Committee (PI 124)**

I undertook to write to you about a small number of items after the appearance of officials from this Agency at the oral evidence session of the Health Select Committee. There are also one or two issues, which, on reading the minutes, I would like to clarify.

Dr Ian Hudson’s previous employment history was raised by Mr John Austin MP and I would be grateful for the opportunity to clarify the position here. Dr Hudson was the Director and Vice President, Worldwide Clinical Safety at Smith Kline Beecham (SKB) from January 1999 to January 2001. Prior to this he was involved in the clinical development of drugs in the inflammation, tissue repair and oncology therapeutic areas. As an employee of SKB, therefore, he was not involved in the original application for a licence for Seroxat in 1990 or in the action to contra-indicate the product for use in children taken by this Agency in June 2003. Since his employment with the MHRA began, he has taken no part in decisions relating regulatory action on this product in the UK or in Europe.

The issue of fees was raised at the end of the MHRA evidence session and I undertook to let you have more information on this issue. Since 1992, the former MCA and, now the Medicines sector of the MHRA, has been fully funded from user-fees. The current fee-scale is attached for information at Annex A. It is worth noting that of MHRA (Medicines) income, 60% comes from capital fees (principally from various categories of applications and inspections), while 40% comes from an annual “service fee” payable by all marketing authorisation holders. This service fee income is devoted principally to pharmacovigilance and enforcement work.

Turning finally to the issue of Seroxat I think it is important to return to the questions raised by John Austin MP and about the position adopted by the MHRA in relation to the frequency of withdrawal reactions. In fact, as was stated in our oral evidence, the MHRA has never indicated that withdrawal was rare. The clinical trials at the time of licensing for Seroxat did not systematically record symptoms occurring after treatment was stopped or reduced and therefore it was not possible to determine a valid estimate of the frequency. As can be seen from Annex B, warnings about withdrawal reactions were included in the Summary of Product Characteristics for Seroxat at the time of licensing. The available information did not allow an estimation of frequency at that time and CSM/MCA did not state that the frequency of withdrawal reactions with Seroxat could be described as rare.

The Agency has kept this product under review and made announcements on specific issues related to this product as the sum of knowledge has increased. Some trials which were carried out after licensing in support of new indications for Seroxat did systematically measure symptoms on stopping treatment and allowed an estimate of frequency to be calculated. For example, an article in Current Problems in Pharmacovigilance in 1993 provided Yellow Card data on withdrawal reactions reported with Seroxat following experience in clinical use and stated that they had been reported more frequently with paroxetine than with other SSRIs. Warnings about withdrawal reactions (especially with paroxetine) are repeated in the British national formulary, supplied to all doctors.

I hope that you find this additional information useful.

4 February 2005
Thursday 3 February 2005

Members present:
Mr David Hinchliffe, in the Chair
John Austin
Mr Keith Bradley
Mr Jon Owen Jones
Dr Doug Naysmith
Dr Richard Taylor

Witnesses: Lord Warner, a Member of the House of Lords, Parliamentary Under-Secretary of State for Health, Dr Felicity Harvey, Head of Medicines Pharmacy and Industry Group, Department of Health and Dr June Raine, Head Post Licensing Division, Medicines and Healthcare Products Regulatory Agency, examined.

Q911 Chairman: May I welcome you to this morning’s sessions of the Committee and particularly welcome our witnesses for what will be, hopefully, the final session of this inquiry which seems to have gone on rather a long time, but we have found it most interesting. May I first of all thank the department once again for its co-operation with the inquiry and perhaps you would like to introduce yourself and your colleagues.

Lord Warner: I am Norman Warner; I am the Parliamentary Under-Secretary of State in the Department of Health, responsible for the area covered by the Committee’s inquiry. On my left is Dr June Raine, who is the head of the Post Licensing Division in the MHRA and on my right is Dr Felicity Harvey, who is the head of Medicines Pharmacy and Industry Group in the Department of Health. So we have the regulator on the left and the department’s policy adviser on the right.

Q912 Chairman: May I start by asking a broad general question? If you have followed some of the developments in this inquiry, you will be aware that a number of key themes have come out of the evidence which we have taken over quite a long period of time. One of them, which in a sense perhaps informed our reasons for looking at this whole area, is that the over-reliance on medicines may well be to the detriment of our overall public health. That has come out in evidence from a range of different witnesses and organisations. What I wondered, to start off with, is how the department actually balances concerns with what we are seeing as, in a sense, the over-medicalisation of society with your role of sponsoring and encouraging and working with an industry which needs to be commercially successful?

Lord Warner: Various approaches have been taken in different countries to this particular issue. I am very struck, when I go to health minister meetings in Europe, how they are often quite detached from the industry area. You can argue whether it is a good thing or a bad thing, but it is striking that there is that difference. What I would say is that, give or take, pharmaceuticals represent about 12% of the NHS budget, that sort of area. So a very large chunk of the NHS budget is going on things other than pharmaceuticals. We also have in this country a very strong use of generics by our doctors who are great users of generics, so there is a balance against what you might call the research-based industry in this area. That has been developed over the years with this strong inclination particularly of GPs to use generics wherever possible. The other thing I think I would say is that it is the responsibility of all of government to try to help research-based industries in the UK. We are dealing here with an industry which has the strongest R&D activity of UK industries. It is very strong and spends £3.5 billion a year on research, which provides a lot of high quality jobs in a knowledge-based industry. There is an important dimension there. I should say that we have kept the balance pretty well and I am not making a party political point here. I think that under successive governments, the balance has been struck between having a health department which has a responsibility as a sponsor department for the industry and is also safeguarding the patients’ interests and the NHS interests through both its regulation and, if you like, its purchasing power. The UK is unique in having a pharmaceutical price regulation scheme on a voluntary basis; it may not always seem voluntary as you are going through some of the negotiations, but I am told, but it is a voluntary agreement. The last one did produce a very substantial reduction in prices for the NHS which does suggest that we are actually able to achieve this balance between being a sponsor of the industry and getting the best value for the NHS.

Q913 Chairman: One of the things which have struck me, in looking at the health service over very many years, is that we have focused very much on a curative approach, on initiatives to do with hospitals and the choice initiative is a very good example now where it is about where you choose to go for your treatment. Only very belatedly have we actually looked seriously at developing a much more radical public health agenda. Am I wrong in getting the impression that the industry has perhaps skewed our thinking, our approach to health, because of its own commercial interests? It is in their interest to create in society an expectation that we can get a cure for every possible problem and there is not a lot of money to be made out of preventive approaches which are implicit within the Public Health White Paper.
Lord Warner: There is a balance to be struck here because there is a short-term/longer-term issue. Clearly the public health agenda is extremely important but as you take forward the public health agenda, and the government’s White Paper on choosing health sets out a very clear and dynamic strategy for helping deal with many of what I may describe as the lifestyle choices that people need to make in order to maintain good health in their communities, we are also faced as a society, and the government has to respond to that, with the fact that in the here and now a very large number of people have painful, deadly, unpleasant conditions where we need the best therapies we can get to respond to those conditions; we need to help provide healthcare professionals with, so to speak, the tools to do their job, so we do need these therapies. We have also seen a growing flow of therapies which enable you to use medication without becoming an in-patient; so you can actually make the health response much less institutional and much more able to enable people to cope with chronic disease conditions without emergency episodes in living in their own home with the appropriate professional support. So there is a balance to be struck, but I would agree with you that probably historically we have been a bit slow to engage with the public health agenda.

Q914 Chairman: One of the other themes which has been within this inquiry quite clearly is the way in which we have seen a pattern of medicines, which have been initially hailed as breakthroughs, being widely promoted for their positives, either being withdrawn or later having had serious questions over their safety profile. I wonder whether you feel that the controversy around medicines such as Seroxat, Vioxx and Celebrex indicate that there is perhaps a problem with the licensing of potential unsafe medicines.

Lord Warner: Whatever pharmaceutical we are talking about, most of them have some degree of downside as well as an upside and the whole point of clinical trials is to try to get to the bottom of that risk benefit balance on particular drugs. This country has followed the lead of other countries as well of having basically a three clinical trial stage system of licensing and an independent regulator trying to get the best data that it can before giving licensing approval. It has always been the case, and it has become more robust, that there is a degree of post-licensing monitoring and surveillance of particular products, so that when problems are identified, whether it is adverse reactions notified through the Yellow Card system, whether it is new clinical trial data or whatever, there is a process by which the regulator can conduct further analysis. There is a good track record on the part of the Committee on Safety of Medicines of taking seriously that data which shows after licensing there can be a problem. You could argue that some of the high profile examples which you have mentioned are demonstrations that the licensing system does work, that there is a good post-licensing system for picking up problem areas and dealing with them. What I should also say is that if we are absolutely frank, we may have been a bit slow in the past in making sure that the regulatory system was as transparent as possible in actually bringing information into the public arena at an early enough stage and I arrived in this job at the same time, pretty well, as the National Audit Office report and the PAC report on the MHRA. There were some pretty valid comments there about transparency, public communication, whether we had done enough to demonstrate the independence and effectiveness of the regulatory system. I do not think there was a fundamental problem, but we have tried to take a number of measures which I think the Committee is aware of, to try to improve that transparency. Certainly there is an area on which we shall continue to need to work away with the industry and that is the whole area of a public register of clinical trials and publication of all clinical trials data, so that it is in the public arena when that information is available in a company or wherever.

Q915 Chairman: One of the underlying themes of the inquiry has been a rather low opinion of the MHRA from a number of witnesses consistently expressing concerns. Your evidence from the department is neutral on that organisation. You have just referred to transparency and the potential for further change. Do you feel that other reforms are needed to address a number of the concerns that we have had put to us have been initially hailed as breakthroughs, being downslide as well as an upside and the whole point of

Lord Warner: It is worth just going back to the NAO report, because whatever else one may think, one would not accuse the NAO of being in the pockets of either government or the industry. They found that the MHRA had made a significant contribution to public health protection through its regulation of medicines and they did not find any evidence that it was too close to the industry. That was the NAO speaking, not me. Certainly, they made a number of recommendations for improving the perceptions around whether the regulation was as transparent as might be. My own frank assessment is that its predecessor body was very professionally sound, though probably a bit lacking in communicating and providing information in the public arena which built public confidence in some of its decision making. That is why we have taken a very hard look at the committee structure and, as you know, we shall be creating a new commission on human medicines which merges the Medicines Commission and the Committee on Safety of Medicines. We are going to require the chairs and members of the commission and the new statutory committees to have no financial interest in the industry, a stronger code of practice on declarations of interest, we have reviewed the yellow card scheme where we think patients ought to be given the ability to report adverse reactions themselves, so we have taken a number of measures to make this more patient conscious so that patients can play a bigger part in some of the risk benefit judgments which actually have to be made in this particular area.
Q916 Mr Jones: The Chairman raised problems developing, three medicines that he mentioned—Serotonin, Vioxx and Celebrex. On Vioxx, there is a problem area now in that you have clear evidence that there are potential risks to some patients using Vioxx, on the other hand, we have a very large number of people in the country who have been using Vioxx for a long period of time without any adverse effects. If the drug is withdrawn, and presumably these people are then prescribed a different drug, for those people what we are effectively doing is increasing their risks because there is a risk inherent with every drug. They have been using the drug without adverse effect and now they are going to be told they cannot use that, they have to use a different one and they do not know whether there is an adverse effect. That is a very difficult issue, but I should be interested in what you think. Is there not a case to be made for saying “We withdraw the drug and we will not prescribe it to anyone new, but those people who are currently using the drug should be able to continue to use it”.

Lord Warner: This is a very difficult issue. That in a sense is why we have an independent regulatory body trying to bring together all the evidence to see where the balance of advantage lies and the balance of advantage often lies in a different position on different products. You put the point very well in the way you described that as the almost perpetual dilemma for drug regulators, either in this country or in other countries: how do you get the evidence to strike the right balance? One could repeat some of your arguments for a number of other products as well in exactly the same sorts of terms. I saw on the television the other night with the phased withdrawal from Co-proxamol that there was a long-term user of Coproxamol who was not terribly pleased that this was happening. I do think it is a bit of a dilemma; I do not think there is any easy answer. There are some issues, which we have begun to think about, about whether the present system is as sophisticated as it might be for regulation and whether you talk about some kind of provisional licensing at a stage after stage three clinical trials or whether you talk about more robust post-licensing surveillance or some kind of restrictions around the class of doctors who could prescribe particular products for a period of time, so that you get a wider usage. I do not know, but there are issues there which are beginning to be discussed where we do need to do some more work within a European framework and with other regulators.

Q917 Mr Bradley: The World Health Organisation recommends that all countries should have a national medicines policy. What are your views on introducing one here, together with a dedicated committee to oversee the quality of use of medicines?

Lord Warner: We do have pretty good data and monitoring of the use of medicines. I know, for example, that there has been some interest in iatrogenic effects of drugs, where the MHRA actually did their own study in this particular area. I do not want to appear complacent, but I think we do have a pretty good system of seeing how drugs are being used, seeing how prescribing is going, whether the balance is right between new drugs, research-based drugs and generics and so forth. We are always going to be in a situation where science to some extent drives the agenda; there will be new discoveries which will drive an agenda and will come up out of the science community for any country. There is a lot in what the WHO are saying and one of the things which we are going to do is to see whether we cannot have, what we are calling at the moment, a Futures Forum, which starts to look ahead, tries to be a bit more anticipatory about some of the areas where we might try to get the science applied faster where there is clear human need. What we have in mind here is that the UK Clinical Research Collaboration (UKCRC), which was set up by government about a year ago, which brings together industry, the research community, the charitable sector, patient interest, we might ask them on a regular basis to discuss where medicines policy might be directed more and relate it more to the progress of science in scientific knowledge. I do not know whether that deals with the kinds of things you have in mind.

Q918 Mr Bradley: Yes. When we were in Australia, we saw the value of having a national medicines policy with broadly based interest groups involved in that process, particularly consumers and users. We were struck that that took a much more holistic approach to medicines in terms of health outcomes as well as economic objectives and the World Health Organisation recommends that looking at it in that way, in the national sense, is a more effective way of ensuring the value of the medicines themselves.

Lord Warner: It is a very helpful suggestion. It is similar to the kind of thinking that has been going through our own minds and I shall certainly take a closer look at the Australian experience there and see if we can learn from that as we take this idea of a Futures Forum further forward. The idea seems to me a sound one and I should certainly want to look at it very carefully to see whether we can build on that.

Mr Bradley: I shall come out with you as I should welcome a return visit.

Q919 Dr Taylor: May I go back to the question of independence of the regulatory agency, which you have already talked about? We are told that the MHRA is one of only two European agencies for whom the operation of the medicines regulatory system is funded entirely by fees derived from services to industry and many people have implied to us that it must be incredibly difficult actually to protect the public from unsafe medicines when you are being paid by the very people who are producing those compounds. How do you rate the independence? How do you ensure it when they are being paid by the very people who they are trying to regulate?

Lord Warner: Just dealing with the European situation first of all, virtually all the European regulatory agencies have a significant contribution in terms of income from the industry that they are
regulating; there is nothing very unusual about that. If you go to Sweden, I think you will find it is about 95%; if you go to the Netherlands, you will find it is 100%, so we are not that out of line.

**Lord Warner:** I do not think we are saying that. We are saying that history has shown that using... If you go to Sweden, I think you will find it is about 95%, if you go to the Netherlands, you will find it 100%, so we are not that out of line.

**Dr Taylor:** Are you saying that the facts we have been given are probably not correct?

**Lord Warner:** I am happy to go back and check. I have two colleagues here who are perfectly free to correct their minister if he has got it wrong and I shall not be embarrassed, but my understanding is that it is about 95% in Sweden and it is about 100% in the Netherlands. They are nodding, so I think it is probably OK. What I was also going to say is that it is just worth thinking back to the dim and distant past when there was significant grant aid from the government to a predecessor body. That was changed because the backlog of licensing applications was enormous, because the income from fees did not seem to be very buoyant in terms of maintaining the capacity of the regulator to deal with the flow of new drugs for licensing. Under a previous government the move to a trading fund basis was to generate buoyancy in the fee income. They then kept pace with the volume of work that was coming into the regulator. That is an important consideration. I go back to what I said about the NAO, there is no evidence that this form of funding has in any way skewed the decision making of the agency. It has also separated operationally within the agency pharmaco-vigilance from the licensing; it has separated that work under the chief executive, so you do not have the same people doing the licensing as are doing the pharmaco-vigilance in post-licensing. Dr June Raine is actually the head of the Post Licensing and she has nothing to do with the licensing applications themselves.

**Dr Taylor:** When the regulatory system came in—and I am old enough to remember the problems with thalidomide and it came in after the thalidomide episode—was it funded by industry right from the start? Has it always been funded by industry? What happened initially?

**Lord Warner:** I do not know whether my historians on my left and right will be able to answer that precisely?

**Dr Raine:** Yes, the initial operations were not funded by industry; this was introduced in 1989.

**Dr Taylor:** So why does it change?

**Dr Raine:** For the precise reasons that the minister has explained, that the operation then was not capable of delivering new licences, delivering new medicines for the benefits they bring in a way that was demanded; it could not meet supply and demand. The funding enables us to match resources incoming to the staff and other resources that are needed to deliver new medicines promptly.

**Dr Taylor:** So what are saying is that the only way of getting enough money into a regulatory system is from the industry. There is no other way.

**Lord Warner:** I do not think we are saying that. We are saying that history has shown that using government grant did not produce buoyant income which enabled the regulatory body to cope with the flow of applications for licences.

**Dr Taylor:** That must have been because the government grant was not big enough.

**Lord Warner:** That could well be the case. If you go from where you are now, whichever government is in office, there is a finite sum of money for healthcare. You now have a judgment call: do you want, for no good grounds, and with no evidence that the regulators are actually skewed in their judgment over the licensing or post-licensing surveillance to take however many millions away from somewhere else in the NHS to fund the regulator.

**Dr Taylor:** I am only trying to establish that with the amount of money that there is available from government sources, there is not enough to do this, so the only source it can come from is industry.

**Chairman:** Just to clarify the historic background to this, may I ask Dr Raine a question? You may not know the answer and it is probably an unfair question. Do you know, when this change took place, how much more money was proportionately able to be brought into this process than was previously available from government? Have you any idea?

**Dr Raine:** In terms of funding? I think it would have gone to a figure of around £30 million per annum to resource the whole of the agency, of course it has gone up since then.

**Chairman:** What was it previously?

**Dr Raine:** I do not have an overall figure, but I do know that a new drug costs about £250 to get the licence and that was not sufficient to recruit and retain the numbers of staff. There was therefore a delay of around three years in some cases before getting a new drug out to patients who needed of it.

**Chairman:** It would be very helpful, if it were possible, for us to have any information on the background and the proportionate increase as a consequence of these changes. It is a very important area.

**Lord Warner:** We are very happy to provide the historical context for this, but it was basically driven by this huge backlog.

**Dr Taylor:** Did you say that the total cost was £250.

**Dr Raine:** No, that was the fee that was charged.

**Dr Taylor:** The fee that was charged was £250?

**Dr Raine:** For a new drug.

**Dr Taylor:** That is staggering. That would be helpful.

**Dr Harvey:** In fact, in terms of the approach of having the regulator with fees to those who are being regulated, this is actually the approach which is taken by many bodies across government. The
MHRA clearly is the regulator for medicines, but there is exactly a similar approach adopted in many regulators that the government has right the way across government. It is not an unusual occurrence.

**Lord Warner:** We have no plans at the moment. These are always difficult issues here about whether people feel inhibited in their free and frank discussion about information in those particular areas. It is an issue we could consider, but I would not want to make any promises. We do have a situation here where we are moving these committees to have more patient representatives in them. We need to take a careful look at whether that would have advantages or whether it might actually, in some cases, inhibit people's frank analysis and comments in some of these areas.

**Q931 Dr Taylor:** That is very helpful; thank you. May I go on to transparency, which we have already touched on a little bit? We are pleased about the clinical trials register and that all the data from that is going to be openly posted. Will you be suggesting that the MHRA should make the data it receives from drug firms open to the public?

**Lord Warner:** There are two aspects to this. There is the obligation on the companies which certainly the ABPI have accepted, that they should be publishing clinical trials data in the public arena anyway. They are under a legal obligation to provide information to the regulator anyway which relates to either an application for a licence or which relates to a licensed product. What we are keen to do and it was done very well by the Committee on Safety of Medicines in the case of Seroxat for example and selective serotonin reuptake inhibitors (SSRIs), is to make sure that those decisions have the supporting evidence put in the public arena, which is a slightly different issue from publishing clinical trials. Instead of the regulator simply saying “We think the risk benefit balance has changed, therefore we think a particular product should be withdrawn” or not, as the case may be, it would actually put the evidence behind its decision much more fully in the public arena. I cite the SSRIs as the example where I think that pattern is established. Certainly I am very keen and the agency knows that the government is keen, that that information is put in the public arena so there is no doubt about why the balance was struck. It relates back to an earlier question about the difficulty of some of these judgments which have to be made. People will be more convinced that the judgments have been fairly made, if the supporting evidence for their judgment is clearly in the public arena.

**Q932 Dr Taylor:** That is very encouraging. Does that mean, with the Freedom of Information Act (FoI), that will be interpreted literally and the MHRA will have to make available the sort of information that is already available in the United States?

**Lord Warner:** This is better linked to a decision-making process. The short answer is, in all probability, yes. I am not saying that we feel you need FoI to drag the information out of the agency. I am saying that it is in our interest and the agency's interest to publish the data which they relied on in forming their judgment about whether or not to withdraw a product which had already been licensed when there were adverse consequences.

**Q933 Dr Taylor:** We are told as well that in the States advisory committees actually sit in public, so everything is known. Is there going to be any move towards that?

**Q935 Dr Taylor:** From what you have said, can we take it that you will ensure that the British public gets the same access to policies and resources that the people in the States have?

**Lord Warner:** We shall probably do things slightly differently. I am certainly not going to go on the record as saying I am going to copy everything that is actually done within the framework of the FDA. We will learn from that.

**Q936 Dr Taylor:** But you will aim for the same degree of discussion?

**Lord Warner:** We are aiming for transparency in this area in order really to enable the regulator to demonstrate that their decisions are well founded. The point I would make is that it is not in anybody's interests to create a climate in which regulators make decision which are then called into question because there is not enough transparency about the way that decision was made.
Q937 Dr Taylor: People need to see both sides of the argument and they need to hear the dissenting voices as well as the supporting voices.

Lord Warner: Absolutely. It is all part of this business of improving public understanding of the difficult judgments that have been made, which have been touched on earlier, on some of these products. Getting the right balance on risk and benefit is very difficult in some of these areas and the more we can have information demonstrating this in the public arena, the better it will be for everybody.

Q938 Mr Jones: I think the committee were very pleased to hear what you said about publishing data and allowing the public to see what the information is. It is likely to improve decision making, not least, I should imagine, probably their competitors would be interested to ensure that there are no glaring faults or missed information in the data. In the absence of that up to now, the MHRA’s reliance on company analysis and summaries of research findings clearly is not justified, at least in every case; I can see that it was not justified with Seroxat for example.

Lord Warner: You have mentioned a particular product, so I am going to turn to the person who led the work in this particular area.

Dr Raine: Perhaps to deal first with the point about the use of summaries. Summary is perhaps a misnomer: these are very large and very detailed analyses of what would be otherwise vast amounts of original patient data. It is the standard practice in European drug regulation, indeed regulation worldwide, to look at analyses and then to drill into the detail that is needed, as it is needed. When we say analyses, we are talking 200 dossiers for an average type of new drug, so to say “summary” is perhaps misleading your thinking.

Q939 Mr Jones: I do not want to go into too much detail, but with that particular drug you were not provided with all the relevant information, were you?

Dr Raine: We were certainly provided with all the information in order to make a risk benefit judgment at the time of licensing. Clearly, when the review was conducted which was published in December 2004, we had access to a far wider body of information but in addition we carried out re-analyses of original trials. It has been done in other situations too, with Epogam, which the Committee has mentioned in the past, we went back to original data. This is the way that regulation works and it is quite proper to operate it in that way. The decision which was published in relation to Seroxat last December took account of population studies, ADR reports, patient experience, as well as original clinical trial data re-analyses in order to make the best balanced judgment that could be made and indeed it is now in the public domain.

Q940 Mr Jones: Are you saying that you, as a body, were given all the information that was available for you to make a reasonable decision at the time you made it?

Dr Raine: Yes.

Q941 Mr Jones: So there was no fault on your side and no fault on the company’s side either then?

Dr Raine: Going back to 1990, the data were provided according to the guidance operating at that time to enable a robust decision on risk and benefit in 1990.

Q942 Mr Jones: 1990. What has happened since?

Dr Raine: Since then, as is normal for medicines, a vast amount of information is gained about clinical use, other studies are conducted in other indications and, as we have stressed, in this case, there was a substantial body of information available from patients themselves. To make a re-visited risk benefit judgment, all of that was taken into account.

Q943 Mr Jones: You do not think you could have improved the situation then at the time?

Dr Raine: In 1990 the product information reflected the understanding of the balance of risks and benefits and the advice of the Committee on Safety of Medicines at that time.

Q944 Mr Jones: May I move on? In the absence of near certain evidence that the regulators tend not to issue formal warnings of risk, are you satisfied the regulators effectively communicate uncertainties of risk to the users?

Lord Warner: The documents the users get are the patient information leaflets, which are themselves modified over time; as new evidence comes around people do revise the patient information leaflet. It is probably the thing on which patients rely most. If you say to me “Are patient information leaflets perfect in every way?” the short answer is that they are not and that is why there is new legislation coming through Europe to ensure that patient information leaflets are themselves produced with much more user involvement in their production. As I recall, I will get my colleagues just to check, that new legislation comes into operation in October.

Dr Raine: Perhaps I might just expand on that. The new requirement that medicines information for patients is tested in the population who are going to be using that medicine was in fact introduced early, so it will become operational from 1 July.

Lord Warner: We are trying to construct a situation in which the document which is the lead document for patients about particular medicines is framed in a way which is most useful to patients. I suspect what lies behind your question is: is it always easy to tell from the document what the real risk benefit to particular people is? I think that is a perfectly fair point to be made and that is why we have to try to improve the quality of the presentation of information in those leaflets. I think you will find that somewhere in each of those leaflets the danger signals are signalled. The question is whether they are signalled in a way which is most helpful or whether they could be made more helpful to patients on a particular product. We have already published a leaflet from the new group that we have set up in this area to try to help patients themselves understand risk issues.
Q945 Mr Jones: What about information given to the prescribers? Is it made clear to the prescribers that this product has this potentially beneficial effect, but that there is a range of unknowns and possibilities that it may have?

Lord Warner: Well of course there is a very vast array of information given to prescribers. There is a National Prescribing Centre and their various bulletins are sent to prescribers. The very fact that we have such a high generics prescribing rate suggests that prescribers are, on the whole, pretty well-informed about the products.

Q946 Mr Jones: As we have had evidence before, the access providers get to information about new drugs comes overwhelmingly from the people who are producing the drugs. Therefore, it is unlikely that the person who is selling the drug is going to highlight what potential risks there would be to that product.

Dr Raine: Perhaps just a word of clarification. The information that the company provides is very strictly controlled in law. The terms of the marketing authorisation include the document called the Summary of Product Characteristics, which is an evidence-based document on which we seek advice from the Committee on Safety of Medicines. The controls on any communication are that they must strictly adhere to those terms. So that is the starting point for advice to the user or the prescriber which is an evidence-based document.

Dr Harvey: May I also add that the National Prescribing Centre does indeed send bulletins to doctors, not just for drugs which are quite a long time post-licence, but it often sends out bulletins at the time, or very shortly after licensing of new drugs, which deal with their clinical and their cost effectiveness. It also sends bulletins through for drugs which are on the horizon, which are likely to be coming to market shortly. So, in fact, prescribers do have information not just from the pharmaceutical industry, but also from other independent sources as well.

Q947 Dr Taylor: May I just follow that up absolutely specifically. To take Vioxx as an example, on the day of release I am sure there was a lot of material, albeit controlled, from the makers. What, for example, would an ordinary GP have had to tell him why to be cautious about Vioxx on the very day that it was released, remembering that the GP probably will not look up the BNF every day, will not read the Drug and Therapeutics Bulletin every day? What would he have had in practice to compete with the stuff from the drug industries?

Dr Raine: May I describe what happened on 30 September 2004? It would perhaps Chairman help happen in a hospital environment. There was not the Committee to know that this was a voluntary decision by the company.

Q948 Dr Taylor: I mean at the moment of marketing, not at the moment when it was decided to put restrictions on it. What I am trying to get at is how we could prevent GPs, who are the bulk of prescribers, going into a new drug with tremendous enthusiasm right at the beginning when the side-effect profile, the problems, cannot be known. I think the minister said that there were thoughts about limiting the numbers of doctors that could prescribe new drugs. What I am getting at is, what actual information, other than from the pharmaceutical industry, would a practicing GP have had about Vioxx on the day that it was liberated to warn him to be a bit careful and not to use it as the first choice non-steroidal anti-inflammatory drug on a patient?

Lord Warner: It is almost impossible to answer your very specific question about one particular day, when Vioxx was put in the public arena. What is a fairer way of trying to answer your question is to go through all the sources of advice and information that are actually sent to GPs which cover all new products. I do not want to sound as though I am reading out a shopping list, but it is important to realise what these other sources are. There are 1,200 NHS prescribing advisers, mainly pharmacists, there are Area Prescribing Committees, there is the BNF, there is NICE advice on particular products, admittedly not on the day that you are mentioning, there is the National Prescribing Centre which sends out MeReC bulletins, newsletters, there is the monthly Drug and Therapeutics Bulletin published by the Consumers’ Association, there is a vast array of information. With respect, Dr Taylor, that does cover things like Vioxx very close to the point when they are being, as you put it, liberated for the GP.

Q949 Dr Taylor: We do know that GPs are faced with a vast amount of information. What I am trying to get at is whether there would be a mechanism for a specific very brief message of caution, or whatever, when any new drug which is potentially an advance is liberated, absolutely obligatory reading somehow to advise caution, so that the things are not thrown around as freely as Vioxx was?

Lord Warner: I am certainly happy to look at the pharmaceutical industry, but also from other independent sources as well.

Q950 Dr Taylor: Yes, we were incredibly impressed with the method of control of prescribing at UCH and the spin-off onto local PCTs. They certainly had controlled the use of some of these new drugs and we
really wondered whether there could be some standardisation of drug usage committees throughout the NHS because where you have a very good one, at UCH, it overspills into the hospital prescribing and the local PCT prescribing and this would seem to us to be quite as important as things like ethics committees, which are standardised, and could make a huge contribution. I think this would perhaps lead to the more rational use of some of the new drugs as they come out. It is really a question of the importance of these committees when they really work and how the government could support these.

Dr Harvey: We do have prescribing advisers at PCT level, but the area prescribing committees are very much around looking at the use of drugs across the primary and secondary care interface and you would expect within those committees that you would have representation from the various NHS trusts within that area, as well as the PCTs, to look at the sort of prescribing habits they have and to look to see what their general policy across the piece is, so I think part of that is possibly covered within the area prescribing committees at the moment. It is actually also fair to say there was a report Primary Care Prescribing a report for Primary Care Trusts by the Audit Commission back in 2003 where they looked at some of the activities that primary care trusts are taking forward around prescribing. As you said, in many cases GPs directly see pharmaceutical representatives, but in some PCTs—and they gave an example of somewhere with a slightly different approach—they actually went to an information centre where that information was then distributed. So there are different mechanisms at PCT level, but the area prescribing committees and indeed the prescribing advisers are very important in giving help to prescribers within primary care.

Chairman: It is probably important to make the point that we did have contact with a GP who was on this particular committee; although it was hospital based of course the PCT was represented. The picture we got was very much of a concern within the hospital environment that patients were being admitted who had been using products that certainly had been looked at by the committee and not seen to be particularly helpful for the condition from which they were suffering. So there was a concern about direct access to GPs and the impact that was having. That was the evidence which came over quite strongly.

Q951 Dr Taylor: Another point from that meeting. They obviously had a very effective formulary and I do not mean anything like the British National Formulary. I mean really just a list of the sorts of things that they would sanction the prescribing of, and it seems to be fairly ridiculous that every PCT, every trust works on their own formulary. Why could there not be a much wider-ranging formulary agreed across many PCTs, across many strategic health authorities and many trusts, rather than everybody trying to invent their own wheel?

Lord Warner: Of course NICE guidelines do that, but they are very specific to specific products, are they not?

Q952 Dr Taylor: They only come in two years after they are put NICE and there is a very limited range.

Lord Warner: May I ask Dr Raine to try to explain the black triangle system, because I think the black triangle system does actually deal with some of the concerns that you actually have.

Dr Taylor: Yes, that was explained to us actually.

Q953 Mr Jones: From the black triangle, can I move to the yellow card, because I think all the evidence we have received says that the Yellow Card system does not work. So, minister, what are you going to do about it?

Lord Warner: All the evidence I have suggests that the Yellow Card system does work, but could be improved, so we are probably coming at this from a slightly different position, if I may put it that way. We did have a review of the Yellow Card system by Dr Jeremy Metters, which was published last May and that was looking at several things. Essentially what he was saying was that, with appropriate safeguards, the information that was available from the Yellow Card system should be available to researchers much more easily, so that became a resource there. I do not think there was any evidence from that inquiry or from any other work that I have seen that the Yellow Card system did not feed in as an alert to ensure that the regulator accumulated information about particular areas causing concern. What it did identify was, in a sense, a gap in the ability of patients to be able to fill in their own yellow cards and send in direct to the regulator, their own perceptions of adverse reactions. I think there is a misunderstanding to some extent about the Yellow Card system. Every time you get a yellow card, it is not conclusive evidence that a particular product is causing a particular reaction in a particular person. It is saying that a particular person has had some reaction.

Q954 Mr Jones: I understand that.

Lord Warner: I get a fairly substantial parliamentary correspondence on the subject of yellow cards.

Q955 Mr Jones: Not from me. I understand that.

Lord Warner: I think it is important. I do not think it is always fully understood.

Q956 Mr Jones: Well I think we understand it, but yes, obviously each individual yellow card does not really tell you a great deal in itself. Where it becomes useful is if you have a substantial basis of statistical evidence from a large number of people who are saying similar things. The reason the Yellow Card system does not work is that you do not have enough information coming in from them; you do not have enough yellow cards being reported to you.

Lord Warner: Volume does not tell you necessarily to ring the alarm bell. We accept that we need to change the system so that it is easier for patients to complete their own yellow cards and make their own notifications and that is why we have, and I will ask Dr Raine to give you a little more detail, a pilot which we are now running in this particular area,
which does try to address some of those concerns, 
certainly in terms of getting a faster, higher volume, 
patient response.

**Dr Raine:** Yes, I would reinforce what the minister 
has said. Every adverse reaction does not need to be 
reported in order to generate signals. The 
importance is to have enough and to have them in 
time to act quickly. That is why, over the years, we 
have expanded the reporting base from the original 
doctors and dentists and coroners to include 
pharmacists and nurses and now patients. It is the 
breadth of capture that we need, plus the facilitation 
of their input via electronic, via a number of 
mechanisms which are currently being piloted as the 
minister says. We now have paper reporting, we 
have reporting via the internet for patients and as of 
the 17 January I am very pleased to say we are up to 
about 35 reports now from patients and this is all 
vitally important in picking up those signals, but it is 
only a part of the comprehensive programme of 
pharmacovigilance that the MHRA operates. It is 
the initial trigger for a number of actions that will 
strengthen, confirm, or refute the signal and enable 
us to take prompt regulatory action and the tough 
decisions which need to be taken to protect the 
public.

**Q957 Mr Jones:** Did you say you are up to 35 reports 
from patients?
**Dr Raine:** From patients in a matter of a week or 
two, yes.

**Q958 Dr Naysmith:** I want to explore a little bit what 
Richard was exploring a minute or two ago, but 
from a slightly different angle. We have had a lot of 
evidence that GPs can sometimes be a bit 
profligate in their prescribing of drugs and that is probably 
related to drug companies targeting GPs in different 
ways. We have heard evidence too that, increasingly, 
nurses are being targeted now that they have 
prescribing powers. As you say, there is lots of 
information about: there are the black triangles and 
there are the NICE reports and there is the *Drug and 
Therapeutics Bulletin* and all that sort of thing. 
However, in the midst of this comes nice glossy 
advertising from drug companies which can be used 
and busy GPs might think this is the right thing, this 
tells them all they need to know. I know that is not 
what the best GPs will do, but it certainly does 
happen with some and from your answers so far it 
sounds to me as though this does not really concern 
you very much, the role of advertising coming from the 
producers in the midst of all this information. 
You seem to think that because all the other 
information is there, then it does not matter too 
much that there is this glossy stuff produced by the 
drug companies.

**Lord Warner:** I certainly would not want to convey the 
sense that I do not take that point seriously. I 
think I was trying to say that there is another side of 
the equation which is the volume of other sources of 
information to GPs that actually exist.

**Q959 Dr Naysmith:** My point is that probably the 
material coming from drug companies outweighs all of 
that information. I know, as Dr Raine told us, 
there are regulations about what can be said and it is 
controlled but . . .

**Lord Warner:** May I just give you a couple of 
statistics which I think slightly call into question the 
idea that GPs are sitting there and just simply 
lapping up everything which is put to them by a drug 
company?

**Q960 Dr Naysmith:** I do not want to give that 
impression.

**Lord Warner:** No, no, but it is important. It is just 
worth bearing in mind that the national average for 
generic prescribing is round about 78%. That figure 
itself is a telling figure in my view, compared with 
many other countries, which does suggest that the 
GPs do take a great deal of notice of some of these 
other sources of information. It is also worth bearing 
in mind my second statistic. The Audit Commission 
did a study a couple of years ago and they estimated 
that wasteful prescribing was round about 2% of 
prescription expenditure in 2003 and that compared 
with a 1994 estimate of 14%. So the Audit 
Commission, which again is pretty independent, 
were saying that wasteful prescribing had dropped 
significantly in 10 years. I would not want to claim 
that there is no GP in this country who may not be 
unreasonably influenced by some of the literature, 
but I think there are quite a lot of powerful checks 
and balances in that, and there is also a good deal of 
self-regulation and control over the way the 
pharmaceutical industry itself can produce its own 
literature. I do not know whether Dr Raine would 
like to give a couple of examples.

**Q961 Dr Naysmith:** Just before that, minister, might 
I ask you whether you think the majority of drug 
adverts encourage the rational use of medicines by 
presenting information objectively and without 
exaggerating the properties of the advertised 
product, which is what it is supposed to be? Do you 
think that is true?

**Lord Warner:** We would be catching a very large 
number of people out if it were true. I would say that 
the number of examples where we have had concerns 
is relatively small and that is why I was going to get 
Dr Raine to talk about the systems we have for 
checking that kind of behaviour.

**Dr Raine:** Certainly the self-regulatory system is one 
which has stood the test of time, but the MHRA is 
ready to back up with investigation and enforcement, any complaint, any problem advert 
which is discovered on scrutiny and also increasingly 
by pre-vetting advertising before it is issued. In the 
light of ongoing vigilance in the area, we have 
overhauled our systems in the last couple of years to 
focus on pre-vetting precisely because of the 
concerns that the Committee has expressed, that 
preventing misleading adverts going out is actually 
where we ought to be, rather than catching them 
once they have gone. I am pleased to say that the 
number of pre-vetted adverts has been steadily 
increasing since we did that.
Q962 Dr Naysmith: We have had evidence that it sometimes takes a long time after a component is made for it to be withdrawn. Are you saying that is now a thing of the past and will not happen any more?

Dr Raine: I can say that with confidence. We now have very tight time targets in place, with the team which operates here to act in response to complaints, to have misleading advertising withdrawn.

Q963 Dr Naysmith: In the very complex negotiations that go on for determining the price, there is an allowance for promotion, is there not, in the formula which enables companies to benefit? That is so, is it not?

Lord Warner: Within the PPRS system?

Q964 Dr Naysmith: Yes.

Lord Warner: Yes, that is correct.

Q965 Dr Naysmith: Do you ever use that as any kind of mechanism for saying someone has a bad record? Can that be done? Can individual companies be treated in that way? You are saying there is no bad record any more, but just if there were?

Lord Warner: No. I am not saying there are no errors, no bad behaviour at all. Not everybody is a saint in this particular area, if I may put it that way. What I think I am saying and I think Dr Raine was saying is that we have certainly tightened up the system for dealing with complaints, so they are dealt with more speedily. I think the Committee wanted to have, and we shall make it available to you, the data on the MHRA staff who are dealing with this particular area. We brought copies along and I will not go through what is in that, we will give that to you. It sets out which particular staff, what their qualifications and experience are, and I think that will be helpful to the Committee to have that. We have focused much more on pre-vetting as Dr Raine was saying. No human system is perfect in all respects, but it is a stronger version of what was there before and we do think we are hitting the nail on the head much more than may have been the case in the past. I certainly do not want to give the impression that we are complacent about this and it is an area which does require continuing vigilance.

Q966 Dr Naysmith: That would deal with the quality aspect, what is said in adverts. What about the quantity, which I was raising at the beginning in terms of the amount of material that comes from the producers of drugs versus the very small amount of information that comes from you, I suspect?

Lord Warner: I am just going to ask Dr Harvey to say something about the way this gets taken account of in the PPRS system which I think is where we left that.

Q967 Dr Naysmith: That would be one mechanism of dealing with it, if someone transgressed.

Lord Warner: Yes.

Dr Harvey: In fact within the new PPRS scheme which came into force on 1 January of this year, the 2005 agreement, the sales promotion allowance of the 1990s scheme is now the marketing allowance and that does limit the amount of advertising literature etcetera the NHS pays for in the price of medicines; there is also an information allowance in a similar manner to the information allowance within the 1999 scheme. It is fair to say that in terms of the marketing and information allowances within the 2005 PPRS scheme, there is a reduction in the allowed expenditure on the promotion side and more of an increase in terms of the allowances around the actual information itself, although the overall allowance, if you take it all together, is the same as it was in the 1999 scheme.

Q968 Dr Naysmith: How do you measure the amount of promotion that goes on, or is it just assumed this is a kind of chunk that everybody takes, a box is taken, you have promoted therefore you get the allowance?

Dr Harvey: In terms of the PPRS itself, the PPRS, as you probably know, works in terms of annual financial returns which companies send to the department on a confidential basis which include their expenditure on promotion. The Department also receives information on how they are making what is now a 7% reduction in prices across their portfolio of branded medicine to the NHS. Those are looked at, those are audited, but they are looked at on an annual basis as part of the return.

Q969 Dr Naysmith: On an individual company basis?

Dr Harvey: On an individual company basis.

Q970 John Austin: May I move on to the issue of the medicalisation of society, the society in which there is a pill for every purpose and a capsule for every condition? Earlier on the Chairman used the phrase disease-mongering. In evidence earlier in the inquiry, we had a suggestion from the organisation No Free Lunch that disease awareness campaigns were undermining our collective sense of well-being so that we were all instinctively reaching for the medicine chest. In their evidence, the Royal College of General Practitioners referred to the invention or creation of diseases, the categorisation of normal behaviour or conditions as abnormal requiring drug treatment. One of the examples given was mild depression, conditions where drug therapies may be either ineffective or inappropriate. We have had evidence as well which quoted an article in the BMJ which said one of the recent examples of the corporate sponsored creation of disease involves an emergent condition called female sexual dysfunction (FSD). Highly inflated and misleading statistics about the prevalence of FSD are being promoted by some drug companies and misleading information is being reported in many media stories. Do you have any fears about this popularisation or creation of disease? What are the implications, not only for drug consumption but implications for public health?

Lord Warner: Gosh, is my reaction. Certainly, if I may put it this way, as a citizen and a father, I have some concerns that sometimes we do, as a society, wish to put labels on things which are just part and
particularly in the area of depression we did ask the Committee on Safety of Medicines and the pharmacy protocol for supplying the product included multiple safeguards to target its use appropriately to patients for maximum benefit and minimum risks. We did not just decide one day to change the basis for getting the 10 milligram version of Simvastatin; that followed scrutiny by the Committee on Safety of Medicines. It went through that kind of process before it was made available over the counter.

Q972 John Austin: I think we will need to look at the published evidence because the information we were given was that there was no published evidence. Lord Warner: Certainly, if it would help, we can give you more detailed chapter and verse about the timings of the meetings, and the process that was gone through. We should be very happy to do that.

Q973 John Austin: I was putting it in the climate of the marketing machine which is suggesting to us that there is a pill for every condition when, as you have acknowledged, the public health agenda would suggest that there may be much more effective ways essentially of looking after our health. Lord Warner: I certainly would not want it to be interpreted, because we had a process for Simvastatin, that I think there is a pill for every eventuality. I do think that we do have a robust process before we move drugs to an over-the-counter basis and in that particular case we can give you some reassurances and we will send you the details.

Q974 John Austin: We should like to see the published evidence because the information we were given was that there was no published evidence.

Lord Warner: Yes; fine.

Q975 Dr Taylor: This is really just a request for straight information which, if you do not have it now, we should like later. It is really about drug-induced illness. Do you have up-to-date figures for admission rates to hospital for that, the costs of that, the death rates of drug-induced illness? We are told that the figures are more readily available in some other countries and I cannot really believe that; I am sure these figures must be available.

Lord Warner: We can send you more details, but there was certainly a study by the MHRA which looked at admissions in hospitals in Merseyside in 2001–02 and it was published in the BMJ in July 2004. It showed that 6.5% of admissions related to arterial or heart disease. Is it really in the public interest to permit drugs, which we know are effective in certain conditions, to be sold over the counter in lower dosages when there is no clinical evidence to suggest that they are effective in any way?

Lord Warner: It might be helpful if I just talked the Committee through what actually happened in the case of that particular drug. Certainly, the safety profile of Simvastatin has been established over a period of about 15 years and the medicine has been prescribed to millions of patients. The safety profile of the very low dosage, the 10 milligram dosage, was thoroughly reviewed, not has been but was, also before the classification of the drug was changed; that was reviewed very thoroughly by the Committee on Safety of Medicines and the pharmacy protocol for supplying the product included multiple safeguards to target its use appropriately to patients for maximum benefit and minimum risks. We did not just decide one day to change the basis for getting the 10 milligram version of Simvastatin; that followed scrutiny by the Committee on Safety of Medicines. It went through that kind of process before it was made available over the counter.
Lord Warner: I do not have that information, but Dr Raine may be able to give you more.

Dr Raine: Certainly the study did look at deaths and I think it was 0.15%. We shall give you full details.

Q977 Dr Taylor: And costs?

Dr Raine: The cost to the NHS projected annually would be £466 million, from that study.

Q978 Dr Taylor: Could you extrapolate that and give us a global figure?

Lord Warner: I think we would need notice of that particular question.

Q979 Dr Taylor: Could we ask you to try to get it for us?

Lord Warner: We will go away and ponder the question and try to give you the best answer we can give you, that is all I can promise. I certainly left my abacus at home.

Q980 Dr Naysmith: One of the things we were talking about earlier was the question of new drugs and their efficacy and safety and so on. This is an old chestnut with this Committee, but we are very much in favour of being able to look at old drugs as well as new ones, through NICE preferably, and we have said before that we think it is under-funded and under-resourced and if it had more money and more resources, then it could answer some of these questions much more quickly. I should just like to ask you whether there are any plans to try to encourage NICE to take on more work, which is what it amounts to basically.

Lord Warner: I am not sure that the Chairman of NICE would think me, if I said that they should.

Q981 Dr Naysmith: I think he would

Lord Warner: I think NICE has been one of the great success stories in terms of the service that they provided to the NHS and doctors and other health professionals. We can certainly look very carefully, and we do look very carefully, at the references to NICE. I think there is a moving pattern really in which we are putting more guideline references to NICE compared with single products which is where much of their early work started. We are trying to get that better balance, so that they look at total disease conditions—it relates back to some of the earlier discussion in this Committee—they take the whole disease condition which a group of people may suffer from and look at what is the best way of treating that and put in place within their guideline, the role of the pharmaceutical product, if there is a pharmaceutical product. That is where we are trying, with the cooperation of NICE, to take many more of the references, so you get a more holistic picture of what is the best therapeutic response to particular sets of disease conditions.

Q982 Dr Naysmith: I remember when it was set up, that we were really going to look at some of the old techniques as well and it tends to get dominated by innovative drug therapies and so on, which is a pity. What you are recommending now, what NICE is doing now, will be very helpful in that respect.

Lord Warner: Fracture clinics was a good example, where you are actually looking at the phenomena which are taking place in the health service and actually balancing out the drug therapy against the whole range of services or responses that you need for people with a particular condition. There has been a very positive response from the NHS at getting that kind of guidance rather that just guidance about a particular pharmaceutical product.

Q983 John Austin: Going back to something you said earlier on when we were talking about mild depression when you made a comment that NICE now recommends against initial drug treatment use in the case of mild depression, I know that follows on as well the expert working group’s conclusions that SSRIs were not effective in the treatment of mild depression. Although I welcome those conclusions, both of the expert working group and NICE and the guidance that NICE has given out, why has the MHRA not advised prescribers of patients of this?

Lord Warner: I am sorry, I am slightly confused there. The basis of NICE guidance is that that then becomes the source of authoritative advice to doctors. One would not expect the MHRA to be communicating that. I am not sure I fully understand the question.

Q984 John Austin: The MHRA’s key conclusion still remains that SSRIs are effective medicines in the treatment of depression. There is no added qualification now that this does not apply in cases of mild depression.

Lord Warner: My recollection is that guidance went out at the same time, but I do not know. Dr Raine, would you like to say something?

Dr Raine: Yes; certainly. The focus of the MHRA work was to review in the context of the safety concerns, risk and benefit, but the therapeutic advice, which was issued at the same time, was very much for NICE’s remit. The two are not inconsistent, they should be read together.

Q985 John Austin: You do not feel the necessity, although you have the opportunity now, to modify your key conclusion.

Dr Raine: No, I do not think it needs modifying. It is to be taken in conjunction: the regulatory risk benefit advice and the NICE guidance on the therapeutic options.

Q986 John Austin: One of the other issues I want to raise is the implication of licensing of drugs for particular purposes. The license use of SSRIs for mild depression led, I am told, to a three-fold increase in prescriptions in the 1990s. Do you have any comments on that?

Lord Warner: I do not have any particular insights to make on that particular surge in the use of that particular product. It is not unusual for new products, particularly when they are thought by
doctors to be useful for their patients, to have a big surge in take-up. One has seen that in the area of attention deficit drugs as well. What I would say is that we have tried to balance that with the kind of guidance that we have given through the NICE process. As I said earlier, the Audit Commission study that I mentioned of wasteful expenditure showed a marked decline in the period between the early 1990s and 2003 in terms of prescribing habits, so we ended up at 2% rather than 14%. That Audit Commission study suggests that prescribers are being more cautious than they were in the past about leaping on band wagons and engaging in wasteful prescribing.

Q987 John Austin: May I come on specifically to the findings on Seroxat and the expert working group? The working group learned of the seven cases of suicide in the original clinical trials, but they appear to have accepted the company’s assurance that none of those cases was linked to adverse drug effects. We now know that GlaxoSmithKline, or SmithKlineBeecham as it then was was aware of the potentially serious consequences of withdrawal symptoms much earlier on, even though they were still maintaining that such cases were rare, which we now know was a fraudulent statement. The MHRA and the expert working group do not appear to have ever examined the raw data; they merely seem to have relied on the information given by the pharmaceutical companies.

Lord Warner: We went over the ground earlier about the general points about raw data; I can go over that again. On the specific issue about whether that particular company did withhold information—and in a sense it does not matter whether it was raw data or a summary of the clinical trials, the same arguments apply to what I am going to say—if they did in fact withhold information, that would be an illegal act under the medicines legislation and the MHRA, through their enforcement arm, are actually investigating the allegations that have been made in that particular case. That investigation is not complete. I cannot at this time, as you will understand, make any further comment on it other than to say if it is found that there is evidence of non-conformity with the medicines legislation in providing the information that is required to be provided, you can take my assurance that there will be vigorous prosecution in that particular case, if that is the case.

Q988 John Austin: I am grateful for that. I was somewhat concerned that someone who could have been a key witness mysteriously could not turn up and give evidence to us when we wanted to ask certain questions at a previous session. My question still remains. There was a detailed 18-month inquiry. If the MHRA does not examine the raw data on suicide cases in a detailed 18-month inquiry, are we to conclude that the MHRA rarely does so?

Dr Raine: Perhaps it would be useful to stress again that in relation to paroxetine we went back and re-examined the original trials. In that case, the rigour has extended to that level of detail. If it would help the Committee, I should be very happy to produce a short note on the precise methodology which was employed just to clarify that point.

Q989 Chairman: It would be helpful.

Dr Raine: The published document we now have is some 200 pages long, so a concise note may be helpful.

Q990 John Austin: Were you looking specifically at anti-depressant safety?

Dr Raine: Selective serotonin reuptake inhibitor safety; that is correct.

Q991 John Austin: You were not looking at the wider issues of risk and benefit in that area.

Dr Raine: Certainly the focus was on the safety concerns. This was the prime reason for the rigorous review. It had to be taken in the context of this very serious illness which is a major burden to the public health. The report itself makes that very clear in one of its first chapters.

Q992 John Austin: May I say that at the last session the Chairman of the MHRA, Sir Alasdair Breckenridge, referred to the importance of not discussing the question of drug safety in isolation and emphasised the need for education of the public in terms of risk and benefit. I presume that is something you would agree with.

Lord Warner: Absolutely. I was very much trying to get that point across in the earlier evidence I was giving. On the issue of raw data, my understanding is that in the inquiry on which you have been pressing us, two products, Epogam and paroxetine were actually subject to very significant partial re-analysis of data. There was a going back into the raw data in order to look at some of the issues around suicides and suicidal indications. In that particular case, the MHRA did not spend the length of time on just one product, it was a large range of products; where there was the need they went back into the raw data to do a re-analysis. It simply is not true that under no circumstances do they use the raw data: in most cases it is not necessary to do so.

Q993 Dr Naysmith: It has been suggested in evidence to us that the post-marketing surveillance function, checking particularly that licensed drugs are safe, should be removed from the MHRA just to avoid possible conflicts of interests arising. What do you think of that?

Lord Warner: My sense is that this does not happen in other drug regulatory bodies. While I make a few more remarks, I give my two colleagues time to consider whether they can think of any other country where that division has been made. I do not think there has been, from recollection.

Q994 Dr Naysmith: Can you understand how, from the outside, it looks as though there must be some conflict of interests when the minister responsible for drug regulation is also the co-chair of the pharmaceutical industry competitiveness task force?
Lord Warner: There are two things, are there not? There is the situation within the regulator and the situation at the political level with the minister. Within the regulator, there is operational separation of post-licensing supervision in the form of Dr Raine and the people who are dealing with the original licensing applications. It is useful to have within the overall body both these functions combined, although there is a clear separation of the staff who are working on those two particular functions and it only comes together in the chief executive across the agency. It becomes easier for the post-licensing scrutiny of a particular product to be carried out if they can get access easily to the data which was around at the time of the licensing application itself: that becomes operationally a simpler thing. I would argue there that there is not much of a case for separating them up into two bodies with all the overheads which go with two bodies when there is no evidence, as I recall, that any other country has gone down that path.

Q995 Dr Naysmith: I think the Netherlands have, have they not?

Lord Warner: There is some doubt as to precisely what they have done.

Dr Harvey: I think in the Netherlands the final decision around pharmacovigilance still sits with the licensing body.

Dr Raine: Yes; absolutely. Although they collect ADR reports and do a certain amount of signal detecting work in a separate body, it is the licensing body equivalent which does the risk assessment and risk management decision making.

Q996 Dr Naysmith: They definitely separate pre- and post-marketing functions in the Netherlands.

Dr Raine: It is not directly comparable in that way. There is a separate collecting of ADRs but not the decision-making process, which is centrally done.

Lord Warner: So the actual decision to withdraw is taken by the same people who take the decision to licence in the first place. I think that is the point my colleagues are making. In terms of your other point about whether the person sitting in my job, past, present or future, is able to strike the right balance, I tried to get the arguments across in my opening responses to the Chairman’s questions. I think a balance can be struck and I think it is important that we do not get into a situation—the only point I would emphasise—where preoccupations with short-term financial issues in relation to healthcare, which is a problem in many countries and certainly a phenomenon in some European countries at the moment, actually dominate the decision-making in relation to the future development of particular products. If there is no scope for encouraging the development of research-based products in this area, the only people to suffer ultimately are the citizens of that country because you diminish the flow of new pharmaceutical products onto the market through a research-based industry. We think that balance has to be struck and under successive governments we have struck that balance by combining in one department the responsibility for running the NHS effectively and being the sponsor organisation for the research-based pharmaceutical industry.

Q997 Chairman: What I think Dr Naysmith is after, and it is an interesting question, is whether you find, as co-chair of the competitiveness task force, also with responsibilities for the regulatory mechanism, that on occasions you have to make some pretty difficult decisions on which side of the fence you may need to go. You have an industry which is hugely important to the economy, employs thousands of people and is a major earner for Britain, but on the other hand you have that very important responsibility in terms of public health. Have there not been situations where you have found yourself in some difficulty in determining exactly whose side you are on at a particular time? Issues must have cropped up which have caused you some problems in that respect.

Lord Warner: I certainly do not want to give the impression that I am cavalier about this. I do think about these issues very carefully and I certainly do not want to give the impression that I am schizophrenic either. What I think I would say is that if you are trying to achieve a balance and that is what you are consciously trying to do, you work hard to achieve that balance. I try to ensure that I hear what the industry has to say, I sometimes, if I am honest about it, take what they say with a pinch of salt and I particularly sometimes take it with a pinch of salt during the course of PPRS negotiations. I would point to the PPRS negotiations as a good example of where this balance can be struck. We certainly did not end up in those negotiations where the industry wanted us to end up and there was much rhetoric from the industry, if I may remind the Committee, about a settlement being forced upon them. There were not loud hosannas in some parts of the industry about the outcome of those negotiations. Equally, however, at the end of the day, the ABPI recommended that settlement to their industry. There are difficult judgments and there is hard bargaining to be done sometimes in some of these areas. We have touched on some of these issues around enforcement, when there is poor practice, if you like, in relation to supplying evidence. Where there is evidence that people have not supplied the information that they will be required to under medicines legislation we will not hesitate to take tough enforcement action. I believe that it is possible to strike that balance, but I can see other people might find that the arguments go the other way.

Q998 Chairman: Cross-dressing in politics is apparently quite fashionable, but you seem to be in an impossible cross-dressing position in the role you have. What I am interested in are your thoughts. What would be the impact if the commercial aspects, the competitiveness task force aspects of your role were actually within DTI and the regulatory remained within Health? Can you see any advantages or can you see any disadvantages? Obviously that is an issue which, as you appreciate, has been thrown around throughout our inquiry.
Lord Warner: Once you separate those two functions it would be far more difficult to get the right balance. You set up scope for conflict departmentally within government if you go down that path and I would still cite Europe in that particular case. Where the going gets rough in public expenditure terms and you have a slightly embattled health minister trying to cope with a burgeoning budget against the wishes of some of his colleagues, this does not of course happen in this particular country, but overseas there are sometimes less favourable circumstances that this government has managed to achieve in this area. Where you get that, there is always the danger that the short-term consideration, in terms of balancing the health budget, will over-predominate. That is the argument I would ask you to dwell on. I would say that can be detrimental to the longer-term interests of the citizens of that country in terms of the health products which get developed. There are countries in Europe which did, 10, 12, 15 years ago, have strong pharmaceutical industries which have actually weakened very substantially over the last 10 to 15 years.

Q999 Chairman: What you are saying is that this cross-dressing I referred to is not an impossible task from your point of view.

Lord Warner: I do not want to come across as a fervent cross-dresser and I never quite see myself in those terms, but if that is the label the Committee wish to apply to me, I am comfortable in that position.

Q1000 Dr Naysmith: There is a slightly different angle to all this, which is that this must mean there is a fairly close relationship between the Department of Health and the pharmaceutical industry. It is possible that means that solutions to health problems are sought more quickly and more readily, from pills and that sort of thing, than other potential treatments which the department also ought to be considering and perhaps promulgating more. It is even more important when you are talking about budgets, because quite often it is cheaper to prescribe pills than it is to prescribe a course with psychologists or psychiatrists or physiotherapists. It kind of skews the thinking about health and public health away from a longer term solution to a lot of problems. What I am asking is whether there is any possibility that could be happening.

Lord Warner: The other argument is: who is doing what? The person in the department who is the lead official on relationships with the pharmaceutical industry is Dr Harvey. She is balanced in terms of all the sources of advice to ministers that feed into public policy decision making by a raft of other people who are arguing the cases for public health, particular disease conditions, mental health, acute services and so forth. At the pinnacle of this is the Secretary of State making judgments based on a variety of sources of influence. There is no one person saying that at all costs we actually have to have a pharmacological solution to this particular health problem. I should say the arguments increasingly are the other way round, where people are being encouraged to take more responsibility for their own health. There is a strong drive in that particular area, giving people more information about their own health conditions, encouraging them to find out what are the best ways of responding to those conditions, a lot more emphasis on choosing lifestyle options which favour health rather than those which do not. That is a set of very strong messages going on in the public arena and the advice which is given to ministers, which is a counter-balance to any suggestion that we might just want to promote pharmaceutical products.

Q1001 Dr Taylor: May I go back very briefly to the cost of adverse drug reactions? I realised rather belatedly that I did not make my question quite specific enough. You told us that about 6.5% of admissions to hospital cost £466 million a year. Does that include the cost of treatment in hospital? Is that a total cost for that?

Lord Warner: I would have to bow to Dr Raine.

Dr Raine: It was a total cost, but we can certainly give you a note on the specifics.

Q1002 Dr Taylor: The other thing which is probably not recognised is the cost of adverse drug reactions in the community. Is there any measure of that? The loss of work which a drug reaction causes for a patient who never goes near hospital. I have only just realised by the mirth which was engendered by my use of the term “global” that you were thinking about the whole world. I was thinking about the global cost in this country, the community and hospital services. Is there any way you could find out about that?

Lord Warner: We will certainly look into it. My impression from the study I cited was that it related to the people who were in that particular hospital, but we need to look at the evidence.

Q1003 Dr Taylor: Hospital admissions are easy to collect; it is what is happening in the community which is more difficult.

Lord Warner: We also have the GP research database. We will genuinely look into the data we have and give you the best estimates we have on that basis. I am afraid I cannot answer in any more detail today.

Q1004 Dr Taylor: Moving on to innovation, we have heard from several witnesses that really the rate of new drug discovery is going down and this is almost inevitable because it obviously becomes more and more difficult to find new answers. A question which has been put to us: would a stricter regulatory system encourage more real innovation? If one had got to 12 beta-blockers and you said enough was enough, 25 non-steroidals and you said enough was enough, would that in any way encourage drug firms, force them to go for real innovations? One would cut the beta-blockers and the non-steroidals well before you got to 12 or whatever the numbers were.
Lord Warner: The whole area of innovation is a complex one. It is wider than just stopping particular pharmaceutical products. I have been involved in that in other aspects of my work as well as the work on the pharmaceutical industry. Certainly you have a pharmaceutical industry which has a very big R&D component; there is no doubt about that. They spend £3.5 billion a year on medical R&D. We have an NHS which is putting in over £600 million to R&D and we have the Medical Research Council and the charitable sector. There is a very big component of medical clinical R&D in this country which is driving an agenda of change in this particular area. What we have found, which is why we set up last year, after a couple of reviews, one by Sir David Cooksey and one chaired by Sir John Pattison, was that there were real issues about how fast we were getting innovation to the bedside from the laboratory. So there were issues around whether we could do a better job on what is called translational research in terms of getting clinical trials off the ground. It is worth bearing in mind that the evidence shows that patients who are in clinical trials tend to do rather well compared with people who are not in clinical trials. Whatever the outcome of the trial, there are benefits for patients. We found that area is one which needs a great deal of attention and that is not just in order to benefit the pharmaceutical industry, it is actually to bring good products faster to the bedside for a whole range of people. We also think, as I was saying earlier, why we want to move down the path of Futures Forum is in some ways similar to the points that Mr Bradley was making about the World Health Organisation having a medicines policy. We think we need to be a bit more holistically looking ahead about the things we should be concentrating R&D effort on a bit more than we have done in the past, which is why we want this Futures Forum. We do know that generally in the NHS you need to use—this is not just about pharmaceuticals but things like devices as well—the purchasing muscle of the NHS to bring some of this innovation faster to the advantage of patients. This is a complex issue where it is not just a straightforward matter of stopping one line of development for a particular range of pharmaceutical products: it is a complex issue about how you foster innovation, the development of new therapies and bringing the new therapies to the patient quickly through a proper trial basis.

Q1005 Dr Taylor: Are there any incentives which could be offered? It is obviously incredibly expensive to develop a completely new treatment for something and it is presumably far cheaper just to develop a minor variant of the drug. Are there any incentives which could be offered to encourage the real innovation?

Lord Warner: It is not quite true that some of the me-too drugs have not themselves been of great benefit to patients. It is not always the case that the first-in-class product has been the one which has been the winner for patients, as you probably know from your own clinical practice. We could certainly send you some evidence. The point I am making is that there comes a point about when you stop me-too and next-in-class in a particular class of drugs. Those would not be easy judgments to make.

Q1006 Dr Taylor: One of our witnesses felt that three beta-blockers would probably have been enough. I wondered whether there was any way the regulatory system could provide an audit and quality control of these sorts of developments and that would therefore produce some regulation of them and a push towards major innovation.

Lord Warner: Thinking about this, particularly in the light of what Mr Bradley was saying earlier, it seems to me that this is the kind of area you would touch on in a WHO recommended medicines policy. You would start to take a picture of where the areas of less involvement were and where the areas of excess involvement were. It seems to me to fit more easily into that kind of work rather than using the regulatory system to try to block entry, if I understand you correctly.

Q1007 Dr Taylor: Yes. I was just wondering how possible it would be for the MHRA, when there were six beta-blockers all with slight differences, to say to a firm which was going to produce a seventh that we do not need it.

Lord Warner: I do not have anything more to add. The firm would still have to show safety and efficacy in their product to the MHRA, if they had a new product in that particular area.

Q1008 Dr Taylor: Back to a point which has continually been made to us, all that has to be shown is that a drug is better than a placebo, not better than a standard. That does seem to me to be a weakness in the system.

Lord Warner: I am not the scientist here.

Dr Raine: It does depend on the therapeutic area; there are different approaches depending on whether comparators are looked at or indeed placebos. We could perhaps give you a short note on how the regulatory system works in that regard.

Dr Harvey: The minister referred to the Futures Forum and the UK CRC. The UK CRC involves all of the major research funders, the NHS patient groups, scientists and the pharmaceutical and medical device industries. It is a way of stimulating research across the board and a way of building on the original cancer research networks we have had in the NHS to build research networks around mental health, children, stroke, Alzheimer’s, et cetera, where one is actually engaging with the major research bodies and the pharmaceutical medical devise, and biotech industries and patients in the sorts of areas which are clinical priorities where actually we need the development of new agents. As the minister was saying the Futures Forum, engaging with the pharmaceutical and indeed the devices industry with these major funders and patients does make it clearer to the industry where the real areas of future priority need are for the NHS.
Q1009 Dr Naysmith: On that, I was speaking earlier about the PPR scheme and the possibility that there was an allowance for marketing it. Is there also a big allowance in it for research. Is that ever used as any kind of driver in this area or could it be?
Dr Harvey: In terms of the 2005 PPRS, you are absolutely correct that in terms of the allowances, the allowance for research and development was increased within this particular agreement and that is particularly to stimulate innovation with development of new active substances.

Q1011 Dr Naysmith: What about quality. Does issue. This particular issue is not peculiar additional element for innovation specifically development allowance, but then there is an allowance for research and development, which the pharmaceutical industry would benefit from, as would the biotech industries.

Q1014 Chairman: One of the things we found interesting was the number of all-party groups within parliament who also have interesting connections, often not known to their members, with industry.

Lord Warner: This is a difficult issue. I should just declare to the Committee that before I became a minister I was the chairman of the National Council for Voluntary Organisations, so I do feel slightly schizophrenic on this particular issue. This particular issue is not peculiar just to the taking of money from pharmaceutical industries for voluntary organisations. All voluntary organisations are confronted from time to time with whether they want to take a particular sum of money or types of funding from a particular source when it may, as they see it, produce a conflict of interests or compromise their own independence of judgment. It is ultimately in this area down to the particular voluntary organisation to consider very carefully whether they are damaging their own reputations by taking money from a source which may call in question the arguments they put forward on behalf of a particular patient group or particular interest. It is not peculiar to the area of taking money from the pharmaceutical industry.

Q1015 Dr Naysmith: Should some sort of statement of interest be required, along those lines?
Lord Warner: Absolutely. They do all have clearly defined charitable purposes in order to be registered as a charity and the funding should not be in conflict with their charitable purpose, whatever that is. They do have to make sure that it is consistent with the benefit to their beneficiaries. Certainly the Charity Commission offers a range of guidance to voluntary organisations. I am certainly happy to look into whether this issue has been raised with them, whether there are particular areas. I do not know whether the Commission has actually taken that in.

Q1013 Dr Naysmith: The minister said early on—I wrote it down—that one of the aims would be to get the science applied faster where there is a clear patient need; or it may have been a clear clinical need, but the rest of it is accurate. That is what we should be trying to do, is it not? If we can do it through that mechanism, then we ought to be looking at it.

Lord Warner: There are various ways. Paediatric medicine is a good example of where one is trying to get the incentives all pointing in the correct direction. If we are frank about it, this has been a rather neglected area in the past, which is why we will be publishing a British National Formulary for paediatric medicine later this year—the work is being done by all the experts in this field—and why we want to give incentives through the PPRS and negotiations are going on in Europe over this particular area. Everyone recognises that one wants to use the mechanisms available to try to get the incentives where there is clear public benefit and paediatric medicine is a good example. It is also worth mentioning that the Chancellor has made available a tax credit for research and development which the pharmaceutical industry would benefit from, as would the biotech industries.

Q1010 Dr Naysmith: Were the companies who had innovated rewarded or will they be rewarded or is this something that everybody gets?
Dr Harvey: No; no. There is a baseline research and development allowance, but then there is an additional element for innovation specifically targeted at the number of new active substances a company has which are in patent. A small company gets slightly larger allowances; very large companies get a fixed allowance per new active substance for up to a maximum of 20 new active substances. This is building on what was there within the 1999 scheme, but is very much more around stimulating innovation.

Q1012 Dr Naysmith: New in terms of fulfilling a need or another version of an existing product. Who will decide that?
Dr Harvey: Technically it could be another version, but it has to be a new active substance in its own right. In addition to that there is also an element of the R&D allowance of up to 3% of NHS sales for the development of paediatric licenced medicines as well. That is new within this PPRS agreement and is very much in line with the minister’s commitment around having more licensed treatments available for children for paediatric use.

Q1016 Dr Naysmith: We have the Charities Bill coming soon which may well be an appropriate route.
Lord Warner: Absolutely. Certainly, if there is an issue, I think it is to a great extent dealt with through the charities route.
Q1017 Dr Taylor: You mentioned the withdrawal of Co-proxamol, which is really quite a milestone, because I suspect it is the first time that a drug which has been around for so long has been withdrawn. I can see some of us being approached in our constituencies at home by long-term rheumatoid arthritis patients who can see no way that they are going to get off it. May I just ask what consultation there was, what bodies were consulted about the withdrawal? Everybody recognises that even in small overdose it is dangerous, particularly with alcohol, but what consultation was there before this absolutely drastic step of getting rid of it altogether was taken, when perhaps it could have been available under some scheme of limited prescribing?

Dr Raine: Recognising the concerns which Dr Taylor has expressed about a very well-established medicine, albeit one without evidence of a favourable risk benefit, that the withdrawal would pose very major issues for clinical practice and for patients, for the first time we conducted a public consultation. We put the evidence base into the public domain and sought comment about the very question you are asking: are there specific groups of patients for whom the benefit risk would be favourable. We asked not just for evidence, but for arguments and opinions. The results of that consultation are published. In the end the CSM had to weigh all this up in light of the scientific evidence and make a very tough decision. What I would say is that we also convened a pain management working group under the leadership of the CSM in order to help that change in practice. Quite clearly, if there is a very small number of patients who do indeed need ongoing supplies, we could consider a named-patient-basis type of arrangement. I hope this gives you the perspective on the lengths to which we went to gauge public opinion in this regard.

Chairman: May I thank you, minister and your colleagues, for an excellent session. You promised to provide us with some further information and we should in the near future. Thank you very much for your help.

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**Letter from the Lord Warner, Parliamentary Under Secretary of State, Department of Health to the Chairman of the Committee (PI 1C)**

You will recall that when I gave evidence to the above inquiry on 3 February I agreed to provide you with extra information on a number of areas, and I am now writing with this additional material.

**MHRA FUNDING**

During the session, Dr Richard Taylor asked about comparisons of funding of regulation of medicines prior to the establishment of the Medicines Control Agency (MCA) in 1989–90, and the current arrangements. I should first like to clarify one point that may not have been clear during the evidence session. In the UK industry has always paid some level of fees towards the regulation of medicines, but before the MCA received Trading Fund status in 1993 this was supplemented by Government funding.

Prior to 1989–90 medicines were regulated by the Medicines Division of the Department of Health and Social Security. In 1987, the then ministers commissioned a review of licensing in the UK. The report from that review showed that the Medicines Division received its funding from two sources:

- 62% from receipts from pharmaceutical companies, of which 89% came from charges on company turnover and 11% from licence application fees; and
- 38% from the Department of Health.

The report noted the growing increase in numbers of applications for licences and the complexity of such applications. It also noted the increasing delays which were denying patients access to medicines and also damaging companies commercial interests. For example, in 1987, the median time taken to grant a licence for an established drug substance which was reviewed by the Committee on Safety of Medicines was 25 months. To resolve issues such as those highlighted in the report the authors made a number of recommendations, not least the move to a funding regime based entirely on fees related to the services provided. This was put into effect when the MCA was given Trading Fund status in 1993.

The Medicines Division budget in 1986–87 was some £9 million (with receipts from the pharmaceutical industry amounting to some £5.7 million). In 2003–04 the Agency’s medicines operation had a budget of some £46 million, which was fully funded by user fees.
Simvastatin

I promised to let you have information on the decision making around simvastatin, and this is in the attachment to this letter.

Merseyside Study on ADRs

Dr Taylor also asked some specific questions about the Merseyside study which looked at adverse drug reactions (ADRs). This study was funded by the MHRA, and looked at admissions to two general hospitals in Merseyside. It excluded patients under 16 years of age and women presenting with obstetric or gynaecological complaints.

There were 1,225 admissions related to an ADR out of 18,820 patients, accounting for approximately 4% of hospital bed capacity. ADRs were responsible for the death of 0.15% of all the patients admitted. This study estimated that that the annual cost to the NHS in 2002 of hospital admissions for adverse drug reactions was £466 million. This is based on the average cost of £228 per medical bed day (data from Institute of Public Finance). The estimate of costs to the NHS does not take into account the bed days saved through the beneficial effects of the medicines.

The study concluded that most ADRs were predictable from the known pharmacology of the drugs and many represented known interactions which were therefore likely to be preventable.

The study did not evaluate the burden caused by ADRs occurring whilst patients are in hospital or ADRs occurring in primary care that do not result in hospital admission, and therefore costs to Primary Care Trusts (PCTs) and costs related to time off work are not known.

Seroxat/SSRIs

Dr June Raine agreed to let John Austin have a concise note on the report into the safety of selective serotonin reuptake inhibitors (SSRIs). Seroxat was the first SSRI to be considered in detail by the Committee on Safety of Medicines’ Expert Working Group on the safety of SSRIs in the context of a Europe-wide review. The Working Group used three separate approaches to analyse the data. The marketing authorisation (MA) holder provided analyses in response to specific questions. Each original clinical trial study report was then evaluated to confirm the consistency and completeness of the MA holder analysis. Finally the Agency conducted a systematic review of the adult clinical trial data on seroxat, going to the level of individual patient data. All three approaches produced the same results ie there was no strong evidence of an increased risk of suicidal events for adults patients exposed to seroxat compared with placebo, although it was not possible to rule out an increased risk. There was no evidence to suggest an increased risk compared with comparator products.

Full details of the analyses of clinical trial data undertaken and the results are available on pages 75 to 83 of the report of the Expert Working Group which is available on the MHRA website.

“Me Toos” and Regulation

I agreed to let Dr Taylor have some evidence where the first in a class has not always proved the most effective for patients. The issue of “me toos” involves balancing the conflicting priorities of the innovative pharmaceutical industry, desirable clinical outcomes and individual patients’ needs. It would be wrong to start from the point of view that “me toos” do not represent any form of clinical advance. There are differences between products that might be “me toos” in terms of safety and possibly in efficacy. Additionally, interactions between the drug and other medicines might be different. A good example is the class of beta-blockers where the first in class was indicated for hypertension and angina. The second and subsequent members in the class allow once daily dosing and more selectivity in action. In particular, later beta-blockers have been shown in large trials to reduce mortality after heart attack (secondary prevention) for which they are now routinely given.

Furthermore, seeking to address issues such as clinical or cost effectiveness of “me toos” through the legislation which underpins the regulatory system is likely to be challenged in the courts as the current system is based on the evaluation of the safety, quality and efficacy of medicinal products. The legislation cannot be used to restrict the commercial freedom of the innovative industry (or any other sector of the pharmaceutical industry).

However, there are other regulatory tools at our disposal which we can use to encourage the development of drugs where there is a clearly defined clinical need. For example, the EC Orphan Drugs Regulation (Reg (EC) No 141/2000) has clearly defined criteria for designation with Orphan Drugs status (the prevalence of the (medical) condition must be less than five per 10,000 of the EU population) and incentives for innovators (additional marketing exclusivity, free access to scientific advice). Similar provisions will apply in the forthcoming EU legislation on paediatric medicines and the UK is also currently implementing its own strategy (consisting of regulatory incentives, information to prescribers and coordination of research to encourage industry to develop paediatric indications for its products.
Such regulatory action as we can take to encourage innovation must be balanced with information to
describes the local and national bodies I described in my evidence. Initiatives such as the UK Clinical
Trials Collaboration which I have asked to organise a “Futures Forum” to advise Ministers on priority areas
for innovation in healthcare intervention.

CHARTIES COMMISSION

I agreed to look into whether the issue of pharmaceutical companies funding patient organisations has
been raised with the Charity Commission. I have done this and the Commission advises that it does not
believe this issue has been raised with them as a policy matter before.

However, the Commission provides advice and guidance for many thousands of cases each year across a
wide range of issues. It is possible that this issue may have been raised on an individual case level. Advice
would have been given in the context of the specifics and merits of the individual cases.

Whilst the Charity Commission has not produced guidance that specifically addresses the issue of
voluntary organisations accepting funding from industry, other Charity Commission guidance dealing with
Trustee responsibility and duty of care to their charity; the independence of charities; and guidance relating
to ethical investment sets out general principles which are applicable. In summary, this guidance covers
principles such as the need to have a clear policy, and the need to act in the best interests of the charity and
its beneficiaries—weighing up both financial and reputational considerations.

The Charity Commission works closely with the Institute of Fund Raising’s Standards Committee on
fund raising issues. The Institute has published two codes of practice that are relevant in this context:

— The Acceptance and Refusal of Donations; and

— Charities Working with Business.

Crucially, it is the duty of Trustees of the charity to determine whether it is in the charity’s best interest
to accept a donation from a source that could, or could be perceived to, compromise the charity’s
independence.

The Charity Commission is currently considering whether there is a need to draw together the range of
inferred guidance in this area into a more accessible format. This could result in a published set of principles
by Spring 2005.

I hope that this addresses the specific points raised by the Committee.

Annex

SIMVASTATIN

Reclassification process

The proposal from Johnson & Johnson MSD Consumer Pharmaceuticals for the pharmacy availability
of simvastatin 10 mg (Zocor Heart-Pro) was first considered by members of the Committee on Safety of
Medicines (CSM) at a clarification meeting in September 2003 and again at a CSM meeting in October 2003.
In light of discussions, CSM then advised that consultation could take place to seek views on the pharmacy
availability of Zocor Heart-Pro.

On 17 November 2003 the MHRA started a consultation exercise with a deadline for comments of
16 January 2004. The consultation document (ARM 18) and the outcome of the consultation exercise are
displayed on the MHRA’s website (www.mhra.gov.uk). One hundred responses were received expressing a
wide variety of views on the proposed reclassification. Overall, about two thirds of respondents were in
favour of the proposal. The responses received were then referred to the CSM for advice. No new issues were
raised in the responses and CSM advised Ministers that simvastatin 10 mg could be safely sold under the
supervision of a pharmacist without a prescription.

Safety assessment

Patient safety is the prime consideration in any decision to make a medicine available over the counter
(OTC). It is assessed against strict criteria relating to its safety in the circumstances in which it will be used.
Simvastatin has been available in the UK since 1989 and many millions of patients have been safely treated.
All medicines have the potential to cause side effects. Most of these side effects are not serious and are
predictable from the known actions of the drug. During the use of simvastatin in clinical practice, there have
been reports of reactions suspected to be associated with the medicine. As with all statins, simvastatin has
been associated with some rare reports of severe muscle damage. The incidence of muscle damage with
simvastatin is dose dependent and is more likely to occur at higher doses or when simvastatin is taken with
other cholesterol lowering drugs. As the pharmacy medicine contains low dose simvastatin (10 mg) the risk
of muscle damage is very small. This is a rare side effect and clear unambiguous advice is in the product
information, patient information and information for pharmacists.
Efficacy of simvastatin

There is a wealth of evidence to support the concept that lowering cholesterol is beneficial and reduces the risk of Coronary Heart Disease (CHD). Similarly there is a wealth of evidence that statins lower cholesterol levels and hence reduce the risk of CHD. The amount by which statins lower cholesterol is dose related, with higher doses resulting in greater absolute reduction. Simvastatin 10 mg has been shown to lower cholesterol levels, however, because the benefit is most demonstrable in patients at higher risk, large scale clinical trials of statins (including simvastatin) have generally targeted high risk patients. The latest research, however, provides good evidence to support the switching of statins to reduce the risk of a first major coronary event in people likely to be at a moderate risk of CHD.

Numerous endpoint studies with statins confirm that lowering low-density lipoprotein cholesterol (LDL-C) reduces the risk of developing CHD. Simvastatin 10 mg produces around a 27% fall in LDL-C or 1.31mmol/l in absolute terms (standardising to a mean starting level in studies of 4.8 mmol/l). Reductions of this order reduce the risk of a major coronary event (CHD death or non-fatal myocardial infarction) by about one third after three years of treatment. The level of absolute risk reduction depends on the starting level of risk. Whilst no specific clinical trials have been conducted with simvastatin 10 mg in this particular patient population, it is reasonable to assume that these benefits would also apply to this group of people given that the effect of lowering LDL-C by simvastatin is consistent between populations, and the relation of LDL-C to risk is linear.

In the self-medication population selected on the basis of age and sex and risk factor status (smoking, family history of early CHD, overweight or truncal obesity and ethnicity), starting 10-year CHD risk is likely to be in the range of 10–15%. Treatment with simvastatin 10 mg in this population will, therefore, produce a valuable reduction in risk, provided people are compliant with the treatment regimen; coupled with diet and lifestyle changes, the benefits to these individuals will be considerable. It is recognised that there are uncertainties about the effect of taking a statin on compliance with behavioural risk-modifications (such as healthy eating, exercise and smoking cessation).

Conclusion

Preventing CHD is a national priority. The National Service Framework for CHD sets out plans to ensure that the best care, in terms of prevention, diagnosis and treatment, is available to everyone. The NSF has prioritised those individuals at greatest risk. Making simvastatin available OTC provides a choice to those at moderate risk of CHD to access a preventative medicine they would not otherwise get on prescription.
APPENDIX 1

Supplementary memorandum by Rethink Severe Mental Illness (PI 2A)

RECOMMENDATIONS TO THE HEALTH SELECT COMMITTEE

These recommendations follow Rethink’s written and oral evidence to the Committee.

PRINCIPLES

That agreed principles govern the relationship between the pharmaceutical industry, the regulatory bodies, and the voluntary sector. These would include:

— transparency;
— balance;
— regulation;
— accessibility; and
— realism.

TRANSPARENCY

— A regulatory requirement should be introduced to compel the publication of the results from all clinical trials and other evaluations of treatments, including those funded by the government; this requires the establishment of a register of clinical trials and evaluations.
— Current regulations governing the declaration of financial interests for those sitting on industry regulatory bodies should be broadened to include all interests relevant to the regulatory process.
— Charities and “patient organisations” should make public their funding sources, sponsorship policies, trustee oversight arrangements and methods used to ascertain the views of beneficiaries.

BALANCE

— Charities and “patient organisations” should seek a balanced portfolio if funding, as no single source is free from influence and perceptions of influence.
— “State” funding should include support for core activities of charities and “patient groups,” including ascertaining the views of members and beneficiaries.
— “State” funding should be provided to an umbrella body for health charities and “patient groups” (possibly the LMCA) to develop standards and guidelines for transparency in the sector, as outlined above.

REGULATION

— Current regulations governing the declaration of financial interests for those sitting on industry regulatory bodies should be broadened to include all relevant interests.
— Patient organisations should be required to set out how they ascertained the views of the people they claim to represent in making any submission to official bodies, in line with the standards and guidelines suggested above.
— Regulatory bodies for medicines and other treatments should include more lay members and representatives of “patient organisations” which meet the standards developed.

ACCESSIBILITY

— Regulatory authorities should have a duty to seek and act upon evidence from charities and “patient groups” of serious adverse effects.
— Where there is early suggestion of adverse effects of treatments, “patient groups” should be contracted by regulatory bodies to survey their beneficiaries, to allow a preliminary indication of the severity and frequency of the problem, and to inform decisions on whether to order full scale formal studies.
— Regulatory authorities should be enabled to contract “patient groups” to produce user-friendly patient information leaflets and other materials, and to advise on PILs.
REALISM

— Government, patient groups and the pharmaceutical industry should co-operate on public education campaigns to achieve a more realistic understanding of the benefits and limitations of medicines.

APPENDIX 2

Memorandum by the Pharmaceutical Services Negotiating Committee (PSNC)

INTRODUCTION

The Pharmaceutical Services Negotiating Committee (PSNC) represents all the community pharmacies in England and Wales who provide NHS pharmaceutical services. We believe that we are able to contribute usefully to the Health Select Committee’s Inquiry into the influence of the pharmaceutical industry, from our experience as the suppliers of over 90% of medicines supplied in primary care. We have serious concerns about the risks and fragility of the present systems.

In this submission we aim to:

(a) describe briefly the supply arrangements under which pharmaceutical products reach the patient;
(b) explain features of NHS funding arrangements that affect or may affect supplies and prices; and
(c) comment on aspects of the present systems that we believe should be of concern to the Select Committee.

A. THE SUPPLY ARRANGEMENTS

Under present arrangements, community pharmacies bear the responsibility for supply of medicines in primary care, for ensuring that any patient can obtain promptly what the doctor, nurse or other health care professional prescribes. They are obliged to supply medicines “with reasonable promptness”. Local NHS authorities and the NHS rely on pharmacies to procure any medicine or appliance that is required and do not concern themselves with how this is done.

This role is not generally acknowledged, but it works extremely well; the costs of procurement in secondary care are extremely high. In primary care, they are borne by the 10,500 community pharmacies that ensure they can meet their patients’ needs. They are able to do this only through the supply arrangements that include manufacturers and three main full line wholesalers who at present provide the necessary support. As we will explain later, the success of pharmacy in meeting patients’ needs is despite, and not a result of, the present funding systems and we believe it is in danger.

The Drug Tariff, which lists medicines and appliances that may be prescribed in primary care includes over 15,000 products. Pharmacies will consider their patient base and local prescribing habits when deciding what medicines to keep in stock and the stock levels. Prices and reimbursement (discussed later) are very important considerations.

Medicines supplied can be grouped into three classes: proprietary medicines, normally still within patent protection; generic medicines, for which the patent has expired and which are prescribed under the generic name; and OTC medicines, which are sold, not dispensed under NHS arrangements, although of course in some cases the same medicine may also be available on prescription.

Proprietaries

These will be obtained from wholesalers, normally one of the three main “full line” wholesalers, ie those who carry the full range of products. These wholesalers offer a twice daily delivery service, and this is how demand is met for less commonly prescribed items, or medicines whose cost is such that pharmacies cannot afford to hold them in stock. Although they accounted for only 45% of prescription items dispensed in 2003, the ingredient cost to the NHS of proprietary medicines was 76% of total spend on medicines.

PSNC cannot say whether the prices paid by the NHS for proprietary medicines are reasonable, but the systems for payment to pharmacies are bad. Many proprietary products have a very high price, over £100 per item. The systems for reimbursement are such that independent pharmacies dispensing a prescription for a UK proprietary medicine will normally lose money: the net reimbursement price will be lower than the purchase price. The larger chains may be able to secure purchase terms that cover the cost or even deliver a very small profit. Pharmacies will seek to minimise stock holdings of highly priced proprietary medicines and are entirely dependent on the full line wholesaler services to be able to provide for their patients.
Full line wholesalers need to carry substantial volumes of the range of proprietary medicines to ensure ready availability for patients. Where, unusually, the pharmacy’s wholesaler cannot supply the item, the pharmacy can contact the manufacturer and establish whether there is a national shortage, and make arrangements to address the patient’s need. Unless the arrangements for pricing allow sufficient margin to enable both wholesalers and pharmacies to supply the products profitably the future of supplies cannot be assured. At present it is the profits on generic medicines that makes the present arrangements work, but these are being threatened.

Relationships with full line wholesalers and proprietary manufacturers are important for community pharmacies. Although pharmacies will order from wholesalers, several of the major proprietary manufacturers have representatives with specialised training in their products who visit community pharmacies. Many of the manufacturers provide training materials for community pharmacists or their dispensing staff, to keep them up to date with disease therapies. They also provide sponsorship for local training meetings and conferences. They are an important source of education for community pharmacy, not confined to promoting a specific product. An example of this is an educational training grant provided by GSK to fund a distance learning programme so community pharmacists can gain accreditation to provide advanced services under the proposed new community pharmacy contract.

The pharmaceutical industry’s support can be construed as no more than a means of developing the market for their products, but this would be unfair in the case of its relationships with community pharmacy, particularly given the low ability pharmacies have to influence prescribing. The motivation for the support is undoubtedly part of activity to develop beneficial use of the manufacturer’s products, but it enables pharmacists to use the information provided to help patients get the best outcomes from their treatment. It is known that around 50% of all patients do not comply fully with the regimen prescribed by their doctors, and there is an important current role, and a far greater potential role within the proposed new contract, for pharmacies to support more effective therapy.

Proprietary manufacturers also provide information “help desk” support for prescribers and pharmacists, manned by health care professionals that deal with queries about the medicines. These may relate to a number of issues, including the patient’s clinical conditions and the suitability of the medicines, to the stability of the product or possible effects of use. Typically, once a product comes off patent these queries will continue to be directed to the proprietary manufacturer, whether or not they relate to the original product or the generic.

**Generics**

Many, but not all, generic medicines have low prices. Generics account for 55% of all prescription items dispensed, and a restricted number of products will account for the majority of this.

Most of this market for independent pharmacies is supplied by short line wholesalers who will supply a limited range of high-volume products; only around 20% of generics are supplied by full line wholesalers. Pharmacies will buy the most commonly dispensed items in large quantities to take advantage of discount opportunities. Some low volume generics will be supplied in the same way as proprietary medicines, through the full line wholesalers.

Generics manufacturers act as typical commodity suppliers and do not tend to provide support or services of the kind provided by proprietary manufacturers. Pharmacy chains may purchase directly from the manufacturers. There is very active price competition and a large number of suppliers for the popular lines.

On some generic products percentage margins are very high. The present systems for pricing generic medicines have meant that products recently removed from patent can have reimbursement prices well in excess of prices available to pharmacies. PSNC is seeking to work with the Department of Health to address this by revisions to the present arrangements.

Pharmacies depend on profits made from generic medicines to offset losses, on proprietary medicines and on the remuneration paid to pharmacies for their NHS work (the Global Sum) which, as has been proved by a recent cost inquiry undertaken by the Department of Health Statistics Unit in conjunction with PSNC, falls far short of the present costs of providing the service.

We are very concerned about the present arrangements, and in particular the dependence on profits from generics to offset losses elsewhere. We do not believe that these cross-dependencies are well understood by the Department of Health or by primary care organisations. Unless future systems allow community pharmacists to operate profitably by continuing to dispense all prescriptions presented, expensive or otherwise, and there appears to be a very real probability that they will not, the systems could break down.

In addition to these problems, the pricing systems are a mess. The calculation of prices to be paid to pharmacies is complex, inequitable and inefficient. The procedure, under which pharmacies send off bundles of prescriptions at the end of each month and receive a cheque from the Prescription Pricing Authority six weeks later, with no ability to understand how the sum has been arrived at, is a disgrace. Proposals to move to electronic prescribing and pricing, and the NHS IT programme as it affects community pharmacy are in disarray.
**OTC medicines**

OTC medicines and toiletry items sold in pharmacies will normally be purchased through the pharmaceutical wholesalers (full or short line), although medium and large chains will deal directly with manufacturers.

We have no figures on the size of this market overall or the prices, but generally margins available to independent pharmacies will be 25–35%. The Office of Fair Trading submitted evidence in court proceedings in 2000 that OTC medicines account for 8–13% of pharmacy turnover.

**B. COMMUNITY PHARMACY INCOME FROM MEDICINES PURCHASES**

Community pharmacies derive around 50% of their total NHS income at present from drug purchase profits.

NHS income represents on average 82% of total pharmacy income. Non-NHS income as a percentage of the total has been declining consistently over the last 30 years with the growth of one-stop superstore shopping.

PSNC is trying to agree a new national community pharmacy contract with the Department of Health and the NHS Confederation. The service framework has been agreed but until very recently progress on funding has been held up by the Department of Health. The funding arrangements must address the problems already identified.

PSNC is anxious to protect the viability of locally situated community pharmacies as well as those in high street and health centre locations. Although many large supermarkets include pharmacies, need for NHS pharmacy services (which as seen from the figures above are the main *raison d'être* for pharmacies) are not normally coincidental with need for a supermarket shop. The government’s policies of access, choice and addressing health inequalities support protection of a wide network of community pharmacies.

Whilst PSNC is open-minded about the sources that provide the income needed by community pharmacies, it believes that use of the competitive purchase pressure exercised by community pharmacy to drive down prices of generic medicines for the NHS has generally worked well, and that pharmacies should continue to be incentivised to purchase at the lowest possible prices.

**C. SUMMARY—ISSUES OF CONCERN**

The concerns have been set out earlier in this submission. We have a fragile edifice at present under which community pharmacies take on the burden for the NHS of ensuring supply to patients. They do this very successfully. Even at times when there have been supply problems, pharmacies have been able to provide medicines for their patients, on occasions by agreeing substitutions with the prescriber when no other option was possible.

Future arrangements must deal with the dangers and flaws we have highlighted in this submission. PSNC continues to try to develop collaboration with the Department of Health to agree future systems that do not prejudice supplies to patients or the continuation and development of convenient local pharmacy services.

We believe that we need to:

— Protect easily available supplies of all medicines and appliances to pharmacies, so there is no risk of medicines needed by patients not being promptly available.

— Address flaws in the present pricing mechanisms:
  — to protect supplies to pharmacies and patients; and
  — not result in pharmacies being reimbursed at less than the purchase price of proprietary, or indeed, any medicines.

— Protect the viability of an easily accessible network of community pharmacies.

— Recognise the role played by the proprietary industry in providing information to help community pharmacists support their patients.
APPENDIX 3

INQUIRY INTO THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY

Memorandum by IMS HEALTH (PI 6)

INTRODUCTION TO IMS HEALTH

1. IMS has been at the forefront of the collection and analysis of healthcare data for more than 50 years. Its complex databases, sourced from thousands of hospitals, pharmacies and GP practices around the world are used widely by Governments, industry, universities and patient organisations to help deliver change in healthcare policy and delivery. In recent months IMS UK data have been used to help:
   — the NHS Prescribing Support Unit to cost out the implications of the new General Practice Contract1 and to help understand why NHS prescribing for controlled drugs in London is low;
   — the Department of Health Cancer Team to analyse the variation of NICE approved cancer drugs;2
   — the National Institute of Clinical Excellence to examine adherence to its published appraisals;3

2. IMS is uniquely positioned to help this Inquiry. IMS collects and processes electronic information on prescriptions extracted from about half the pharmacies in the UK. This information has been combined on a confidential, and anonymised, basis with industry promotional information.

3. In addition IMS collects information on the overall volume of industry promotion in three key areas—representative calls, direct mail and advertising.

4. This information gives IMS a deep understanding of the patterns of prescribing in primary care and the impact of pharmaceutical representative promotion.

SCOPE OF RESPONSE

5. This response to the Inquiry focuses on the provision of drug information and promotion, the third point raised by the Committee in its Terms of Reference. Within this area IMS’ response deals primarily with the effect of representative promotion.

6. Given the importance of drugs approved by the National Institute for Clinical Excellence, this response focuses specifically on the impact of representative promotion on those products that have both been analysed by IMS and which at that point in time had received a favourable review from NICE. The product areas that form the basis of this review are thus:
   — Proton pump inhibitors—used in the treatment of gastro-oesophageal reflux disease.
   — Atypical antipsychotics—used in the treatment of schizophrenia.
   — Cox II inhibitors—used in the treatment of osteo and rheumatoid arthritis.
   — Glitazones—used in the treatment of Type II diabetes.

OVERALL TRENDS IN PHARMACEUTICAL SALES FORCE PROMOTION

7. As measured by IMS4, the overall number of representative calls has fallen in recent years (−6% over five years). This level of effort has also been concentrated on fewer products, in part due to fewer new products being launched and corporate mergers. In 1999 16.3% of details were for the top 10 most detailed products. In 2003 this figure had risen to 22.4%.

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1 The Prescribing Support Unit, January 2004: National Prescribing Cost Implications of the GMS contract.
2 Variations in usage of cancer drugs approved by NICE: Report of the review undertaken by the National Cancer Director
3 http://www.nice.org.uk/page.aspx?o=202198
4 Representative details are measured using a panel of 200 doctors per quarter who record the number of representative details they receive and the messages communicated. This is projected to a national total.
THE EFFECT OF SALES FORCE PROMOTION

8. Variation in the costs and volume of GP prescribing is often put down to industry promotion. Certainly studies have long shown that industry representatives are a primary source of information on new products. The causes of prescribing variation cannot, however, be so simply explained.

9. A recent study found that about a third of the variation in prescribing can be explained by differences in the breakdown of a practice’s list by age, sex and temporary resident status. More than a third of the remainder can be explained by the differences in the proportion of patients on low incomes. NHS Scotland’s Information Services Division also pointed out in their report on the allocation of resources to English regions that other factors such as the number of GP partners, and the distance the patient must travel to surgery or hospital also have a part to play.

10. Nonetheless it is clear from the IMS analysis of the three examples set out in the table below that representative promotion of NICE approved products can have a supportive effect. The growth of prescriptions in those doctors who received calls from representatives was larger than in those doctors who had not received any calls. Significantly, moreover, in a separate analysis done for NICE by an independent health economics agency using another of IMS databases, there was no evidence that, in the example common to both analyses, the increase in prescriptions was inappropriate. The increase in prescribing occurred in patients with the relevant risk factors. From these analyses it can be seen, therefore, that representative promotion has the ability to counter any tendency to under use appropriate medicines.

<table>
<thead>
<tr>
<th>Product 1—GPs thought to be interested</th>
<th>0.11</th>
<th>0.22</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPs receiving no calls by representatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPs called on by representatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product 1—GPs thought to be less interested</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Product 2</td>
<td>3.02</td>
<td>7.75</td>
</tr>
<tr>
<td>Product 3</td>
<td>3.7</td>
<td>4.8</td>
</tr>
</tbody>
</table>

11. The IMS evidence below also indicates that the influence of the representative can be an effective support for NHS decisions. At the same time it is clear from the same analysis that it can be difficult for representatives to have an effect where local opinion is not favourable.

| Market share (%) at end of study period for Product A where Hospital opinion was: |
|----------------------------------------|-----------------|-----------------|
| GPs not seen by rep | No endorsement | Low endorsement | High endorsement |
| 1.72 | 2.21 | 4.63 |
| 5.6 | 4.17 | 8.36 |
| GPs seen by rep |                      |                  |                  |

| Market share (%) at end of study period for Product A where PCT opinion was: |
|----------------------------------------|-----------------|-----------------|
| GPs not seen by rep | Negative | Neutral | Positive |
| 1.25 | 2.00 | 3.92 |
| GPs seen by rep | 2.96 | 4.02 | 6.31 |

12. It is also clear that doctors exercise their own judgement. In all the cases of NICE approved products where the prescribing of competitor products was examined by IMS, representative promotion was supportive of the therapeutic class, not just the brand.

13. In the case described in more detail below, moreover, representative promotion also appeared to be associated with an increased level of use of older, and the less expensive, products. This phenomenon may be due to one of three factors, or a combination of all three:
— a “halo” effect whereby discussions about the therapy area encourages doctors to pursue new treatment patterns;
— doctors receive information from other representatives to ensure a balanced view;
— representatives focus mainly on those doctors with the highest opportunity, or interest, to prescribe or treat particular diseases.

6 Prescribing Support Unit: Personal communication.
7 Allocation of Resources to English Areas. ISD Consultancy Services 2002.
8 http://www.nice.org.uk/page.aspx?o=202198
### Summary

14. Based upon the evidence analysed above, representatives do have an effect on doctors’ prescribing in general practice but this is by no means the whole story. Doctors exercise discretion. Hospitals and PCTs can constrain or promote representative impact. At the same time, within the subset of products examined here, it is clear that representative promotion has acted to support the uptake of NICE approved products or classes of drug.

### APPENDIX 4

**Memorandum by CancerBACUP (PI 7)**

1. **Introduction**

1.1 CancerBACUP is the leading national charity providing information and support to people affected by cancer. The charity’s specialist cancer nurses answer more than 60,000 enquiries a year from patients and carers on all aspects of cancer and its treatment. CancerBACUP’s services include a telephone helpline, a wide range of booklets and factsheets, an award-winning website and a network of local information centres. In addition to providing information and support, CancerBACUP works to promote patient-centred services and equitable access to high quality treatment, information and support for everyone affected by cancer.

2. **CancerBACUP Funding**

2.1 In 2002–03, CancerBACUP’s total income was £3,909,876.\(^9\) Donations from pharmaceutical companies represented less than 10% of this figure. A summary is given below of where the charity’s money comes from and how it is spent.

#### Where the money comes from

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donations from individuals</td>
<td>47%</td>
</tr>
<tr>
<td>Publication income</td>
<td>15%</td>
</tr>
<tr>
<td>Donations from charitable trusts</td>
<td>13%</td>
</tr>
<tr>
<td>Donations from companies*</td>
<td>9%</td>
</tr>
<tr>
<td>Special event and trek income</td>
<td>9%</td>
</tr>
<tr>
<td>Grants receivable</td>
<td>5%</td>
</tr>
<tr>
<td>Investment income</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>*This includes, but is not limited to, pharmaceutical companies</td>
</tr>
</tbody>
</table>

#### How the money is spent

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer support service</td>
<td>47%</td>
</tr>
<tr>
<td>Publications about cancer</td>
<td>19%</td>
</tr>
<tr>
<td>Fundraising costs</td>
<td>13%</td>
</tr>
<tr>
<td>Advocacy</td>
<td>6%</td>
</tr>
<tr>
<td>Special events and trek costs</td>
<td>5%</td>
</tr>
<tr>
<td>Publications costs</td>
<td>4%</td>
</tr>
<tr>
<td>Research and evaluation</td>
<td>2%</td>
</tr>
<tr>
<td>Marketing and communications</td>
<td>2%</td>
</tr>
<tr>
<td>Management and administration</td>
<td>2%</td>
</tr>
</tbody>
</table>

\(^9\) 2002–03 is the most recent financial year for which accounts have been finalised.
2.2 CancerBACUP seeks funding from pharmaceutical companies to pay for booklets and other publications, and for specific events and campaigns. Such funding allows the charity to spend the money donated by members of the public—which is the biggest single source of our income—on providing services directly to people affected by cancer.

3. **Policy and Guidelines on Working with the Pharmaceutical Industry**

3.1 As the UK’s leading provider of information and support to people affected by all types of cancer, CancerBACUP relies on its reputation for independence, impartiality and a commitment to the highest standards. The charity recognises that accepting funding from pharmaceutical companies is something that needs to be approached with caution. We therefore maintain a written policy and guidelines statement on working with the pharmaceutical industry. This sets out the terms under which we will accept funding from individual companies.

3.2 CancerBACUP believes it is important to maintain cooperative relationships with companies that manufacture and market cancer drugs and other treatments. We maintain relationships with a wide range of companies and are not reliant on a single one.

3.3 The charity accepts financial support from pharmaceutical companies and groups of companies if there are strong grounds for believing it will result in benefit to our service users and supporters, and if there is no attempt on the part of the company or companies to influence CancerBACUP policy or actions either explicitly or implicitly.

3.4 It is our view that relationships between CancerBACUP and individual pharmaceutical companies can and should be based on equal partnership. The charity will not enter into a relationship designed to give one company obvious competitive advantage over another, and where possible we favour the use of funding consortia based on two or more companies working together. However, CancerBACUP will enter into strategic partnerships with individual companies if these match the charity’s corporate objectives.

3.5 We recognise that patient groups and pharmaceutical companies inevitably have some shared interests. While we are not interested in profits, we are strongly committed to ensuring that people with cancer have access to the most effective, up-to-date treatments available. We would be doing the patients we seek to serve a disservice if we failed to make the case for equitable access to treatments that have been recommended as clinically and cost-effective.

4. **Endorsement of Pharmaceutical Products**

4.1 CancerBACUP supports the availability of the widest possible range of effective treatments, whether drugs or otherwise. The charity does not endorse individual treatments, of whatever kind, because we believe that people living with cancer need the widest possible range of treatment options and the freedom to integrate them as they wish. CancerBACUP seeks to encourage active partnership between patients and health professionals and the discussion of all available options, in the interests of informed choice on the part of the patient.

4.2 CancerBACUP retains full editorial control over all our publications, and we will not put ourselves in a position of appearing to promote or endorse specific products.

4.3 However, if there is widespread consensus that a particular type of treatment might be beneficial for cancer patients—if, for example, it has been recommended by the National Institute for Clinical Excellence (NICE)—then the charity has no hesitation in calling on NHS funders to make resources available to implement NICE guidance.

5. **Examples of Successful Partnerships**

5.1 Some examples of successful joint initiatives between CancerBACUP and the pharmaceutical industry are given below. These examples show that relationships with industry are not always financially based.

5.2 **Distribution of CancerBACUP helpline cards and posters**

CancerBACUP aims to let everyone affected by cancer know about our telephone helpline, which is run by specialist nurses who can answer any question about any type of cancer. However, as a medium-sized charity with limited resources, we are not in a position to pay for widespread advertising of our service.

Over the last 12 months, more than 75,000 cards and 35,000 posters giving details of the helpline have been distributed to cancer centres, GPs’ surgeries and pharmacies across the UK by sales representatives from ten major companies. There is no branding—other than the charity’s own—on any of the materials. This has helped a greater number of people gain access to CancerBACUP’s information and support than the charity would have been able to reach without this assistance.
5.3 Campaign to highlight access to treatment for advanced breast cancer

In October 2003 CancerBACUP publicised data given to the charity by Roche showing substantial regional variations in access to trastuzumab (Herceptin), a treatment recommended by NICE that can prolong the lives of some women with advanced breast cancer. The data was compiled by analysing sales of Herceptin region by region and matching this with projected numbers of patients who would be eligible for treatment.

The charity welcomed this information, which was not available from any other source, as it gave us an opportunity to highlight continued problems faced by patients who cannot obtain the treatment they need because local decision-making in the NHS conflicts with national guidance. As a result, the national cancer director undertook an investigation into access to cancer treatments recommended by NICE and produced a series of recommendations that will help ensure that more patients receive the treatment they need.

5.4 Living Everyday

CancerBACUP worked in partnership with Ortho Biotech on an information campaign called “Living Everyday” to help people affected by cancer-related fatigue gain access to an information pack on fatigue produced by the charity. CancerBACUP produced the pack in recognition of the fact that people with cancer identify fatigue as their most important untreated symptom.10

As has already been stated, CancerBACUP does not have the resources to pay for national advertising. Ortho Biotech provided a grant to enable us to advertise the information pack in the national press over a five-month period in 2001. As a result, 1,760 packs were sent out to people who responded to the advertising campaign, which was aimed specifically at people undergoing treatment for cancer.

5.5 Fringe meetings at party conferences

CancerBACUP believes that political party conferences offer an important opportunity for the charity to discuss with policy-makers and influencers the issues of greatest concern to people affected by cancer, and to increase our own understanding of the wider context in which policy-making takes place. We regularly organise fringe meetings at each of the three main party conferences to provide a forum for patient-centred debate on cancer care.

The cost of hosting and publicising these events is high for an organisation like CancerBACUP, therefore we welcome the opportunity to host fringe meetings in association with a pharmaceutical partner. We have previously worked with Aventis in this way and are currently working with Lilly. It is our practice to be open about such partnerships; the meetings are publicised as a joint initiative and the theme is agreed by both partners.

APPENDIX 5

Memorandum by the American Pharmaceutical Group (PI 13)

1. THE AMERICAN PHARMACEUTICAL GROUP

The American Pharmaceutical Group (APG) was set up in 1985 to improve understanding of the industry, and the healthcare contribution of the American companies.

The APG companies include all the major UK-based pharmaceutical companies with American parents. They account for over 35% of National Health Service (NHS) sales of prescription medicines by the UK-based industry, making it the largest national grouping in the country. As the US is the most competitive market for medicines in the world, responsible for over half of the developed world’s R&D, the APG adds a special perspective.

The aims of the APG are to:

- Ensure an overriding commitment to better patient care and information.
- Maintain a reputation and standing as a high quality, responsible and well-informed Group, making a constructive contribution to health care policy and debate.
- Advise how the UK can attract inward investment from the US.
- Take a lead role on policy issues affecting health care and pharmaceuticals, such as patient empowerment and competition.

THE INFLUENCE AND ACHIEVEMENTS OF APG COMPANIES

It is almost impossible to imagine an NHS without modern vaccines, without medicines for pain and infection, for diabetes and gastric disorders, for cancer and heart disease, and for a multitude of other conditions. It would be a service in which the large mental NHS hospitals of the 1950s—the so-called Cinderella services—would still be with us today.

This is a world that has been transformed for NHS patients. The pharmaceutical industry in general and APG companies in particular are proud of their massive contribution towards the reduction of suffering among patients in the UK. The industry has done more good for the public than probably any other sector in the country.

The APG believes that these tremendous successes should be understood, appreciated and encouraged. It is recommended that this should be the base from which the industry should be viewed by the Health Committee.

The positive aspects of the pharmaceutical’s industry’s influence can also be seen in medical education, clinical guidelines and supporting non-directed research.

All APG companies will do even more for patients in the future. Advances in all the main diseases will flow from APG research and innovative medicines, assuming that the right conditions for the industry are provided. If the right conditions are absent, the industry will suffer but, more to the point, so will a large section of the patient population.

2. INFLUENCE THROUGH PUBLIC/PRIVATE PARTNERSHIPS

The APG has always welcomed and supported the principles of co-operation and partnership between the private sector and the NHS, within a framework in which the service to the NHS patient remains almost entirely free at the point of delivery and is based on clinical need. This co-operation is very true of the pharmaceutical sector, but has been greatly extended in recent years and has very often involved companies with US parents.

This was illustrated by the present Government bringing in the private sector to work with the public sector in the design and construction of new NHS hospitals and healthcare centres, to such an extent that currently 90% of new hospital schemes now operational under the NHS Plan were delivered under the Private Finance Initiative.

However co-operation does not stop there. 80 Treatment Centres will provide at least 250,000 additional NHS operations a year by end-2005, almost half of them provided by the private sector; and extra use of the independent sector is being made by the NHS, particularly in orthopaedics.

In many ways, the pharmaceutical industry has been the trail-blazer in this development. Co-operation with Government was developed in the 1990s through the Ministerial Industry Strategy Group and later through the Pharmaceutical Industry Competitiveness Task Force. This has helped provide the stability and understanding that is required.

In addition, co-operation on the ground has been achieved by APG companies working with the NHS on such projects as:

— A personal development programme for Mental Health Act Commissioners.
— Palliative care pain management for advanced and/or metastatic cancer.
— Nutritional screening of older patients.
— Review of medications by pharmacists and improving prescribing for over 65s.
— Implementing medicines-taking concordance.
— An induction programme for Primary Care mental health link workers.

The boundaries between the public and private sectors are being blurred in these areas, so that a more balanced approach to the policy-making and delivery of healthcare is being achieved.

3. THE CHALLENGE TO THE UK-BASED INDUSTRY

Yet despite the strengths of the UK-based pharmaceutical industry, of which the APG is a leader, and the co-operative approach between the industry on the one hand and the Government and the NHS on the other, the future of the pharmaceutical industry in this country cannot be taken for granted.

The biggest rival to the UK is no longer found in the continent but across the Atlantic. The last decade has seen a significant shift in the pharmaceutical industry away from Europe and in favour of the US:

— Europe was responsible for discovering 97 new molecular entities between 1988–92 but, by 1998–2002, this had fallen to 68. Over the same periods the US numbers rose from 52 to 77, overtaking Europe (source: July 2003 G10 Medicines Conference).
— Between 1990 and 2002 pharmaceutical spending in Europe on R&D rose from €7,941 million to 
€19,800 million; but over the same period spending in the US rose from the €5,342 million to an 
enormous €27,890 million, far above the level of Europe (source: ibid).

— Europe accounted for 37.8% of the world pharmaceutical market in 1990, falling to 25.4% in 2002. 
By contrast, the percentage for the US and Canada rose from 31.1% to 50.9% over these years 
(IMS World Review 2003 and IMS Consulting).

The consequences of a further decline of the industry in the EU are that competitive R&D resources are 
reduced, which means slower development of new medicines and hence a lower standard of care for patients 
than would otherwise be the case. The EU and the UK in particular would also carry less weight in the global 
pharmaceutical economy and hence in their international work on access to medicines in developing 
countries.

Low utilisation of new medicines

There are specific areas of concern in the UK. Out of 10 comparator developed countries (Australia, 
Canada, Germany, France, Italy, Japan, Switzerland, UK and US), the UK had the lowest take-up of new 
medicines launched within the last five years, and the proportion is falling. On current trends, the UK has 
been already or soon will be overtaken soon by Japan, the only country with a worse record, so UK patients 
will receive more dated medicines than any other comparator country. (PICTF Indicators 2003, published 
April 2004)

One aspect (but only one aspect) of this poor take-up is the persistence of postcode prescribing across the 
NHS, although NICE was established in part to eliminate this. All patients should have the right to know 
about the best medicines that are available and to receive them, so that postcode prescribing is eliminated. 
However patients suffering from diseases such as cancer and rheumatoid arthritis, and conditions like 
schizophrenia, and many others, are not receiving the medicines they need. Professor Mike Richards, the 
NHS Cancer Director, has found that although variation in usage of cancer drugs lessens over time:

... it does exist across the country and cannot be accounted for by differences in casemix and, for 
most drugs, is unlikely to be accounted for by cross boundary flows alone. (Report of the review 
undertaken by the National Cancer Director, June 2004)

4. RELATIONS WITH VOLUNTARY BODIES AND HEALTH PROFESSIONALS

The APG takes seriously its relations with voluntary bodies, which are open and transparent.

APG member companies believe that patients are entitled to and should receive proper information, as 
allowed by law. Patients increasingly expect this and that a new generation of “informed patients” is on the 
rise. The All-Party support given to this concept is welcome.

There is a commonality of purpose in informing patients between voluntary bodies and APG member 
companies. Both sides work together towards a common aim, to empower patients and their families, 
putting into practice the aims of patient information.

The APG abides by the Association of the British Pharmaceutical Industry’s (ABPI) Code of Practice, 
(April 2003, Clause 19) which requires that:

— There must be a declaration of sponsorship of meetings and in related papers.
— Meetings must have a clear educational content.
— The hospitality associated with meetings must be secondary to their nature.

The APG endorses the Guidelines set out in June 2000 by the Long-term Medical Conditions Alliance, 
which includes the following statement:

We encourage the use of available funding so long as the [Voluntary Health Organisation’s] 
independence is not compromised in any way and so long as there is total transparency in the 
relationship. Contracts between the parties are helpful in this respect, and indeed are sometimes 
required by law.

In its dealings with health professionals, APG members are governed by the ABPI Code of Practice. All 
APG members belong to the ABPI. The Committee may wish to note that this Code of Practice was created 
almost half a century ago, goes beyond UK legal requirements, is widely regarded as successful and effective, 
and is regularly reviewed and updated.

APG members are also members of the Pharmaceutical Research and Manufacturers of America (PhRMA), 
and abide by its strict Code on the Interactions with Healthcare Professionals (July 2002) in 
relation to marketed products and related pre-launch activities.
5. **Clinical Trials**

All clinical trials are made available by APG companies to the licensing authorities so that they can judge the safety, quality and efficacy. Information is also made available to health professions through scientific journals and medical publications.

The APG is attracted by the concept of a publicly available register of late-stage clinical trials, on the grounds that patients should have more information about medicines. This could be achieved by building upon the ABPI Clinical Trials Register.

This should be in respect of licensed medicines, as those which fail to obtain approval are of most interest only to competitors and might deter companies from testing products in sensitive areas if publication was obligatory.

However there are some serious issues to be resolved:

- Whether the trials registered should include not just those carried out in the UK, but should be extended to all trials in the EU and, in the medium term, to those elsewhere. After all, the industry is a global one.
- Achieving agreement with the potential audiences on what information is most useful. For the general public and healthcare professionals not participating in trials, a short summary of the final data may be of value, with any database being most effective if the details to be included are agreed across the industry. For patient participants in clinical trials, the existence of plans for certain studies may be important, and the opportunity to participate in such studies is a clear benefit from early awareness.
- Whether the writing and circulation of summaries of clinical trials should be drafted and made available by the companies themselves or by a responsible third party (perhaps at European Union level). The perceptions of the public would be an important factor.

**APPENDIX 6**

**Memorandum by the Prescription Medicines Code of Practice Authority (PI 14)**

**Summary**

1. The importance the pharmaceutical industry places on its relationships with health professionals and others with regard to promotion and other activities is demonstrated by The Association of the British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry (current edition 2003) and the transparency of the complaints procedure. The ABPI Code has the support of the Medicines and Healthcare products Regulatory Agency (MHRA) and health professional organisations. Many countries have used it as a model for their own codes. Companies not in membership of the ABPI can agree to comply with it and most do so. Health professionals are aware of the Code and submit complaints as do pharmaceutical companies and others. The complaints system gives equal status to the complainant and the respondent. Both parties have the right to appeal and to attend appeal hearings. Publication of virtually a complete record of the submissions and rulings contributes significantly to effective self regulation and is a powerful sanction.

**Introduction**

2. The PMCPA was established by the ABPI to administer the ABPI Code of Practice for the Pharmaceutical Industry\(^{11}\) independently of the ABPI itself. The PMCPA is also responsible for providing advice, guidance and training on the Code. The PMCPA is not part of the day to day management structure of the APB and this is explained in Paragraph 26 below. The relationship between the APB and the PMCPA is set out in a Protocol of Agreement.\(^{12}\) Neither the staff of the APB nor the APB Board of Management play any role in relation to the consideration of complaints. The APB Board has a role in relation to sanctions in serious cases once the adjudications have been made and this is explained in Paragraph 30 below. Unless additional sanctions are necessary the first notification from the PMCPA of the outcome of complaints is when consideration of the case is completed and the PMCPA circulates to the APB Board draft case reports prior to their publication. The PMCPA is regarded as a body that carries out a public law function and is thus subject to judicial review.

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\(^{12}\) Protocol of Agreement between the Prescription Medicines Code of Practice Authority and The Association of the British Pharmaceutical Industry. Available from the PMCPA.
3. The ABPI Code covers the promotion of medicines for prescribing to health professionals and appropriate administrative staff and also covers information about such medicines made available to the general public. It also applies to a number of non-promotional areas. The ABPI Code does not cover the promotion of medicines for purchase by the general public; this is covered by codes established by the Proprietary Association of Great Britain.13

4. The ABPI Code aims to ensure that the promotion of medicines is carried out in a responsible, ethical and professional manner. It seeks to achieve a balance between the needs of patients, industry, health professionals and the general public. The ABPI Code is drawn up in consultation with the British Medical Association (BMA), the Royal Pharmaceutical Society of Great Britain (RPSGB) and the MHRA. The ABPI Code has been regularly revised since its inception in 1958, currently a new edition is agreed approximately every two years. The ongoing review of the Code and its operation will take into account a current European wide review of codes of practice and the conclusions of the Health Select Committee Inquiry.

5. Compliance with the ABPI Code is a condition of membership of the ABPI. About 60 companies which are not members of the ABPI have also agreed to comply with it. The ABPI Code thus covers most of the relevant companies in the UK.

6. The ABPI Code reflects, extends and provides detailed guidance above and beyond the UK legal requirements, which were first introduced in the Medicines Act 1968. The UK legal requirements are now based primarily on a European Directive.14 The European Directive and UK law allow for voluntary control by self regulatory bodies and recourse to such bodies in addition to statutory control. The MHRA’s stated view is that the control of medicines advertising is based on the long established system of self regulation which it sees as working successfully in the UK and that the statutory powers are to underpin and support self regulation, providing a means of enforcement should self regulation fail.15 The role of the MHRA is restricted to the administration of UK law which covers the promotion of medicines for prescribing and the promotion of medicines for purchase by the general public. The MHRA occasionally forwards complaints to the PMCPA for consideration under the ABPI Code.

THE PROVISION OF DRUG INFORMATION AND PROMOTION

7. The ABPI Code applies to the activities of pharmaceutical companies and covers promotion in whatever form, whether it be printed, verbal or electronic as set out in Clause 1.2 which defines promotion as any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines. Exemptions are also set out in Clause 1.2 and include those in the European Directive. The Code of Practice booklet includes supplementary information giving guidance on interpretation of the Code, guidelines on company procedures which represent good practice, and the Constitution and Procedure for the PMCPA, which sets out how the Code is operated together with the sanctions.

8. Pharmaceutical companies are required by Clause 7.1 of the Code to promptly provide health professionals and appropriate administrative staff upon reasonable request with accurate and relevant information about the products they market.

9. Clause 3 states that medicines cannot be promoted before they have been granted a marketing authorisation which permits their sale or supply and that promotion must not be inconsistent with the summary of product characteristics (SPC). Clause 7.2 requires information, claims and comparisons to be accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of the evidence and reflect that evidence clearly. Material must not mislead either directly or by implication. Material must be capable of substantiation and substantiation must be provided on request from a health professional or appropriate administrative staff unless the request relates to the validity of the indications approved in the marketing authorisation (Clauses 7.4 and 7.5). When material refers to published studies references have to be cited (Clause 7.6). Data on file when used as a reference has to be supplied on request (Clause 7.7). Artwork including graphs and tables must comply with the Code (Clause 7.8). It must not be stated that a product has no side effects, toxic hazards or risks of addiction. The word safe cannot be used without qualification (Clause 7.9). There are restrictions on the use of the words “the”, “unique” and “new” (Clauses 7.10 and 7.11).

10. Prescribing information (a succinct summary of relevant information in the SPC together with the cost and legal classification) in accordance with Clause 4.2 must be provided in all promotional material unless the material is an abbreviated advertisement (Clause 5) which is an advertisement limited in size, content and use, or the item is a promotional aid as described in Clause 18. The non-proprietary name has to appear immediately adjacent to the most prominent display of the brand name in a specified size (Clause 4.3). The Code limits journal advertising such that no journal advertisement can be more than three pages long and no issue of a journal may bear advertising for any one product on more than three pages, including inserts (Clause 6).

11. Extremes of format, size or cost must be avoided (Clause 9.7) and promotional material should only be distributed to those persons whose interest in the material can reasonably be assumed (Clause 12.1).

12. Clause 15 sets out the requirements for representatives, including that they must maintain a high standard of ethical conduct. The Code applies to what representatives say and do as well the materials they use. The Code prohibits the use of any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview. There are limits on the frequency of visits by one representative to an individual doctor. Representatives have to inform their companies about any information received which relates to the use of the medicines they promote and must carry or have available the relevant SPCs. Companies must prepare detailed briefing material for representatives on the technical aspects of their medicines and how they are to be promoted. This material is requested by the PMCPA when a complaint is made about what a representative has said.

13. Clause 16 sets out the training requirements. All relevant personnel must be fully conversant with the requirements of the Code and representatives must pass an examination within two years of commencing such employment.

14. A sample is defined in Clause 17 as a small supply of a medicine for the purpose of familiarisation and acquiring experience. The provision of samples is limited to no more than 10 samples per year per product per health professional qualified to prescribe the product. Samples can only be supplied in response to a signed and dated written request. Companies have to comply with individual hospital arrangements and have systems of control and accountability.

15. Clause 18 prohibits the provision or offer of any gift, benefit in kind or pecuniary advantage as an inducement to prescribe, supply, administer, recommend or buy any medicine apart from promotional aids and competition prizes. Promotional aids must be inexpensive, cost the company no more than £6 plus VAT, and be relevant to the recipient’s profession or employment. Competitions must be a genuine test of skill and prizes must be few in number, relevant to the recipient’s profession and each cost no more than £100 plus VAT. The ABPI Code permits the provision of medical and educational goods and services to enhance patient care or benefit the NHS but these must not be an inducement to prescribe, supply, administer, recommend or buy any medicine. Detailed guidance is given in the supplementary information to Clause 18.1.

16. Clause 19 covers meetings and hospitality. All meetings, including sponsorship of scientific meetings and payment of travelling and accommodation expenses in connection with such meetings, are covered. Hospitality must only be provided in association with scientific meetings, promotional meetings, scientific congresses and other such meetings. It must be secondary to the purpose of the meeting and the level must be appropriate, with the cost not exceeding that which the recipients would normally adopt when paying for themselves. Hospitality can only be provided for persons who qualify as proper delegates in their own right.

17. When meetings are sponsored by pharmaceutical companies this must be disclosed in all the papers relating to the meeting (Clause 19.3). Material relating to medicines and their uses, whether promotional or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. There is an exemption for market research which needs to state that it is sponsored by a pharmaceutical company (Clause 9.10).

18. Companies are required to formally certify promotional material in its final form before it is issued, as set out in Clause 14. Companies are also required to certify all meetings which involve travel outside the UK. Certification is undertaken by two nominated signatories, one of whom must be a registered medical practitioner and the other must be some other appropriately qualified person, often a pharmacist. The names of the signatories have to be provided in advance to the PMCPA and the MHRA. The certificate for promotional material must certify that the signatories have examined the material in its final form and that in their belief it is in accordance with the Code and the relevant advertising regulations and it is not inconsistent with the marketing authorisation and the SPC. Companies are advised to examine non-promotional material, such as press releases, market research, financial information for shareholders, the stock exchange and the like to ensure that it is non-promotional. The use to which an item will be put is also an important consideration. Certificates and other details have to be preserved for not less than three years after final use of the material and be produced on request from the PMCPA and/or MHRA.

19. In addition to the clauses mentioned above, there are requirements that high standards must be maintained at all times and that material and activities must recognise the special nature of medicines, the professional nature of the audience and must not be likely to cause offence (Clauses 9.1 and 9.2). Clause 2 of the Code is used as a sign of particular censure. It states that activities or materials associated with promotion must never be such as to bring discredit upon or reduce confidence in the pharmaceutical industry. Any breach of the Code is seen as a serious matter, but a breach of Clause 2 is seen as a particularly serious matter.
PROFESSIONAL AND PATIENT EDUCATION

20. If education for health professionals is promotional in nature then it is clearly covered by the Code. The legitimate exchange of medical and scientific information during the development of a medicine is not prohibited, provided such activity is not promotional (Clause 3).

21. Patient education is covered by Clause 20 which deals with relations with the general public.

22. Medicines must not be advertised to the general public if they are prescription only medicines or may not legally be advertised to the public. There is an exemption for vaccination campaigns approved by the Health Ministers. Companies can provide information both to patients and to the public provided it meets the requirements of Clause 20.2. Information must be factual, presented in a balanced way and must not raise unfounded hopes of successful treatment or be misleading with respect to safety of a medicine. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. European public assessment reports, SPCs, and package leaflets may be provided to members of the public on request and may be made available on websites. Companies can also provide materials about a medicine to patients who have already been prescribed that medicine, provided that such material is factual and non-promotional. Companies may conduct disease awareness or public health campaigns provided the purpose is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine. Particular care needs to be taken where a company’s product, even though not named, is the only medicine relevant to the disease or symptom.

23. The Code also covers the Internet. Sites that are open access, ie available to all, must comply with Clause 20 of the Code ie no promotion of prescription only medicines to the general public. Websites with access restricted to health professionals may include advertising that complies with the Code.

THE CONDUCT OF MEDICAL RESEARCH

24. Clinical research is comprehensively covered by law. The only relevant requirement in the Code is Clause 10 that clinical research and the like must not be disguised promotion.

ADDITIONAL POINTS

Source and outcome of complaints

25. Complaints submitted under the ABPI Code come from three main sources: health professionals (40 (30%) of the 131 complaints received in 2003); companies (46% of complaints received in 2003) and those nominally made by the Director of the PMCPA (17% of complaints received in 2003). The Director takes up public criticisms of the industry such as published articles and the like. Companies occasionally make voluntary admissions to the PMCPA and anonymous complaints are considered. The 131 complaints received in 2003 led to 122 cases for consideration, some complaints related to matters not subject to the Code (no prima facie case) and others were withdrawn. Of the 122 cases considered in 2003, 97 (80%) were found in breach of the Code and 20% were found not to be in breach. Cases often consist of more than one allegation. In 2003, 366 allegations were considered with 208 (57%) ruled in breach and 43% ruled not in breach. In 2003, of the 65 rulings appealed 45 (69%) were unsuccessfully appealed and 20 (31%) were successfully appealed. Comprehensive information is published in the PMCPA Annual Report. The PMCPA also carries out a regular scrutiny of advertisements and raises matters with companies which are usually settled without recourse to a formal complaint.

CONSTITUTION AND PROCEDURE

26. Complaints are first considered by the Code of Practice Panel, which consists of the Director of the Authority, Heather Simmonds (pharmacologist), the Secretary, Etta Logan (solicitor) and the Deputy Secretary, Jane Landles (pharmacist). The PMCPA is appointed by and reports to the ABPI Board of Management but it is not part of the day to day management structure of the ABPI. The Director of the PMCPA reports to the Code of Practice Appeal Board for guidance on the interpretation of the Code and the operation of the complaints procedure and to the President of the ABPI for administrative purposes.

27. The Panel considers each case on written evidence only and has access to expert assistance such as a medical opinion. The parties are provided with full details including the outcome. Both the complainant and the respondent can appeal the Panel’s rulings to the Code of Practice Appeal Board; both see all relevant submissions and are entitled to attend or be represented at an appeal. Appeals can however be on the basis of written documents only. The Appeal Board has two roles, to hear appeals and to supervise the activities of the Panel. The Appeal Board is made up of 19 members including an independent legally qualified Chairman, Mr Nicholas Browne QC. In addition there are six other independent members: three medically qualified; one a pharmacist; one representative of the interest of patients and one from an independent body involved in providing information on medicines. All independent members are appointed in consultation.

with the MHRA and, in addition, the BMA for the medical members and the RPSGB for the pharmacist member. The remaining 12 members are from pharmaceutical companies, four medical directors or equivalent and eight senior executives. All members of the Appeal Board are appointed by the ABPI Board of Management. The Appeal Board also receives details of all cases completed at the Panel level.

SANCTIONS

28. In each case where a breach is ruled, the chief executive of the company concerned must give an undertaking that the practice in question will cease forthwith, if it has not already ceased, and that all possible steps have been taken to avoid a similar breach in the future. This means that materials have to be recalled immediately and destroyed. Companies cannot wait until replacement material is available. Companies are required to comply with undertakings given (Clause 22). The major sanction is the publication of comprehensive reports on all completed cases in the Code of Practice Review which is published quarterly, widely circulated and freely available to all. The medical and pharmaceutical press frequently publish details of cases and occasionally details appear in the national press. Additional sanctions are imposed in serious cases.

29. The additional sanctions available to the Appeal Board include a requirement to recover items given in connection with the promotion of a medicine and a requirement for a company to undergo an audit of its procedures in relation to the Code, together with the ability to impose requirements on the company concerned to improve its procedures. The Appeal Board rarely requires recovery of items ruled in breach, although this sanction has recently been used in relation to a complaint made in 2003. Two of the complaints received in 2003 were the subject of an audit. This involves the Director of the PMCPA and either the Secretary or Deputy Secretary conducting an in depth analysis of the company’s procedures for complying with all aspects of the Code including interviews with the chief executive, medical director, registered signatories and other employees, including a representative. A detailed report with recommendations is considered by the Appeal Board which can require a reaudit to check that the recommendations are implemented.

30. The additional sanctions available to the ABPI Board of Management include a public reprimand, audit (as for the Appeal Board), publication of a corrective statement and suspension or expulsion from the ABPI, or, for a company not a member of the ABPI, to advise the MHRA that responsibility for that company under the Code can no longer continue to be accepted. A public reprimand takes the form of an article on the front page of the Code of Practice Review and is often reported by the medical and pharmaceutical press. Arising from the complaints considered in 2003 one company was publicly reprimanded. It is more usual for audits to be required by the Appeal Board, although in 2003 the ABPI Board of Management required a company to undergo a reaudit in relation to a complaint considered in 2002, the initial audit having taken place in 2002. The ABPI Board has never required a company to publish a corrective statement nor has a company been expelled from membership of the ABPI. Companies have been suspended from membership of the ABPI, but this sanction has not been used since 1993. Two companies have been removed over time from the list of non-member companies complying with the Code.

FINANCES OF THE AUTHORITY

31. Administrative charges are paid by pharmaceutical companies ruled in breach of the Code and companies which make unsuccessful complaints. The charges are £1,250 per matter if a case is settled at the Panel level and £5,000 per matter if an appeal is unsuccessful. No charges are paid by complainants outside the pharmaceutical industry. Administrative charges are not regarded as being fines.

32. The PMCPA is self financing with its income coming from an annual Code of Practice Levy paid directly to the PMCPA by members of the ABPI, administrative charges and charges for attending seminars on the Code. Further details appear in the Annual Report and the Protocol of Agreement.

APPENDIX 7

Memorandum by the Association of Information Officers in the Pharmaceutical Industry (PI 15)

1. INTRODUCTION

The Association of Information Officers in the Pharmaceutical Industry (AIOPi) is the professional organisation for individuals in the pharmaceutical industry who are involved in the provision and management of information. It represents members from most pharmaceutical companies in the UK, including all the major research-based companies. Members are involved in a range of roles, but the following are of particular relevance to the Health Committee’s inquiry:

17 Code of Practice Review. Published quarterly and available from the PMCPA.
Medical Information

Medical Information departments provide evaluated information on clinical aspects of medicines to healthcare professionals (e.g., physicians, pharmacists and nurses) and to patients. The information provided is obtained from published literature such as reports of clinical trials, and from unpublished data held by the company, such as details of the formulations of medicines.

Pharmacovigilance

Pharmacovigilance is the process of monitoring the safety of medicines and collecting and analysing reports of possible side-effect. Pharmacovigilance departments provide information to healthcare professionals to aid safe and effective use of medicines.

AIOPI is making this submission in order to provide information relevant to the Health Committee’s terms of reference concerning the pharmaceutical industry’s role in:

— the provision of drug information and promotion;
— professional and patient education;
— regulatory review of drug safety and efficacy.

2. Provision of Information about Medicines and Promotion

Medical Information and Pharmacovigilance departments in pharmaceutical companies provide factual, verifiable information about medicines to healthcare professionals, and to patients when appropriate. Information is usually supplied in response to inquiries; it is not sent proactively as a form of promotion.

Research-based pharmaceutical companies have more information about the medicines that they market than any other source. They have information about the efficacy and safety of these medicines from the pre-clinical studies, clinical trials, and safety studies that have been carried out and they may have access to information from studies still in progress. It is essential for the appropriate and safe use of medicines that health professionals have access to all relevant information. It is a difficult and time-consuming task for them to find the information that they need from the many medical and scientific journals in which clinical trials, case reports, reviews, adverse event reports and other clinical information are published. In addition, especially when a new medicine is first available, some of the information may not yet have been published. Medical Information and Pharmacovigilance departments play a crucial role in supporting health professionals by finding and supplying the published information and unpublished data that they need. In this way they also help to ensure safe, appropriate use of medicines for patients’ benefit.

The value of these information services has been confirmed in surveys carried out by NHS hospital pharmacists of pharmaceutical companies’ Medical Information departments (1). In the most recent survey, performed in 2003, pharmacists across the country contacted company Medical Information departments on 239 occasions on a single day (see http://www.aiopi.org/attachments/UKMIExec.pdf). The most common reasons for contacting the Medical Information departments were:

— the company was the only source of the information needed (47% of cases);
— the company was a more comprehensive source of information than other sources (37% of cases);
— it was quicker to obtain information from the company than from alternative sources (10% of cases).

The importance of the service provided by Medical Information departments is emphasised by the fact that in over 70% of cases, the information requested by pharmacists in this survey directly or indirectly affected patients’ treatment. Pharmacists rated the knowledge and competence of the Medical Information departments as excellent or good in 86% of cases.

Medical Information and Pharmacovigilance departments operate to high standards. The activities of Pharmacovigilance departments in collecting and reporting details of possible side-effects of medicines are governed by statutory and regulatory requirements and are subject to regular audits to ensure compliance. Appropriate standards for the provision of information services by Medical Information and Pharmacovigilance departments are set out in AIOPI’s UK Guidelines on Standards for Medical Information Departments (see Annex). A fundamental principle, which also accords with the ABPI Code of Practice, is that information supplied must be accurate, fair, objective, unambiguous and up to date and must reflect all the available evidence clearly.

Particular care is taken in dealing with requests from patients. AIOPI’s Guidelines on Standards for Medical Information Departments state that such inquiries must be answered with care and judgement. Departments may provide factual, non-promotional information about a medicine. However, if a patient requests advice about his or her treatment, or information outside the scope of the relevant Summary of Product Characteristics or Patient Information Leaflet, he or she will be recommended to consult a doctor, pharmacist, or other healthcare professional as appropriate.

It should be clear from the above that pharmaceutical companies, through their Medical Information and Pharmacovigilance departments, provide non-promotional information about their medicines that is essential for the safe, effective and appropriate use of those medicines.
3. **Professional and Patient Education**

The pharmaceutical industry plays an important role in educating health professionals and patients about medicines. As discussed in the previous section, research-based companies have more information about their medicines than any other source. It is appropriate that this information is made available in the form of educational programmes and materials to help health professionals to use medicines appropriately.

Medical Information and Pharmacovigilance departments have a role in many companies in the production of educational items such as monographs and other factual material on new products for health professionals. They may also be involved in production of material for patients such as patient information leaflets.

The aim of educational materials is to provide evidence to health professionals to help them in assessing a medicine, or to provide helpful information to patients who have been prescribed the medicine. As is the case when handling inquiries, Medical Information and Pharmacovigilance departments operate to high standards and the information in educational materials must be factual and must reflect the available evidence.

4. **Information Provided in the Review of Drug Safety and Efficacy**

Pharmacovigilance departments play an essential role in the review of the safety of medicines. They are responsible for collecting case reports of possible side-effects (adverse events) and for submitting such reports to the Medicine and Healthcare Products Regulatory Agency (MHRA) in the UK and equivalent bodies in other countries. Companies' Pharmacovigilance departments analyse these reports in order to assess any risks associated with a medicine, identify new side-effects or detect altered patterns of side-effects. This information is provided to health professionals to help ensure that patients are not exposed to unnecessary risks. If severe side-effects are discovered, or if the risk/benefit profile of the drug is altered a company will act promptly to notify the MHRA and doctors.

It is a key requirement of Pharmacovigilance departments that they act ethically and in accordance with statutory requirements. There are requirements in the UK and other countries that companies must report serious side-effects to the relevant regulatory bodies promptly within specific deadlines. Companies devote much effort to ensure that these requirements are observed. They have standard operating procedures to ensure that staff understand their responsibilities, and all staff involved in pharmacovigilance undergo extensive training.

Pharmaceutical companies do not wish patients to be harmed by their medicines. The information provided by Pharmacovigilance departments to health professionals can help to ensure that risks are minimised and that, if side-effects do occur, the best available information is provided to help the health professional and patient decide on the most appropriate course of action.

5. **Conclusion**

The information services provided by the pharmaceutical industry through its Medical Information and Pharmacovigilance departments are of significant help to the NHS. They provide factual information that may be difficult or expensive to find through other sources or that may not be available elsewhere. These departments operate to high professional standards in accordance with the AIOPI guidelines, the ABPI Code of Practice and statutory requirements.

The industry advertises its products and promotes their appropriate use. Such promotion is governed by the requirements of the Medicines Act and the ABPI Code of Practice. The activities of Medical Information and Pharmacovigilance departments are non-promotional in nature and their value to healthcare professionals has been endorsed by the UK Medicines Information Pharmacists Group within the NHS.

**Reference**

INTRODUCTION

High quality up-to-date information about medicines is essential for their safe and effective use in treating patients. Pharmaceutical company medical information departments are a leading source of such information, including information that is not available from other sources. The importance of this role is recognised in the ABPI Code of Practice* (Clause 13) which states that companies must have a scientific service which is responsible for information about medicines which they market.

Appreciating the need for high standards in the provision of medical information, AIOPI has drawn up the following guidelines after consultation with key customers. The original guidelines were written in 1995 with the latest revision in 2004.

Adherence to the guidelines is necessarily voluntary. They are however recommended to all companies as representing practicable standards indicative of a high quality of service in medical information.

ACCESS TO THE MEDICAL INFORMATION SERVICE

— Companies must have a clearly identified resource to deal with medical, pharmaceutical and technical enquiries.
— The telephone number(s) of the medical information service should be advertised in appropriate publications such as the ABPI Medicines Compendium, MIMS, the British National Formulary (and their electronic versions), and the UK Company website. Where appropriate, a direct-dial number to Medical Information should be used.
— Any medical information provided via either an open or password protected website should comply with these guidelines and with the ABPI Code of Practice.

PROCEDURES FOR HANDLING ENQUIRIES

— Procedures should be in place to ensure that customers are routed to the appropriate department as rapidly as possible.
— Procedures should be in place for answering enquiries from healthcare professionals, from patients and the public, and from other groups, eg press, police, coroners and solicitors.
— Letters, faxes and e-mails must be read promptly and dealt with appropriately. Where possible e-mails should be acknowledged promptly.
— A standard procedure should be in place for handling telephone calls covering:
  — Speed of response—calls should be answered with minimal delay. The use of answering machines, voice-mail and interactive voice routing (IVR) systems to deal with medical information enquiries should be avoided. However, if direct-dial answering machines or voice-mail systems are used, there must be an automatic re-routing facility or alternative number for callers to obtain an immediate response in emergencies. If IVR systems are used, the menus should be kept to a minimum.
  — Identification of the person answering the call—it must be made clear immediately to the caller whether he/she is talking to a person who will be able to answer the enquiry or to someone who will take a message. Where company policy permits, it is recommended that medical information staff identify themselves to customers by first name only.
  — Manner—persons answering telephone calls must at all times be helpful, courteous and easily understood.
  — Enquiry details—staff should be appropriately trained and/or use prompt lists when taking details of telephone enquiries to help ensure that they are properly understood and that sufficient details are taken.
  — Call transfers—transferring calls inconveniences callers and should be avoided or, if essential, kept to the absolute minimum (ideally no more than one transfer within or from the department). Relevant details should be provided to the recipient of the call.

— Putting customers “on hold”—if it is clear that it may take longer than two minutes to answer the customer’s question, then he/she should be told this and given the option of holding or being rung back by an agreed time.

— Return calls—if a return call has to be made to the enquirer a deadline for this must be agreed and adhered to.

— Cover—there must be a procedure to ensure that appropriate staff are available or can easily be contacted throughout office hours, including lunch times, and that deputies are available when staff are out of the office eg during holiday periods. An appropriate procedure must also be in place to deal with emergency out-of-hours enquiries (evenings, weekends, public holidays etc).

— All reasonable steps must be taken to identify enquirers, who should be answered in accordance with their status or profession.

— A policy should be agreed with the company’s legal department on the length of time, types of enquiries and what level of detail should be retained for legal, regulatory audit and potential litigation purposes. Such records may include:
  — details of the enquirer;
  — the nature of the enquiry;
  — when it was received;
  — the degree of urgency;
  — referral to other departments or individuals;
  — details of information provided;
  — who provided the information and when;
  — any follow-up.

**Supply of Information to Healthcare Professionals**

— Companies should have a procedure to ensure the most current prescribing information is displayed in relevant hardcopy and electronic publications. Details of changes to Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) should be sent to publications such as the electronic Medicines Compendium website (www.medicines.org.uk), MIMS and electronic MIMS (www.emims.net), BNF, Chemist & Druggist, and Pharmaceutical Journal. Additional methods of supplying SmPCs and PILs to healthcare professionals and the public (eg post, via representative, e-mail, Internet) may be used as appropriate and as permitted by current legislation and codes of practice.

— To facilitate safe dispensing of products, all healthcare professionals involved in dispensing, including community pharmacists, require prior warning of new product launches. It is standard practice for companies to send letters to wholesalers, after licence but before launch, to enable stock purchase. Companies should also circulate wholesaler letters to groups such as the National Pharmaceutical Association (www.npa.co.uk) and the UK Medicines Information network (www.ukmi.nhs.uk). All letters should be accompanied by full prescribing information and PIL where possible.

— When products are discontinued, changed or divested, medicines information centres (www.ukmi.nhs.uk) must be promptly notified directly or via the pharmaceutical press. In the case of divested products a procedure must be agreed for transfer of information to the new owner to enable that company to maintain an adequate medical information service. For discontinued products, the DoH/ABPI Best Practice Guidelines for discontinuation should be followed (www.doh.gov.uk/discontinuedmedicines/discontinuedmedicines.pdf)

— A procedure should be in place to notify appropriate medical staff and pharmacists of urgent important information, eg availability, contra-indications, warnings and adverse effects. All such letters/notices should be sent to all UK Medicines Information centres.

— Requests from external customers for information relating solely to another company’s product should be referred promptly to that company.

— In response to a request for advice on the treatment of an individual patient using a prescribed medicine, factual information may be given. The decision about treatment remains the responsibility of the patient’s prescriber. Medical information departments should be aware of the needs of healthcare professionals and should be as helpful as possible in sharing expertise, knowledge and information to aid decision-making. If a medical opinion is required the enquirer should be referred to a company medical adviser or other medically qualified person.
— Information provided should normally be within the terms of the product licence. However, information may be supplied in response to enquiries from appropriate health care personnel on an unlicensed drug or on the use of a licensed drug outside the terms of the product licence, provided it is made clear to the enquirer that use of the product in this way is unlicensed and remains totally the responsibility of the prescriber.

— Information on new drugs before marketing or on unlicensed products may be provided to healthcare personnel on request. Information may also be provided pro-actively to those involved in planning the introduction of new products provided that this complies with the supplementary information to clause 3.1 of the ABPI Code of Practice.

Enquiries from the Public

— People are increasingly aware of and involved in their own medical care, and information of a medical nature is becoming more accessible (eg via NHS Direct or the Internet). This means that patients who are already well informed about their condition and its treatment may be contacting companies. Their current level of knowledge about their treatment should be assessed before any information is given.

— Enquiries from the public, including patients, must be handled in accordance with the requirements of the ABPI Code of Practice (specifically Clause 20). Such enquiries must be answered with care and judgement, and a decision must be taken in each case as to whether the company can responsibly answer the enquiry.

— Factual information about a medicine may be given, but anyone requesting information or advice outside the scope of the relevant SmPC or PIL should be recommended to consult their doctor, pharmacist, or other healthcare professional as appropriate.

— Many health information and patient organisations now exist and it may be appropriate to give details to members of the public so that they may obtain more information about specific conditions. There are also a number of publicly available documents which might be appropriate eg SmPCs, PILs, EPARs (European Public Assessment Report).

— Additional information may be provided in response to public enquiries about General Sales List (GSL) or Pharmacy only (P) products. As the public are exposed to claims about efficacy, relevant factual information can be provided depending upon company procedures. However, the information provided must not be promotional or be seen to be making any promises regarding efficacy and safety. Any enquiries regarding the use of GSL/P products in patients with concomitant illness or taking other medicines should be referred to their doctor, pharmacist, or other healthcare professional.

— In some situations when people request information on personal medical matters it may be appropriate to provide information directly to their doctor such that they can discuss it at their next visit. Under such circumstances permission must be obtained from the patient. The nature of the enquiry and the limitations placed on the company in supplying information directly to the patient must be explained to the doctor.

— Some enquiries from the public may alert the company to possible adverse reactions that have occurred in association with the use of a specific product. In such situations permission must be sought from the patient to contact their doctor, and the company’s usual pharmacovigilance procedures must be initiated.

Enquiries About Adverse Reactions

— Enquiries about adverse reactions, overdose or use during pregnancy concerning any of the company’s products may require involvement of the company’s pharmacovigilance function. If the enquiry is of a general nature, and no patient has experienced an adverse reaction with a specific product nor has it been used in a pregnant patient, the enquiry should be handled in accordance with the usual methods for answering enquiries of a clinical nature.

— Adverse reactions or overdose: it should be established whether the enquiry concerns the clinical use of any of the company’s POM, GSL and P products, and devices. If so, details of the adverse event(s) should be taken, and the company’s pharmacovigilance procedure followed. The National Poisons Information Service may be an additional resource for enquirers dealing with overdoses.

— Use during pregnancy: it should be established whether the enquiry involves use of any of the company’s products in a pregnant patient. If so, details should be taken and the case followed up in accordance with the company’s usual process for obtaining such information; companies should actively seek information about the outcome of pregnancies following use of any of their products.
TIMELINESS

— The answer and any subsequent follow-up should be supplied within a deadline agreed with the enquirer. If a response cannot be supplied by the deadline, the enquirer should be notified that there will be a delay and should be given the reason and a new deadline.

— In the absence of an agreed deadline, enquiries should be answered as quickly as possible. A reasonable standard may be five to 10 working days depending on the nature and complexity of the enquiry. The enquirer should be notified if there will be a delay.

— A procedure must be in place to ensure that urgent requests on safety or other issues are expedited.

INFORMATION RESOURCES

— Medical information departments must have a minimum set of up-to-date information resources to enable them to provide comprehensive information on all the products for which they are responsible. Further guidance on recommended textbooks and electronic sources is provided by AIOP (see www.aiopi.org.uk).

— Medical information departments must be able to easily identify published references on the products for which they are responsible. They must also have access to relevant unpublished information where it exists, including adverse reaction reports, pharmaceutical information such as stability studies, and clinical data.

— Information professionals must have (or have ready access to) detailed knowledge on the products supplied by their company. There should always be someone available to provide a knowledgeable response in the absence of the recognised product expert.

— A procedure must be in place to ensure that information resources are kept up to date.

— For discontinued products only concise product histories (e.g., alternative suppliers where appropriate) need to be kept.

ENQUIRIES VIA THIRD PARTIES

— Medical information departments often receive enquiries via third parties such as company representatives. Departments should therefore ensure that such third parties are briefed on the appropriate use of the services provided. Third parties should have a thorough understanding of the services that can be provided and the standards and regulations to which the department operates.

QUALIFICATIONS AND TRAINING

— Medical information professionals should have suitable qualifications or experience. This would normally be a degree in pharmacy, pharmacology or a life science or an appropriate equivalent qualification or experience.

— All medical information professionals must receive training appropriate to the level of their responsibilities. They should have an up-to-date working knowledge of the following subjects if they have not been covered in previous training, academic studies or job experience:
  — pharmacy and pharmacology;
  — drug development;
  — areas of medicine related to products for which they are responsible;
  — information sources and information technology;
  — evaluation of information;
  — communication skills and written presentation of information;
  — pharmacovigilance;
  — regulatory affairs;
  — regulations and codes of practice;
  — health economics and evidence-based medicine;
  — customer care;
  — public relations and marketing of medicines.

— AIOP endorses the MSc/Diploma in Pharmaceutical Information Management run by the City University London as well as the MSc/Diploma in Pharmacovigilance run by the University of Hertfordshire.
QUALITY STANDARDS

— Medical information staff must demonstrate high standards of customer care, with a helpful and responsible attitude, and effective communication skills.
— Medical information departments must set and monitor compliance with quality standards, which should include the following:
  — information supplied must be accurate, fair, objective, unambiguous and up to date and must reflect all the available evidence clearly;
  — comparisons between products must be based on an objective review of all the evidence and must reflect that evidence fairly—differences between products must not be exaggerated;
  — information must be relevant to the enquiry and the specific needs of the enquirer;
  — any additional product-related information supplied that is not directly relevant to the enquiry must be treated as promotional material, must comply fully with the ABPI Code of Practice and must be appropriately certified;
  — for those enquiries requiring a literature search, a search record should be maintained and details should be provided to the enquirer if appropriate;
  — the term “Medical Information” must not be used to describe promotional materials or materials used for promotional purposes;
  — companies should put into place a procedure to encourage feedback and deal with complaints about their medical information service.

AUDITS AND PERFORMANCE INDICATORS

— Medical information departments must have appropriate systems in place to monitor their performance and should carry out audits at regular intervals. Appropriate performance indicators include the following:
  — telephone calls should be answered quickly (within five rings);
  — during office hours appropriate staff must be available to deal with telephone enquiries at all times or must be able to be reached with minimal delay (no more than five minutes) when information is required urgently;
  — enquiries requiring a written response should be answered in a timely manner or by a deadline agreed with the enquirer. In the absence of an agreed deadline, a reasonable standard may be five working days for straightforward enquiries and 10 working days for more complicated enquiries;
  — customers’ views of the quality of service and information provided should be assessed periodically, for example by questionnaires relating to specific enquiries or surveys. An industry standard questionnaire should be used to encourage benchmarking. Additional questions can be added to the core questions;
  — for appropriate enquiries, feedback should be obtained from the enquirer on the value of the information provided—how it was used and what actions/decisions were taken because of it.

For the current version of this document, please consult the AIOPI website (www.aiopi.org.uk)

APPENDIX 8
Memorandum by EMG European Medicines Group (PI 17)

1. THE EUROPEAN MEDICINES GROUP

1.1 The European Medicines Group (EMG) is the UK voice of research-driven pharmaceutical companies headquartered in Europe who develop and supply prescription medicines to the NHS. It has 21 member companies who employ around 12,500 people and invest approximately £250 million in medicines research and development in the UK each year. The purpose of EMG is to help patients, carers and policy makers understand the contribution of the European Pharmaceutical industry to the UK and to ensure that UK patients have the level of access to new, innovative medicines and to information about their medicines that is currently enjoyed by their European neighbours.

1.2 The EMG is in agreement with the evidence submitted to this Inquiry by the Association of the British Pharmaceutical Industry (ABPI). It offers its own response based on:
  — its ability to provide informed comment on how the UK compares with other European healthcare models that are based on a mixture of public and private provision and are more closely aligned with NHS values than many models from elsewhere in the world;
the specific interest that EMG has in patient access to medicines and to medicines information that has arisen out of marked differences between the UK and neighbouring European countries with respect to those two important issues; and

— the intelligence it has accumulated, working with third party organisations and individuals over the past three to four years, on the attitudes and behaviours relating to these marked differences in practice between the UK and other European countries.

1.3 The EMG is committed to working in partnership with the relevant stakeholders to promote an environment that improves access to effective modern medicines and that allows people seeking medicines information to source it from wherever they wish. In seeking to attain these improvements, EMG always works with total regard for the statutory and self-regulatory controls that provide an appropriate framework of checks and balances to ensure probity and good practice.

1.4 This paper sets out how EMG approaches achieving its purpose and provides comment on the Terms of Reference of the Inquiry that are limited to patient aspects of drug information and education and to product evaluation.

2. Provision of Drug Information and Patient Education

2.1 Like the Government, EMG believes that there is considerable potential to improve the health of UK citizens by giving them direct access to high quality health and medicines information. The focus of our activity is complementary to the various Government initiatives and strategies designed to improve health and medicines information and empower patients to take more responsibility for their own health.

2.2 EMG does not advocate advertising prescription only medicines to the general public but does support people's right to request and receive medicines information from whichever source they choose, which includes amongst others, information from manufacturers. The ready availability of good quality information, appropriate to the patient's needs at the time, is the foundation for involvement in treatment decisions and supports ongoing self-management of chronic conditions.

2.3 Although the volume of health and medicines information from a wide range of sources is increasing, much of this is not subjected to any regulation or standard and the quality is often questionable. This is likely to detract from, rather than improve health outcomes. The quality of information relies on interested parties agreeing and enforcing a set of standards and it is this aspect of information provision, as opposed to controlling the sources of information, that will best serve the demands of the public.

2.4 The provision of information about medicines by the pharmaceutical industry is governed by local implementation and interpretation of European regulations for medicines labelling and advertising and by the industry's own Code of Practice. EMG has noted and welcomes the approach taken by the UK Medicines and Healthcare products Regulatory Agency (MHRA) which is more supportive of public access to information about medicines than the approach observed with some other European Regulatory bodies. It has developed helpful guidelines for providers of disease awareness programmes to the public and has supported the Medicines Partnership in the development of Medicine Guides accessible via the Internet. Although there is potential for considerable improvements in facilitating public access to medicines information, the UK is in fact amongst Europe's leaders on this issue. We would recommend that this Inquiry recognise this leadership role and encourages it to be sustained and further developed.

2.5 EMG has been, and remains, concerned that changes to European legislation have the potential to infringe the public's right of access to information and may represent retrograde steps for the UK. In particular, the prohibition on advertising prescription medicines to the public must not be extended to, or interpreted as preventing, the provision of information to those people seeking it. The EMG has briefed a number of interested parties on this position including Health Ministers, UK and European Parliamentarians, civil servants at the Department of Health and representatives of health professional bodies and patient organisations. Support for this position has been strongly received from the parties consulted, and EMG would encourage further support from this Inquiry.

2.6 Over the last four years, EMG has also held discussions with a number of stakeholders from all the above groups and, in particular those groups who represent the interests of patients either generally or for people with specific conditions. The purpose of this ongoing interaction has been to better understand the information needs of patients and the public, how these are currently served and what changes are needed to better meet the increasing demand for good quality information about health and medicines.

2.7 A consistent view expressed in our interactions with patient organisations and other interested parties, is that the industry should be able to provide information to people seeking it provided that the appropriate quality standards are in place. It has also been repeatedly put to EMG that the industry is currently over-interpreting the regulatory framework and unnecessarily restricting its activities rather than responding to the public demand for information. A broader engagement between the manufacturers of medicines and the patients that rely on them is being actively sought by patient organisations, who point out that it is unrealistic to expect people to take medicines on a daily basis, often for the rest of their lives, whilst they are provided with much less information and support from the manufacturer than is currently available for most consumer goods.
2.8 Over 30 patient groups attending a Patients Association meeting jointly sponsored by EMG and ABPI expressed the view that the currently available patient information on medicines was inadequate to meet the needs of patients and any limitations imposed on the sources of information would serve to exacerbate this situation. This is contrary to the opinion expressed from some quarters advocating controlling information by limiting the information providers. Patient groups consider this view to be both practically impossible and an unacceptable form of censorship.

2.9 EMG recommends this Inquiry encourage interpretations of the existing regulatory framework that realise the benefits of better access to medicines information for people that seek it. A modern interpretation developed by a broad church of stakeholders, including patients, representation from the industry, the MHRA and other interested parties needs to ensure the information needs of today’s patients are properly taken into account throughout the course of the conditions that they have to live with.

2.10 Members of EMG wish to make available clear, accurate and relevant information in user-friendly formats both in response to direct personal requests and through access to a library of health and medicines resources available via company websites and other gateways available to those seeking information. It believes a modern interpretation of the current regulations would enable this to be achieved without the need for legislative change.

2.11 In response to desires expressed by patient organisations with whom we have worked over recent years, EMG is planning to facilitate a workshop, inviting all the relevant stakeholders, the purpose of which will be to agree how to progress and improve health and medicines information for UK citizens in the future to better serve their requirements and assure against any retrograde steps emanating from future changes to European legislation.

3. **Product Evaluation, Including Assessments of Value for Money**

3.1 EMG welcomes the various Government initiatives to improve the utilisation of medicines in the UK. NICE, the Scottish Medicines Consortium and latterly the All Wales Medicines Strategy Group have been set up as a means of assessing the clinical and cost effectiveness of new medicines across the UK and enabling patients to gain faster access to innovative treatments.

3.2 In practice however, Government intentions have not yet been realised and the UK still has one of the slowest uptakes in Europe of innovative new medicines with health outcomes in areas such as coronary heart disease and cancer being poorer than in other comparable European countries.

3.3 To examine the variation in medicines uptake between the UK and other European countries in more detail, EMG has interrogated the relevant data to produce a series of nine case studies for specific medicines.\(^{18}\) Some, but not all, of these medicines have undergone review by NICE that, in the majority of cases, resulted in the Institute setting out the circumstances in which their use represented reasonable value for money to the NHS and recommending such use. The points below summarise some of the findings (full copies of the case studies are available on request):

- Uptake of cancer medicines launched in the five years from 1997–2001 ranges from 8.7–12.9% of the average of seven major markets in Europe; uptake of new medicines to tackle serious neurological conditions ranges from 17–23.5%.

- On average, other major European countries treat more than twice as many patients with Herceptin\(^ \text{®} \) per head of population compared with the UK, while Switzerland treats more than three times as many patients.

- Over four times as many patients in France and Belgium receive newer chemotherapy agents for colorectal cancer as in the UK, three times as many in Switzerland and Italy, 2.5 times as many in Germany and Finland, and twice as many in Norway.

- Patients with cancer-related anaemia in the UK are the least likely to be treated with recombinant human erythropoetin compared with other major countries in Europe, where usage is at least seven times higher than in the UK.

- Young people with cystic fibrosis have one of the lowest levels of treatment with Pulmozyme\(^ \text{®} \), the only licensed treatment proven to improve the clinical parameters of the disease.

- Uptake of angiotensin-II receptor blockers, the latest generation of medicines to control high blood pressure, is at least half that of France, Spain, Germany, and Italy.

- France treats almost nine times more patients with standard therapy for Hepatitis C than the UK; on average, other EU countries treat more than six times more patients.

- The UK spends less than any other EU country on Photodynamic Therapy with Visudyne\(^ \text{®} \), the only proven treatment for age-related macular degeneration, the most common cause of blindness in the over 50s. UK spend is one third of the average use per head of population in other EU countries.

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\(^{18}\) The case studies were developed between 2001–04 and do not include comparison with the countries joining the EU in 2004.
3.4 EMG has discussed these case studies with a wide variety of interested parties including Health Ministers, Parliamentarians, civil servants at the Department of Health and representatives of health professional bodies and patient organisations. In order to better understand why the uptake of new medicines in the UK is slower relative to comparable European countries, EMG has also facilitated discussions with local NHS organisations at a range of levels and is in the process of sharing its findings with the relevant stakeholders.

3.5 The reasons for slow uptake identified in these discussions are varied and highlight that there is no solution that can be applied to all local NHS organisations. Three key areas that could impact on better utilisation of new medicines and local implementation of national policy and guidance emerged as:

   — The impact of NICE evaluation of the value of medicines to the NHS and in particular, the need for a clear definition of what implementation of its guidance means in practice as well as clear accountability and responsibility for managing NICE guidance in local organisations.

   — A need for dedicated and accessible funding specifically to support innovative interventions, with the proviso that such funding does not lead to budget distortions in other areas of healthcare.

   — A need for processes for sharing good practice within an agreed set of criteria amongst local NHS organisations in order to overcome the variations in patient access to treatment that currently exist.

3.6 EMG believes the pharmaceutical industry has a legitimate and valuable role to play, alongside NICE, the Department of Health and other organisations to promote consistency in access to innovative medicines between different parts of the country and comparable access to other European countries. Our interactions with other organisations suggest greater involvement from the industry in ensuring implementation of guidance and thereby improving access to medicines for patients would be welcomed and should be encouraged.

3.7 EMG welcomes the recent appointment to the NICE Board of an Implementation Systems Director and is planning to facilitate a discussion group of interested stakeholders, including NICE and the DoH, with the purpose of considering how NICE implementation can be taken forward and better delivered at the local level, specifically, whether the role of a local NICE liaison officer might be a practical solution and if so, what that role might look like. We would encourage this Inquiry to support the need for clearly defined local accountability to improve implementation of national policy and guidance at the local level.

APPENDIX 9

Memorandum by Novartis (PI 20)

INTRODUCTION

1. As members of The Association of British Pharmaceutical Industry (ABPI), Novartis fully endorses the Association’s submission made to the Health Select Committee. The following submission should be read in conjunction with the ABPI’s more detailed submission, and is designed to give a fuller picture of Novartis in terms of Novartis’ ethos and principles, as well as providing information on the UK’s contribution to the efforts of the global organisation.

2. We are proud that Novartis’ products reach patients in the NHS everyday, actively reducing morbidity and mortality. All Novartis’ staff are committed to our mission to serve innovatively, responsibly and sustainably and to operate at all times in an ethical and transparent way, whether that be through playing a legitimate role in policy making or in communicating about our products to healthcare professionals.

NOVARTIS GLOBAL—INNOVATIVE, RESPONSIBLE, SUSTAINABLE

3. Novartis is a Swiss research-based company created in 1996 from the merger of Ciba-Geigy and Sandoz whose history dates back to 1758. Our core businesses are in pharmaceuticals, consumer health, generics, eye care and animal health. As both the fifth largest pharmaceutical company and also the world’s second largest producer of generic (non-branded) medicines, Novartis occupies a unique position within the pharmaceutical industry.

4. Our name, derived from the Latin novae artes, meaning “new skills”, reflects our commitment to focus on research and development to bring innovative new products to the communities we serve, including those in the UK. To this end, Novartis currently operates in over 140 countries worldwide employing 78,500 people. In 2003 the company spent approximately £2.06 billion on research and development.
5. Novartis aspires tirelessly to be a responsible and conscientious global citizen with values based on trust, transparency and accountability. This involves active societal engagement in areas where we have the expertise and know-how to contribute, proactively helping where it is needed most, and establishing and implementing transparent ethical standards, policies and processes across all of our activities. Novartis applies all of its ethical standards globally and regularly exceeds the standards and legal regulations required in many countries around the world including the UK (eg Novartis’ advertising standards).

6. Our primary and most important mission is to discover, develop, sustainably produce and distribute high quality medicines, addressing unmet medical needs. We want to provide affordable, and thus accessible, well established treatment options to the best of our abilities and as far as our resources permit, for as many people as possible. By pursuing these goals, to be “innovative, responsible and sustainable”, we can best provide value to our customers and, most importantly, to society as a whole by helping patients live longer and live healthier.

**Novartis in the UK**

**Contribution to UK plc**

7. In the UK Novartis employs around 3,000 people at 11 sites across the UK. Our sites are at Frimley (pharmaceuticals and HQ), Horsham (R&D, consumer health and manufacturing), Grimsby (manufacturing), London (research and a charitable foundation), Dundee, Litlington and Braintree (animal health), Southampton and Farnham (eye care), Bordon (generics) and Alfreton (manufacturing). The pay and benefits provided to our UK employees was worth £117.9 million in 2003, with a further £8.5 million paid in tax.

**Innovative**

**Innovative Medicines for and From The UK**

8. The pharmaceutical division in the UK currently markets medicines in a range of disease areas, and much research and trial work for these drugs was funded by Novartis through hospitals and academic centres in the UK. In recent years particular attention has been paid to our oncology unit, which has developed the innovative drug Glivec (see case study below), for patients with chronic myeloid leukaemia (CML) and gastro intestinal stromal tumours (GIST). Much of the ongoing research work in the use of Glivec is currently being carried out at the Hammersmith Hospital. Femara, our treatment for breast cancer (beyond the use of tamoxifen which is used for the first five years of treatment post surgery), decreases mortality by 40% in patients for whom no other medicine was previously available. Femara is also licensed for treatment pre-surgery to shrink tumours and allow less invasive surgery. The research work in this area was funded by Novartis, and a significant amount took place in UK hospitals, with the first use of Femara in patients taking place at the Royal Marsden Hospital.

9. In the field of transplantation Novartis pioneered the discovery of the immunosuppressant Neoral (cyclosporine), which made possible the advances in transplant surgery of the eighties and nineties. Much of the early research into the development of cyclosporine was conducted with the Papworth Hospital where many of the first patients received the drug, first in renal transplants, and later in heart and lung transplants. Today Novartis is still a world leader in the research and development of drugs in this field.

10. Visudyne is our innovative treatment in the field of ophthalmology, for patients with AMD (age related macular degeneration), the largest cause of blindness in the over 50s. No treatment was previously available for this condition. In addition to these treatments we also provide medicines in the areas of cardiovascular disease, Alzheimer’s disease, treatment resistant schizophrenia, asthma and pain relief.

**Research and Development in the UK—a Global HQ**

11. Innovation is at the core of what we do at Novartis globally and the UK plays an important role in this regard. Novartis spends £50 million each year on R&D alone in the UK. In addition, the company opened a £42 million research centre, one of the largest respiratory research centres in the world, alongside our existing facilities in Horsham. The new facility is capable of accommodating 200 scientists and is part of the company’s investment in respiratory disease research in the UK. The work currently being undertaken focuses on chronic asthma and COPD (chronic obstructive pulmonary disease). Horsham is now the global HQ for Novartis’ research and development in respiratory disease.
Research and Development—Investment in UK People and Science

12. The Horsham site not only provides employment for 500 people in the UK (250 each in research and development). The £1 million invested each week enables Novartis to attract significant numbers of early and late phase clinical trials to the UK, and initiate clinical research collaborations and consultative agreements with NHS and non-industry research partners. This work does not include the large number of projects at NHS hospitals, which we fund each year through grants. The wider benefits to the UK are harder to quantify, such as the career opportunities we provide to scientists and the research scientists of the future through our programmes for school leavers, undergraduate degree placements and post graduate employment as well as a host of initiatives to promote science in schools. An integral part of this commitment to science education is the “Visions of Science” photography awards, exhibitions and lecture series which are held across the UK, in coordination with the Daily Telegraph and NESTA (National Endowment for Science Technology and the Arts).

Innovation in the UK—unseen costs

13. Novartis’ commitment to innovation is reflected in the excellent pipeline of new medicines which the company enjoys. In October 2003 the city analysts, Lehman Brothers, reported Novartis as having the top rated pipeline in the industry. As a consequence of this successful pipeline, Novartis has participated in thirteen NICE appraisals of its products to date. The volume of work arising from NICE technology appraisals has led Novartis to make a considerable investment in a dedicated team of health economists and pharmacists, as well as enrolling the assistance of outside academic centres, to ensure that we can provide NICE with the detailed information which they require. With appraisals taking anywhere from nine months to over two years, this represents a significant investment of time and resources by Novartis UK.

14. There are other additional costs to working in the UK which are not incurred elsewhere, such as the security measures required to protect our staff from animal rights extremists. Novartis UK has spent an extra £1 million on security measures at its sites in the last two years alone. There are also extensive costs associated with running trials or research projects in NHS hospitals. In addition to funding for the laboratory time and the researchers themselves, most hospitals make a charge for “overheads”. In most cases these extra costs are reasonable and amount to between 30–40% extra. However, some NHS hospitals arbitrarily charge in excess of 100% extra. These costs and the other additional costs of operating in the UK are often cited when Novartis UK is competing at a global level to win investment in R&D, clinical trials or other projects.

Responsible

Global Responsibility

15. As part of our commitment to Corporate Citizenship, Novartis is committed to trying to help on a case by case basis where there is immediate need with products, funds and other supportive measures. This encompasses free or subsidised treatment programmes in developing and industrialised countries, discounts and access to health programmes for patients without adequate medical insurance or other similar measures in industrialised countries. In addition, the company also makes ad hoc donations aimed at addressing special needs such as leprosy, tuberculosis and disaster relief in various parts of the world. Novartis is also proud that it was the first pharmaceutical company to sign the United Nations Global Compact, which now forms the basis of our Corporate Citizenship Guidelines and which include a commitment to fair working conditions, business ethics, human rights and third party management. Each of these policies is integrated into audit programmes across the UK Company and the Company’s employees are required to adhere to them.

Global Action from the UK—Malaria, TB, and Leprosy

166 One major commitment by Novartis is the work we are currently doing in partnership with the World Health Organisation (WHO). In a unique private-public partnership with the WHO, Novartis’ drug for treatment resistant malaria, Coartem, is currently being made available in developing countries at cost whilst the company is currently working with the not-for-profit health organisation, Malaria Venture, to develop a paediatric formulation of the drug. These projects have already treated 650,000 patients since launch. Part of the development of Coartem took place in the UK at the Novartis Horsham site whilst other work was carried out, and continues, with the Tropical Disease Unit at Oxford University.

17. In December 2003 Novartis also signed a five year agreement with the WHO to provide half a million tuberculosis treatments free of charge as part of the work of the Global Fund to Fight AIDS, Tuberculosis and Malaria. Novartis is also committed to eradicating leprosy and as such we are working with the WHO by providing free MDT treatment. So far 2,500,000 patients have been reached—600,000 in 2003 alone.

18. In addition to these projects the Novartis Foundation for Sustainable Development has, for last 25 years, been funded by the company. The Foundation is independent of the economic interests of the Novartis group of companies and seeks to support innovative, performance-related development projects.
In some projects the Foundation seeks to provide assistance through drug provision—not just where we manufacture the treatment (eg in malaria and TB) but also for diseases where we don’t (eg AIDS). The Foundation also collaborates in several non-drug projects as part of a commitment to improve access to healthcare in developing countries. For example, in Tanzania we work with partners Terre des Hommes to provide psychosocial support for AIDS orphans, including regular sessions to help them cope with their bereavement, training of teachers and social workers in basic psychology skills and, with a sustainable focus, the development and implementation of income-generating activities, supported by the orphans organisation and youth bank. The Foundation is currently planning to extend the project to Eastern and Southern Africa.

Developing Drugs—The Not For Profit Future

19. In the past the pharmaceutical industry has been criticised for concentrating on those diseases more prevalent among industrialised nations. In contrast to this perception, in July 2004 Novartis officially opened the Novartis Institute for Tropical Diseases (NITD) in Singapore. The purpose of the Institute is to discover novel treatments and prevention methods for major tropical diseases and to make them available without profit. Novartis believes that this is an innovative, responsible and, crucially, sustainable commitment to fighting tropical diseases. Whilst the set-up costs are being committed now (£108.4 million in partnership with the economic development board in Singapore), the real value of this project will be the availability and access to effective treatments across the developing world in the years to come.

Responsible Marketing—Globally and in the UK

20. Novartis is fully committed to the ABPI code of practice which regulates our pharmaceutical promotional practice in the UK. In addition, the Novartis’ pharmaceutical division has also proactively implemented a Marketing Code to ensure consistently high standards in our promotional activity. In order to secure adherence to the code, sales and marketing management personnel are trained in workshops, while a compliance organisation within the division conducts various audits. Violations of the code have resulted in dismissals.

Working with Patient Groups in the UK

21. Patient groups, who effectively represent the interests of those patients, will always take a keen interest in the development of new medicines which may benefit their members. The Novartis pipeline of innovative treatments has attracted considerable interest in regards to availability of places on clinical trials, dates for the licensing of particular products, availability on the NHS and, of course, issues such as clinical safety and efficacy. Within the bounds of commercial sensitivity Novartis works to ensure that accurate information is provided transparently. Within this context, we are also committed to publishing the results of all our clinical trials and were one of the first companies to sign up to the ABPI register of clinical trials.

22. In respect of sponsorship or funding, Novartis seeks to be an ethical partner in our collaborations with patient groups, with the nature of the partnership set out explicitly at the outset. Our experience of UK patients groups is that they are keen to set out the parameters of the relationship and what is appropriate. This reflects a desire amongst patient groups to protect their independence which Novartis fully supports. Invariably such groups also have independent links with senior clinicians, who they will consult to ensure that the information we provide is accurate. Not only would it be ethically inappropriate but the sophistication and scrupulousness of UK patient groups and the veracity of the British press represents checks and balances to prevent this kind of unhealthy relationship developing.

23. Novartis does not provide funds for all the patient groups with whom we work—we are also happy to share information which is important to patients. In many circumstances, particularly where innovative or novel drugs are concerned, we are clearly best placed to provide the information about the medicines we have developed and, where appropriate and where our strict guidelines allow, we provide this information to patient groups. Novartis has often provided sales data to the Department of Health directly in order to help the Government carry out audits of services and to ensure that treatments are reaching patients appropriately. However, whether a relationship involves sponsorship or just the exchange of information and ideas, Novartis places the highest value on being a transparent and legitimate partner.

Sustainable

Sustaining the Environment and Growth in the UK

24. Sustainable growth is a cornerstone of the Novartis approach to business. This reflects a commitment to growth in the UK as well as a commitment to sustainable environmental policies at our R&D and manufacturing sites. As part of this commitment we are committed to reporting our CO2 submissions in absolute terms and we continue a programme of remediation at our older sites in the UK. The new Respiratory Centre in Horsham for example, was designed to reduce the amount of chemicals used at the site.
25. However, for Novartis UK, sustainability also means attracting and retaining investment in the UK from our global company. When making the business case for such investment, there are a number of key elements such as the state of the UK market as a place to do business (including the PPRS, reimbursement, NICE etc), the availability of the relevant skills and education and the threats posed by animal rights extremists.

26. Novartis UK is proud that we have won the development of a new manufacturing site as part of our chemical operations in Grimsby. The existing site has a hard won reputation for cost effectiveness, reliability and efficiency of production and supply. Part of the success of the plant has been the excellent links with local universities and schools to sustain the expertise required. The new building to be opened in 2005 is a £160 million investment, which should help to sustain and secure Novartis’ operation in Grimsby, and the manufacturing jobs which it provides in the medium to long term.

CONCLUSION

27. Novartis is committed to bringing innovative, affordable and accessible products to the communities that we serve in the UK in a responsible and sustainable way. With our 3,000 UK-based staff, operating in a complex regulatory framework, it is vital that the UK has a supportive innovation environment and that there is recognition of the operating environment of R&D in the UK, including those difficulties imposed by animal rights activists and the problems that still exist with implementation of NICE guidance.

CASE STUDY—GLIVEC (IMATINIB)

WHAT IS CML?

Chronic Myeloid Leukaemia (CML) is a debilitating cancer occurring predominantly in older patients. Although relatively rare, it is one of the four most common types of leukaemia. There are approximately 500–800 new cases diagnosed in the UK every year and about 4,000 patients in total. CML accounts for about 500 deaths a year in England and Wales.

Symptoms include feeling very tired and breathless. Patients are often anaemic, due to a shortage of red blood cells. The disease progresses through three distinct phases: the chronic phase (typically lasting from three to four years), the accelerated phase (typically lasting from three to nine months), and blast crisis (typically lasting from three to six months). As a patient moves through these stages, the disease usually becomes increasingly refractory to therapy and, therefore, more difficult to treat. The greatest chance of altering the normal progression of the disease is in the chronic phase.

TREATMENTS FOR CML

Glivec (imatinib) is used as a first line therapy in the treatment of CML and is considered the gold standard in treating the disease. Prior to the introduction of Glivec, treatment was limited to chemotherapy with hydroxyurea and busulfan, but mainly interferon-alfa. Associated 100-day mortality rates ranged from 30–60%. Where a suitable donor can be found, bone marrow transplant is still the only known cure. However, only 20% of the CML population are eligible for this complicated procedure.

GLIVEC (IMATINIB)

Glivec is an innovative treatment that has produced startling life-prolonging results in some patients previously with little hope. It is part of a new class of drugs called signal transduction inhibitors and works by stopping the enzyme that causes the leukaemia cells to grow. Glivec is well tolerated by patients and is a simple oral therapy (tablets). It is the first cancer treatment to target cancer cells specifically whilst leaving the healthy ones alone thus leading to fewer unpleasant side effects than conventional cancer treatments. In addition, Glivec has been shown to have a significant survival advantage over interferon alpha. Studies have shown that at 24 months 79.2% of patients at chronic phase on Glivec experienced a complete cytogenic remission as compared to 18.5% on interferon plus chemotherapy. Glivec patients were also able to maintain their quality of life (QoL) whereas those in the interferon group experienced a decline in QoL that was evident within the first month of treatment.

Glivec was given regulatory approval in record time in both Europe and the United States because of its impressive results. It has also been awarded orphan drug status in the US, EU and Japan demonstrating the importance of Glivec to the medical community and patients.

Prior to it receiving health authority funding, Glivec was made available to over 500 patients in the UK alone via a compassionate programme, under which the drug was provided free of charge until it became commercially available.
GIST

In addition to CML, Glivec is also licensed for patients with gastrointestinal stromal tumours (GIST). Prior to Glivec, if surgery was not curative or an option, other methods for treating GIST were limited and offered little hope of recovery. Now treatment with Glivec has been demonstrated to result in a reduction in tumour size (over 50%) in more than half of patients with advanced inoperable (unresectable) or metastatic (that has spread to other parts of the body) GIST. Nearly 83% of patients had a response in their tumour and a study has shown that after 34 months of treatment with Glivec, 50% of patients are still alive. This compares with a historical median survival of 12 months for patients not treated with Glivec.

There are currently studies under way looking at optimal use of Glivec in GIST and how it might be used in association with both pre-operative and post-operative surgery.

APPENDIX 10

Memorandum by Cephalon UK Limited (PI 23)

INTRODUCTION

1. Cephalon welcomes the opportunity to give evidence to the Health Committee inquiry into the influence of the pharmaceutical industry on health policies, health outcomes and future health priorities and needs.

2. Cephalon is a research based pharmaceutical company founded in 1987. Our mission is to discover, develop and market innovative products to treat sleep and neurological disorders, cancer and pain. The company employs nearly 2,000 people worldwide, 75 of these being based in the UK, including commercial, research and regulatory functions.

3. To balance the inherent risk in drug development, our business strategy is based on a model of combining in-house research and development capabilities with acquiring and marketing innovative, high growth products. Cephalon is a small pharmaceutical company committed to providing patients and the medical community with novel therapies to treat unmet medical needs.

4. Cephalon is a member of the Association of the British Pharmaceutical Industry (ABPI) and is active in the small companies’ forum.

Drug innovation

5. In line with our mission, the main focus for drug innovation lies within sleep and neurological disorders, cancer and pain. Sleep disorders are a major contributing factor to fatal road accidents, heart disease, lost productivity and impaired quality of life for hundreds of thousands of patients in the UK. Cephalon has developed and markets the first non-stimulant treatment for excessive sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and moderate to severe chronic shift work sleep disorder.

6. Another first in class, we have the only prescription medicine approved in the world for the treatment of breakthrough pain in opioid tolerant cancer patients.

We are conducting an 800 patient clinical trial evaluating an oral kinase apoptosis inhibitor (prevents cell death) for the treatment of Parkinson’s disease that has the potential to slow the progression of this debilitating brain disorder. By uncovering the cell signalling pathways that command a cell to survive and divide—or, conversely, to die—Cephalon is paving the way for novel therapeutics.

The conduct of medical research

7. As a pharmaceutical leader, Cephalon invests around 28% of its sales revenue in research and development, equating to about $300 million this year. This investment is key to building a balanced pipeline of new chemical entities, new indications and product enhancements. Most of the research to date has been conducted in the USA, though there is increasing involvement in the UK.

8. We are collaborating with Cognitive Drug Research Limited in the UK to study the degree to which a new product affects cognitive function in the treatment of excessive sleepiness.
The provision of drug information and promotion

9. All activities based around information provision and promotion are conducted in line with the ABPI code of practice which prohibits the advertising of prescription only medicines to the general public.

10. A team of 26 sales people are involved in our activities in the UK and Ireland across neurology and pain divisions. Promotion is principally to physicians in the secondary care setting though this activity is now broadening to include a wider audience in the evolving NHS. The sales team is supported by a small marketing function, training department, NHS Affairs manager and three medical information pharmacists.

11. Our medical information pharmacists are able to respond quickly to requests for information from both healthcare professionals and the public in the form of both verbal and written information.

12. Websites are available for both the public and healthcare professionals in the UK and USA.

13. Due to the small nature of the company, Cephalon employs the services of external professional organisations to work with us on programmes of raising public and professional awareness of our therapy areas. They co-ordinate a Working Group on Sleep Disorders and assist in securing media coverage. External creative companies are utilised to advertise our products and services to healthcare professionals.

14. Being a small company with limited market access, and operating in therapy areas which do not appear in Government priorities can be a significant barrier to success. This lack of critical mass often means that the innovative areas in which smaller companies operate do not achieve the high profile and share of voice with policy makers that the larger companies experience.

Professional and patient education

15. Around 40% of our promotional budget in the UK is spent on medical education. This includes attending national and international congresses, the production of training CD-Roms, patient information leaflets, other clinical resources as a service to medicine and unrestricted research grants. Cephalon collaborates with patient groups and charitable trusts in providing information and supporting national events. Such joint activities include disease awareness programmes, publications about disease management and programmes and campaigns designed to improve the health and social care of people living with specific diseases.

16. In our experience, MPs and others are very interested in these areas once we have the opportunity to bring them to their attention, because there is a strong public interest case to be heard.

Regulatory review of drug safety and efficacy

17. All products and materials are subject to review by the Medicines and Healthcare Products Regulatory Agency (MHRA). For any product that the company holds a marketing authorisation, Cephalon is under an obligation to report any adverse drug reactions (ADRs) according to a set of criteria including seriousness, expectedness and relatedness/causality. Submission of such reports must take place within 15 days of the notification of an ADR and is in line with legal and corporate responsibilities. These are reported to the global product safety department in the USA.

18. Our products have licences either granted in the UK or through mutual recognition across Europe.

19. We comply fully with all regulations governing our products.

Product evaluation, including assessments of value for money

20. Where company products have been assessed by the National Institute for Clinical Excellence, Cephalon has registered as a stakeholder and taken an active role in the consultation process. On a more regional level, the company has also made submissions to the Scottish Medicines Consortium (SMC) and the Midland Therapeutic Review and Advisory Committee (MTRAC).

21. In the absence of an in-house pharmacoeconomic function, Cephalon looks outside the organisation for independent economic reviews of products by those with the necessary expertise and we find this to be effective.

Case study: raising awareness of sleep disorders

22. Despite excessive sleepiness affecting more people in the UK than Parkinson’s disease and multiple sclerosis combined, there are currently no National Service Frameworks, guidelines from the National Institute for Clinical Excellence (NICE) or Department of Health policy papers governing the treatment of sleep disorders.
23. Untreated cases of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) are costing the NHS £432 million per year. This figure is based on the fact that 80% of patients are unaware of their condition and do not seek treatment, leading to hospital admissions and treatment for related conditions such as cardiovascular disease.

24. The incidence of traffic accidents among people with an untreated sleep disorder remains high—people with OSAHS have been shown to be 7–12 times more likely to have a road traffic accident than those without the disorder. 20% of accidents on motorways in the UK are caused by excessive sleepiness. The estimated cost to society of a single fatal road accident in the UK is £1.25 million.

25. The Quality Adjusted Life Year (QALY) is a recognised measure to gauge a patient’s quantity and quality of life. One year of perfect health life expectancy is worth one QALY, with the score operating on a sliding scale in which zero equals death. The cost per QALY of treating obstructive sleep apnoea (OSA) with continuous positive airway pressure (CPAP) is between £1,500 and £4,400. To put this into perspective, renal dialysis costs £26,000 per QALY and chemotherapy treatment for non-small cell lung cancer £15,000 per QALY. NICE regards spending of under £30,000 per QALY as cost effective, but in spite of the relatively low cost of improving the quality of life of patients with OSA, sleep clinics are being closed, and those which remain lack adequate funding, with patients often waiting 12 months for treatment.

26. Cephalon, in partnership with the Sleep Apnoea Trust, supports the activities of a Working Group on Sleep Disorders, chaired by Alice Mahon MP. The Group seeks to improve diagnosis and treatment of sleep disorders that remain one of the most under-diagnosed and under-treated group of medical conditions, although excessive sleepiness is a major contributing factor to fatal road accidents, and drastically impairs the quality of life of sufferers and their families.

27. Despite MPs in the Working Group continuing to enquire of the Department of Health as to whether there are plans to develop national guidelines on sleep disorders, we have been unable to elicit an answer. Neither have we been able to establish which civil servant/minister has responsibility for sleep disorders. In January 2003 Alice Mahon MP raised the issue of sleep disorders in the Commons, with the then Leader of the House, Robin Cook.

Mrs Alice Mahon (Halifax): Has my right hon Friend the Leader of the House seen early-day motion 410, on avoidable accidents caused by sleep deprivation?

That is a very serious subject. From the answers that I have received from the Department of Health, it is clear that many primary care trusts and hospital trusts do not take the matter seriously. They do not offer a cost-effective treatment that could save many lives on our roads, as the majority of accidents are caused by people who suffer from sleep apnoea. Will my right hon Friend find time for a debate on what is a very serious matter?

Mr Cook: My hon. Friend raises a matter about which she has expressed concern on the Order Paper. She makes some important statistical points about the importance of the disorder. I am sure that Ministers at the Department of Health will want to make sure that the NHS responds to the problem properly. I shall ensure that they write to her setting out the strategy for dealing with this disorder.

28. Despite receiving this assurance from a senior Government minister, no strategy has been forthcoming. Since sleep disorders are clearly an important issue and treatment of them is both clinically and cost effective, the Sleep Working Group is pressing on with this work to seek a comprehensive strategy and proper NHS response. We are sure Ministerial undertakings of this kind are made in the best of faith. It is, however, unfortunate that the market place seems to be overly crowded with voices seeking the ear of government.

29. Given the particularities of smaller pharmaceutical companies such as Cephalon and of those like us who work in novel and innovative therapeutic areas we would be delighted to give oral evidence to the inquiry if invited.

APPENDIX 11

Memorandum by Critical Psychiatry Network (PI 31)

BACKGROUND

The Critical Psychiatry Network is a group of practising Consultant Psychiatrists based in the British Isles, who are critical of orthodox beliefs in psychiatry, especially the importance attached to biological interpretations of distress. The Network first met in Bradford in January 1999, and seeks to influence thinking and practice in the mental health field. We are sceptical about the validity of the medical model of mental illness. We disagree with the emphasis placed on biological research and treatments. We do not seek to justify psychiatric practice by postulating brain pathology as the basis for mental illness. We believe that
the practice of psychiatry must recognise the primacy of social, cultural, economic and political contexts. We welcome the Health Committee’s inquiry into the influence of the pharmaceutical industry in the NHS. It is timely given the widespread public and professional concerns.

**INTRODUCTION**

The factual basis upon which our evidence rests is that the great majority of common psychiatric conditions (such as depression or psychosis) are unlike other medical disorders in that there is no evidence to support the view that these conditions are caused by underlying disturbances in brain function. Psychiatric conditions are not medical condition like liver or kidney failure, both of which have identifiable pathological causes that predict treatment response and outcome. This has a number of consequences:

1. Explanations of mental health problems are strongly contested. Many service users reject the idea that their problems arise from disordered brain chemistry to be rectified by psychiatric drugs.

2. The problems of definition and validation of illness in psychiatry means that the field is more open to manipulation by commercial interest than other areas of medicine.\(^2\)\(^,\)\(^3\)

3. Psychiatry is unlike any other branch of medicine in that patients may be compelled to take medication for lengthy periods of time against their consent\(^4\). The government is about to introduce new legislation to replace the 1983 Mental Health Act, in which these powers of compulsion will be extend into the community. This change in the law has major ethical implications. It is absolutely essential that there should be no concerns about the integrity of the factual basis of the evidence for the efficacy or safety of drugs that are likely to be used in this way. All the evidence indicates that this is not the case.

We must emphasise that we are not against the use of medication in psychiatry. We use it daily in our work. Our view is that there has to be a more rational basis for the use of medication than is currently the case, one that is free of commercial pressure and interest, and more honest about the limitations and potential harm that medication can cause.

**SPECIFIC POINTS**

1. **Drug innovations**

   Our view is that commercial rather than clinical or scientific demands are becoming the dominant driving force for “innovation”, thus the popularity of cheaper “me too” options, and the promotion of new “disease concepts” to allow the re-badging of old products to expand markets without major development costs.\(^2\) An example of the latter is the granting of a product licence for the use of Fluoxetine for the treatment of “premenstrual dysphoric disorder”, a disorder constructed to create a new niche for the drug as its patent was about to expire. Other examples include social anxiety disorder and post-traumatic stress disorder.

2. **The conduct of medical research**

   Perhaps more so than any branch of medicine, psychiatry is open to the influence of external interests, including the pharmaceutical industry. This can be seen in the influence that the industry has on the design, conduct and reporting of psychiatric research, which all serve to promote the sponsor’s drug in the most favourable light.\(^5\)\(^,\)\(^6\) This has major implications for the design, conduct and interpretation of scientific studies of the efficacy of drugs in psychiatric conditions. There are high levels of media and public concern specifically about the influence of commercial interest on scientific knowledge, specifically in relation to side effects of the SSRI class of drugs.

3. **Provision of drug information and promotion**

   We are deeply concerned about the influence of pharmaceutical company representatives in shaping the opinions of mental health professionals through promoting their companies’ products. We believe that they have an inordinately powerful influence in this respect. Their work represents the triumph of the science of marketing over the marketing of science. We believe that the health service and general public needs to be better informed about the *modus operandi* of pharmaceutical company representatives.

   We believe that the interests of the public would be better served in this respect if Trusts had clear policies dealing with the relationships between clinical staff and representatives. For this reason we have recently undertaken an audit of all 83 mental health trusts in England by letter addressed to each Trust’s chief executive. At the time of writing the response rate is 73%. The figures for the 61 respondents are as follows:

<table>
<thead>
<tr>
<th>Have a policy in place</th>
<th>Draft policy</th>
<th>Considering a policy</th>
<th>No plans</th>
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<tr>
<td>(N) (%)</td>
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<td>(N) (%)</td>
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<tr>
<td>32 (52%)</td>
<td>9 (15%)</td>
<td>14 (23%)</td>
<td>6 (10%)</td>
</tr>
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</table>
The Health Committee will no doubt be aware of growing trend to introduce nurse prescribing in the NHS. We broadly welcome this development, but we believe that it makes the introduction of clear policies regarding contact with pharmaceutical company representatives even more important. It is known that representatives “groom” community psychiatric and ward nursing staff, especially when psychiatrists working closely with these nursing colleagues will not see representatives. Our view is that very close scrutiny must be made of the possible influence that representatives may have upon nursing colleagues in this respect. There must be very tight policies governing the type of preparations to be prescribed by nursing staff, particularly with regard to new drugs. All Trusts must have agreed policies that specify what is and what is not acceptable in terms of the relationship between clinicians and representatives.

For these reasons, our view is that pharmacists working in the NHS, especially specialist pharmacists working in mental health, are a more appropriate source of impartial advice about pharmacotherapy for people with mental health problems. Mental health specialist pharmacists have a thorough understanding of the mode of action, effectiveness, risks and side effects of psychotropic medication. Although their sources of information are culled from the industry, they are (or should be) removed from the immediate commercial interests that drive the work of company representatives. They are thus better placed to appraise the claims made for the effectiveness of different drugs.

We are also deeply concerned about the growing trend for direct to consumer advertising, not out of the need to protect professional interest, but because it is in the interests of the pharmaceutical companies to shape the way the public understands emotional distress in order to market their products. We cannot overstate the power and influence of the pharmaceutical industry in alliance with influential elites (like psychiatrists) in this respect.

4. **Professional and patient education**

Biological explanations of mental disorder dominate contemporary psychiatry, despite the absence of convincing evidence that conditions such as depression and schizophrenia have a biological basis. The education of psychiatrists continues to stress the importance of concepts such as schizophrenia, despite the overwhelming evidence that the concept is seriously flawed. In our view one of the main reasons for this is that it serves the interests of the pharmaceutical industry.

We draw your attention to an important paradox here. Government policy in the health service has rightly attached particular importance to social and contextual factors, and the democratic ideals of greater public involvement in the health service. This is of particular importance in psychiatry, where many service users feel alienated and excluded from society, especially those from our Black and Minority Ethnic communities. Despite this, the education and training of psychiatrists, arguably the single most powerful and influential group of professionals in mental health services, is dominated by biological accounts that are incapable of responding to the social, cultural and political realities of many patients’ lives.

5. **Regulatory review of drug safety and efficacy**

No comments.

6. **Product evaluation, including assessments of value for money**

Economic evaluations often use measures derived from value judgements, so it is very important that the researchers are impartial. Economic evaluations funded by drug companies show their own products favourably. The National Institute for Clinical Excellence (NICE) does not appear to take into account the source of funding of research studies that it cites in evidence for the efficacy of drugs in producing its guidelines.

**Recommendations for Action**

We believe the following actions are necessary:

1. The use of monies from the pharmaceutical industry to subsidise continuing medical education, both locally and nationally, must be examined. Policies and procedures must be introduced in discussion with the Department of Health, and bodies responsible for postgraduate medical education, to minimise or eliminate the use of such monies, at least for local teaching. This is a key route of influence upon trainees.

2. If sponsorship is deemed essential, the use of blind trusts should be investigated as an alternative to direct sponsorship.

3. Declarations of interest must be strongly enforced. The medical Royal Colleges should establish Registers of Members’ Interests, which require all members to disclose annually the value of gifts and sponsorship received from drug companies. This information must be in the public domain, along the lines of the Register of Members’ Interests in the House of Commons. If it is acceptable
and right that members of the public can access their MP’s business interests, we believe that the
same standard should apply to other public servants, such as members of the medical and nursing
profession.
4. Our view is that bodies like the Royal College of Psychiatrists have a duty to ensure not only that
its members reach required educational standards, and that these standards are maintained
(continuing professional development), but also that these standards are maintained alongside
probity and transparency in terms of potential conflicts of interest.
5. All NHS Trusts should have comprehensive policies concerning sponsorship and the
pharmaceutical industry. These policies should set out what is and what is not acceptable in the
relationship between employees (ie all clinical workers, not just medical staff) and the industry.
6. We are extremely concerned about the possible influence of pharmaceutical company interests on
government bodies, especially NICE and NIMHE. These bodies must be unimpeachable. They
must be able to demonstrate that they are completely objective, and free of potential sources of
bias and conflicts of interest, in the way they select and evaluate their sources of evidence. Links
between officers of these organisations and the industry must be in the public domain. There must
be no industry funding for any aspect of the activities of these organisations.

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APPENDIX 12

Memorandum by the Category Manager, Boots the Chemists (PI 34)

INTRODUCTION

I am the Category Manager, Dispensing Buying, for Boots The Chemists, based at our Head Office in
Nottingham. The subject of my submission is Parallel Imports of Prescription Only Medicines. Re your
Terms of Reference, this topic probably relates most closely to “the provision of drug information and
promotion” but also touches on “product evaluation, including assessments of value for money”.

____________________________________________________________________________________
The main thrust of my submission is to draw the attention of your Committee to the difficulties experienced by UK community pharmacies, including Boots, in sourcing stock of Parallel Imports, due to the activities of the major pharmaceutical companies.

1. **Background**

The current UK system of reimbursement to community pharmacy of NHS prescriptions encourages pharmacists to buy at the lowest possible cost, and most of this cost benefit is “clawed back” by the DoH by means of a discount inquiry. One way of achieving low cost purchasing is for pharmacists to purchase branded drugs from EU countries where the cost price is lower than in the UK. The importing of PI’s into the UK has been taking place for many years and is undertaken by most pharmacies, independents as well as multiples. Indeed, the DoH assumes a level of PI purchase when setting the clawback rate. Therefore, parallel trade in POM’s achieves two objectives:

(a) It helps underpin the viability of community pharmacy in the UK.

(b) It helps make savings to the NHS drugs bill.

2. **Quotas in Europe**

Sourcing of PI has become more difficult recently, mainly due to the introduction of a quota system by pharmaceutical manufacturers, which limits the quantities of POM’s available to each wholesaler in each EU country. Manufacturers will claim they are trying to more closely match supply to national demand, but in reality they are trying to restrict any surplus available in low-cost countries for export to higher-cost countries such as the UK. This happens in spite of further confirmation, in January 2004, from the European Commission that parallel trade in pharmaceuticals is legal and should not be restricted. We can provide specific examples of products previously freely available as PI where supply has ceased but the specialist importers from whom we purchase will be able to provide more detail. A list of importers’ contact names and addresses can be provided if required.

3. **Quotas in the UK**

One pharmaceutical manufacturer, Eli Lilly, has introduced a quota system in the UK. They call this their Supply Chain Management System, which allocates a quantity of product to each wholesaler, based on previous demand. Previous demand covers only UK stock and excludes any PI purchased. The quantities are allocated unilaterally by Lilly and no discussion takes place with the wholesaler. This has resulted in Boots regularly running out of stock of some products towards the end of each quota period and being unable to supply our pharmacies from our central warehouse. As a result; we have had to fall back on our emergency wholesaler, Alliance Unichem, to make up the shortfall, and this in turn has caused out of stocks for them. We know of at least one instance when one of our pharmacies has been unable to fulfil a patient’s prescription as a result. In spite of repeated requests to correct this, Lilly refuse to meet or to adjust our quotas.

4. **Patient Safety**

Parallel trade in the UK is carefully regulated by the MHRA and has a good patient safety record. In spite of this, there appears to be a growth in subjective opinion, suggesting this may not be the case in the future. A recent example is the report published in May 2004 on Parallel Trade in Medicines by the Social Market Foundation, the research for which was funded by Pfizer. While this report was on the whole well-balanced it did contain some remarks which are either exaggerations or difficult to substantiate. For example:

(a) IMS, who are a well-respected data analysis company in the pharmaceutical industry, are quoted as saying that a medicine can change hands up to 20 or 30 times through parallel trade. IMS have subsequently admitted to me on the telephone that this was a throw-away remark which amounted to “hyperbole”. A contact name and address can be provided if you wish to follow this up.

(b) Suggested links between parallel trade and counterfeit medicines entering the EU, when in fact there is no evidence to substantiate this.

We understand that Pfizer are also funding another report, to be undertaken by another research think-tank called Civitas, which is aimed at a specific investigation of the safety of parallel imported medicines.

5. **Internet**

It is important to distinguish between legitimate parallel trade in prescription medicines, which is restricted to within the European Union countries, and carefully regulated, and individuals sourcing medicines themselves from other countries via the internet. The latter clearly could incur patient safety risks which do not apply to true parallel trade.
CONCLUSION

Parallel trade in prescription medicines is a carefully regulated, legal activity which contributes to savings in the NHS drugs bill, helps underpin the viability of community pharmacy in the UK and poses no risk to patient safety. The UK Government should, therefore, do all in its power to ensure that quotas do not prevent supply of Prescription Only Medicines to community pharmacies and put patient safety at risk.

APPENDIX 13

Memorandum by Long-term Medical Conditions Alliance (PI 36)

INTRODUCTION

LMCA believes that well conducted, transparent relationships between voluntary health organisations (VHOs) and the pharmaceutical industry can be highly beneficial to patients, and are possible without any compromise of the independence of the VHOs concerned.

Nevertheless, these relationships are complex and can be challenging. The press and public are rightly concerned that (VHOs) should be free from commercial interest or pressure. This concern is frequently heightened when a VHO is in receipt of financial or other support from industry, and it is right that these relationships be subjected to regular review and scrutiny. Many VHOs have rigorous policies to govern their relations, and keep them under regular review.

However, the public also needs to be assured and we therefore welcome the Health Select Committee Review of the influence of industry on patients, consumers, the general public and representative bodies, and are pleased to offer evidence to the Committee. Our evidence focuses on two related aspects of the remit of the review: (d) “provision of drug information and promotion” and (e) “professional and patient education”.

We would be willing to provide further written or oral evidence to the Committee.

1.1 About LMCA

The Long-term Medical Conditions Alliance (LMCA) is the umbrella body for over 115 national voluntary organisations working to meet the needs of people with long-term health conditions. Our vision is of a society in which people with long-term health conditions have control over their lives and can live them to the full.

As well as seeking to influence health policy in the interests of people living with long term conditions, LMCA provides a range of services to its member organisations. This has included producing guidance on how to develop and maintain appropriate working relationships with pharmaceutical industry, in the form of our report, “Working with the pharmaceutical industry—guidelines for voluntary health organisations on developing a policy” (attached).

Our evidence draws on our experience in the field of partnership working between the pharmaceutical industry and patient groups/voluntary health organisations, and on the good practice among our member organisations. It outlines:

(a) The need for constructive relationships between VHOs and pharmaceutical industry.
(b) Issues surrounding industry support for VHOs, particularly in relation to provision of drug information and patient education.
(c) Good practice which VHOs have adopted to ensure they are not unduly influenced by industry and how patient groups have been able to influence industry in the interests of patients.

2. THE NEED FOR CONSTRUCTIVE RELATIONSHIPS BETWEEN VHOs AND PHARMACEUTICAL INDUSTRY

2.1 Promoting the needs of patients

2.1.1 Long-term conditions such as MS and epilepsy are frequently lifelong and incurable. Many people living with these conditions will need to take drug treatments to manage their condition, often for the rest of their lives. These treatments—and their side effects—can have a profound impact on quality of life, and indeed mortality.

2.1.2 The decisions and activities of the manufacturers of these treatments have significant consequences for patients, and it is essential that those who develop, manufacture and market such products understand their needs.
2.1.3 VHOs play a unique and crucial role in representing these needs and views. By developing constructive relationships with the pharmaceutical industry, VHOs report they have been able to exert influence on behalf of patients across a range of issues, from identifying patient-centred outcomes for trials and research to ensure treatment regimes meet the needs of patients, to helping ensure that the information which manufacturers provide on treatments and their side effects is accessible and appropriate to the patients’ needs.

2.1.4 LMCA therefore believes that constructive relationships with pharmaceutical industry are an important mechanisms for VHOs to ensure that the needs of their patients are heard and acted upon.

2.2 Meeting patients’ information and education needs

2.2.1 People with long term conditions can face a bewildering array of treatment options. Access to high quality, accurate information on treatments, side effects and alternatives, is key in enabling patients to take control of their condition and play a full and effective role in their own care.

2.2.2 Despite the plethora of health information in newspapers, magazines and TV, people with long-term conditions still report difficulty in finding the information they need. They also tell us that “more and better quality information” would make a significant difference to their lives. (This view is endorsed by the finding that almost 90% of respondents to the government’s choice consultation in autumn 2003 wanted more information to make decisions and choices about their treatment or care.)

2.2.3 Manufacturers of medicines are required to provide information, and indeed research by the National Asthma Panel revealed that patients are keen to receive more information from manufacturers. By maintaining dialogue, and advising where appropriate, VHOs have helped ensure that the manufacturers provide the right information to enable patients to understand their treatments and to use them to gain maximum benefit.

2.2.4 However, VHOs themselves are among the most trusted sources of information services for patients and have a wealth of experience in developing clear, accessible, unbiased information on treatments and services. Increasingly, pharmaceutical companies disseminate independent, VHO produced information materials.

2.2.5 VHOs also play a key role in providing high quality patient education programmes and materials, equipping patients to become effective, informed and economical users of treatments and services.

2.3 Securing resources to support the work of VHOs

2.3.1 Producing and disseminating patient information and education materials and services forms the core activity of many VHOs. However, this is frequently cost- and labour-intensive.

2.3.2 Few VHOs are able to fund their work solely through unrestricted donations from the public. As a result, many are reliant on grants from external organisations in order to continue to provide the high quality services which their patient members need.

2.3.3 The pharmaceutical industry has a tradition of supporting patient groups’ work, through grants, support-in-kind or joint activities, from funding towards written grants to funding for self-management programmes. This support has enabled many VHOs to extend their services, to the benefit of patients.

2.4 Maintaining independence

2.4.1 Whilst this support is valued, a VHO’s independence can theoretically be affected by almost any collaboration or donation. Given the privileged position which VHOs enjoy in the public’s trust, organisations need to be especially careful to ensure that receiving funding from any source (pharmaceutical industry or elsewhere) does not jeopardise their independence or their ability to provide impartial information, advice and support to patients.

2.4.2 It is a responsibility which organisations like LMCA take extremely seriously. VHOs are, by their very nature, fiercely independent organisations, resistant to any attempt to coerce or influence. While VHO’s are proactive and assertive, seeking to establish appropriate relationships with NHS, Government and industry in order to exert influence on behalf of their patients, they are unafraid to criticise industry supporters, in public if necessary.

2.4.3 They are also acutely aware of the need to consider the ethics of how and from whom they raise funds, and of the need for complete transparency about funding. Indeed, VHOs routinely declare sources of support and sponsorship, to a degree not matched in other sectors and organisations.

19 National Asthma Campaign: August 2002 by the National Asthma Campaign (now Asthma UK).
2.4.4 Where support is sought from pharmaceutical industry, many VHOs have established clear and uncompromising policies and procedures to safeguard against undue influence and exploitation. In its guidance to VHOs, LMCA recommends establishing clear written policies based on agreed principles of:

— Integrity and openness about sources of funding.
— Maintaining independence.
— Equal partnership—between recipient of support and supporter.
— Transparency—about objectives and anticipated benefits on both sides. This last point is especially important—successful partnerships are those where both partners gain. Pharmaceutical companies aim to be profitable and will have a marketing agenda, however provided this is acknowledged, and the VHO is satisfied that the relationship will benefit patients first and foremost, this need not preclude constructive partnership working.

2.4.5 These policies and frameworks will typically cover: boundaries to agreements; specific written arrangements and contracts; product endorsement; standard acknowledgements; use of logos; editorial independence; and “get-out” or decline options. LMCA also recommends regular review of policies and arrangements.

2.4.6 Such measures are particularly important where a pharmaceutical company or companies provide support for provision of drug information or patient education materials. It is standard practice for VHOs to insist on complete editorial control at the outset of any such arrangement, and to clearly acknowledge the source of funding on published materials. It is also common practice to have medical advisory panels to cast a critical eye and guard against bias.

2.4.7 Certain behaviours and practices are widely regarded as inappropriate, such as implicitly or explicitly endorsing a particular brand, or engaging in activities which confer a commercial advantage on a particular company. (Indeed, both charity law and agreed best practice preclude the exploitation of a charity’s name for non-charitable purposes, and the Charity Commission takes this very seriously.) Whilst instances of this occur from time to time, they are rare.

3. PUTTING POLICIES INTO PRACTICE

3.1 Recent research by the Health Coalition Initiative\(^{20}\) confirmed that many VHOs (and indeed pharmaceutical companies) have developed and implemented these clear policies, alongside contracts for specific projects, clear governance and review arrangements and operating agreements.

3.2 The pharmaceutical industry itself increasingly also wants to see good practice in its links with VHOs, as evidenced by the work of the Health Coalition Initiative in bringing patient groups and pharmaceutical industry together to review ways of joint working.

3.3 As a result, many VHOs and pharmaceutical companies have been able to establish and manage constructive, transparent partnerships and activities to the benefit of patients. Initiatives have included:

— Good practice development.
— Publications.
— Events and conferences.
— Training, for example in self-management.
— Promotion of VHO Membership.
— Information on medicines.

4. CONCLUSIONS

4.1 LMCA believes that provided there are effective safeguards and procedures in place, well conducted, transparent relationships between voluntary health organisations (VHOs) and the pharmaceutical industry can be highly beneficial to patients, and are possible without any compromise of the independence of the VHOs concerned.

4.2 LMCA is not aware of any substantial evidence that causes serious concern about relations between its member organisations and the pharmaceutical industry.

4.3 LMCA believes that voluntary health organisations provide very valuable and independent channels for information, and that information about medicines should not be censored or controlled by any powerful monopolistic organisation—whether Government, NHS, professions or industry.

\(^{20}\) Health Coalition Initiative is an informal network bringing patient organisations and pharmaceutical companies together to share good practice and develop better understanding of either sector. Activities have included workshops and seminars on patient involvement policies, information on treatments and involving users and carers in research. HCI is currently developing good practice guidance for relationships between patient organisations and industry.
APPENDIX 14

Memorandum of the Alzheimer’s Society (PI 41)

1. THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY

1.1. The Alzheimer’s Society is the UK’s leading care and research charity for people with dementia, their families and carers.

1.2. Dementia affects over 750,000 people in the UK alone. The Alzheimer’s Society has over 25,000 members and works through a network of over 250 branches and support groups. It provides information and support for people with any form of dementia and their carers through its publications, helplines, website and local network. It advises professionals, runs quality care services and campaigns for improved health and social care and greater public understanding of dementia. The Society funds an innovative programme of biomedical and social research in the areas of cause, cure and care.

1.3 Research and drug development by the pharmaceutical industry has resulted in the licensing of four drugs which have substantially improved the lives of many people with dementia and their carers. The Alzheimer’s Society shares some common aspirations with pharmaceutical companies—namely, the development and use of drug treatments that can treat the symptoms of dementia and ultimately cure or prevent the diseases that cause dementia. However, we believe there are questions to be asked about the influence that the pharmaceutical industry has over drug development and access to research data. We have outlined these below. We also discuss the difficulties in the relationship between patient organisations and pharmaceutical companies.

2. DRUG INNOVATION AND LICENSING

2.1. Pharmaceutical companies are commercially driven and therefore there exists less incentive for them to develop or license drug treatments for which there is a limited market. The cost of clinical trials and submitting a licence application makes it uneconomical to produce drugs for rarer and more unusual diseases.

2.2. A clear example of this is the lack of licensed drug treatments for non-Alzheimer’s dementia. Although there is some disagreement over the precise numbers, the proportions of those with different forms of dementia can be broken down as follows:

<table>
<thead>
<tr>
<th>Type of Dementia</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>55%</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>20%</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>15%</td>
</tr>
<tr>
<td>Fronto-temporal dementia incl.</td>
<td>5%</td>
</tr>
<tr>
<td>Pick’s disease</td>
<td></td>
</tr>
<tr>
<td>Other dementias</td>
<td>5%</td>
</tr>
</tbody>
</table>

2.3. The four existing drug treatments used by people with dementia are licensed only for the treatment of Alzheimer’s disease. Therefore, for 45% of people with dementia there are no licensed drug treatments. We know that the drug treatments licensed for Alzheimer’s disease are sometimes prescribed for people with other forms of dementia and that, in many cases, they provide benefit. The Alzheimer’s Society recently conducted the largest ever consumer survey of people’s experience of drug treatments: \( \text{I} \) found that similar proportions of people with vascular dementia (VaD) and dementia with Lewy bodies (DLB) as those with Alzheimer’s disease felt that the treatments were effective (71% of people with VaD, 79% of people with DLB and 73% of those with Alzheimer’s disease considered treatment effective). Clinical trials also confirm that dementia drugs are effective for types of dementia other than Alzheimer’s disease.

2.4. However, the Society was disappointed that the planned National Institute of Clinical Excellence (Nice) technology appraisals of drug treatments for non-Alzheimer’s dementia have been delayed because the drug treatments are not licensed for this use. Lack of Nice guidance creates unnecessary barriers to the provision of potentially effective drug treatments for people with non-Alzheimer’s dementia. To overcome this, the Society believes that a more flexible approach should be adopted. While Nice would generally appraise drugs within their licensed indications, for rare conditions where there is no incentive for drug companies to apply for a licence, Nice should carry out appraisals if there is sufficient evidence about the efficacy of the drug.

2.5. Nice could also be more flexible in their interpretation of the licensing indications. For example, Nice guidance on drugs licensed for Alzheimer’s disease could be applied to people with dementia with Lewy bodies. This type of dementia is often called Lewy body variant of Alzheimer’s disease and does not have a separate classification from Alzheimer’s disease in the ICD-10 (International standard classification of diseases and related health problems—tenth revision). Strictly adhering to the licensing indications for the dementia drugs means that people with dementia with Lewy bodies can miss out on potentially beneficial treatment.
2.6. Indeed, the draft scope of the Nice dementia clinical guideline acknowledges that drug treatments are often used beneficially outside their licensing indications. The scope states that “where evidence clearly supports it, recommendations for use outside the licensed indications may be made in exceptional circumstances.”

2.7. The domination of the pharmaceutical industry over the development of drug treatments for dementia means that there is an emphasis on searching for new compounds that will be profitable for the drug company rather than looking at other, less profitable, types of therapy. For example, aspirin for treating vascular dementia or the efficacy of vitamins in treating or preventing dementia have not been fully explored and developed. Moreover, when successful trials are completed there is often very limited publicity. A recent example of this is a trial which found vitamin A supplementation maintains cognitive function.\textsuperscript{viii}

2.8. The Society believes that the pharmaceutical industry’s influence on the innovation of drug treatments can mean that patients miss out on potential benefits. Public-private partnerships can be an effective strategy for developing drug treatments for conditions that do not have a sufficiently large potential market for the drug companies to otherwise take an interest and should be encouraged.

3. THE PROVISION OF DRUG INFORMATION AND PROMOTION

3.1. Pharmaceutical companies will be particularly keen to influence patients, clinicians and patient groups at the time when a new drug is licensed. It can be difficult for a patient group to interpret from the promotional literature and claims of benefit what the new drug will mean for the patients they represent.

3.2. When the drugs for Alzheimer’s disease were first licensed the Alzheimer’s Society were praised for being a “voice of reason” amidst the hype of a cure for Alzheimer’s. At that stage the Society was almost neutral about the drugs as it was unclear what benefits they would bring. It can be hard to translate claims of “improvements in quality of life” into actual benefits that people with dementia and their carers would experience following initiation of drug treatment.

3.3. It was only when we began to hear reports from people with dementia and their carers and then conducted our own research that we were in a position to say that drugs worked for some people. We were able to say that while they did not work for everybody, the drugs brought significant benefits for some people and we could say what these benefits were. This knowledge gave us the confidence to campaign on behalf of those with dementia for greater access to drug treatments.

3.4. The Society has lobbied for consumer input into the development and design of clinical trials. We believe that this increased involvement would allow consumers to have a better understanding of the drugs, the benefits and side effects they bring and whether the drugs are safe.

4. RESTRICTED ACCESS TO RESEARCH DATA

4.1. The Alzheimer’s Society has serious concerns relating to the influence of the pharmaceutical industry over the publication of clinical trial data. Data that suggest a company’s drug is less effective, safe or cost effective than another drug for the same condition pose a risk to the company. This can create pressure to (1) publish only favourable trials (2) omit negative data from trials with some positive outcomes. A number of papers discuss possible publication bias, which can arise from multiple publication of the results of one clinical trial, selective publication of positive results and selective reporting of analyses of the data.\textsuperscript{x, xi, xii} Clear examples of this are evident in the literature pertaining to the treatment of behavioural symptoms in people with dementia with atypical antipsychotics. Whilst there are four published trials indicating efficacy, there are at least a further three trials which have not been published that failed to demonstrate significant benefit. Furthermore, only one of the four published studies mentions the risk of serious adverse cerebrovascular events, although a meta-analysis by the Committee for the Safety of Medicines based on source data clearly demonstrated this risk across all of the trials.

4.2. Prescribing of drug treatments will be guided by the available evidence. This applies to individual clinicians’ prescribing decisions and local and national guidance, including Nice guidance. It is vital that the available evidence is accurate and unbiased. Lack of access to the full range of clinical trial results can lead to the issuing of incorrect or harmful advice.

4.3. Failure to publish trial results also fails to acknowledge that people who have agreed to participate in the trial have been willing to take part because they thought that they would help to further medical knowledge. It is unlikely that they would have been willing to participate in the trial had they thought the results of the trial would never be made available to others.

4.4. The Alzheimer’s Society strongly welcomes and supports the recommendations recently put forward by the Cochrane Collaboration relating to the prospective registration of randomised clinical trials. These can be found at www.cochrane.org. Prospectively registering trials would help to reduce duplication of research, allow patients to find out if there are any relevant trials that are currently recruiting and help to ensure that the results of all trials are available and included in systematic reviews.
5. Professional and Patient Education

5.1. The Alzheimer’s Society has had a policy on working with pharmaceutical companies for a number of years. It has enabled the Society to have open and transparent discussions with pharmaceutical partners in a field that is changing fast. Indeed, the Society was praised for its transparency in a Which? report which found that out of 125 patient groups, only two—the Alzheimer’s Society and Diabetes UK—had an accessible and clear policy on their websites.

5.2. The Alzheimer’s Society accepts donations and educational grants from pharmaceutical companies. The Society’s audited income in the financial year 2002–03 was £27 million. In the last two financial years (2002–04) donations from the pharmaceutical industry totalled £68,258. This is expected to represent just over 0.1% of the Society’s income. Donations are only accepted in accordance with the Society’s Guidelines for working with pharmaceutical companies. (see Annex 1).

5.3. Nevertheless, in spite of our strict guidelines, public accusations have been made about the Society and our relationships with pharmaceutical industry. Our role as a trusted and credible source of independent and reliable information and advice on all forms of dementia is crucial. We are fiercely independent and place a high value on maintaining this role. As a result, the Society will not accept sponsorship from a pharmaceutical company and their logo must not appear alongside the Alzheimer’s Society logo.

5.4. Pharmaceutical companies are strictly regulated by the industry. The pharmaceutical companies cannot, for example, promote the drugs for dementia to members of the general public. The Society is acutely aware of the importance of its role both as an information provider for people with dementia and their carers but also as a lobbying organisation that raises the profile of the need of people affected by dementia and of the treatments and services required. To put it crudely, patient groups can undertake promotional activities that pharmaceutical companies cannot. While we take great care in not doing the pharmaceutical companies’ marketing and lobbying for them, the Society has played a key role in raising awareness of the available drug treatments, the need for early diagnosis and highlighting examples of postcode prescribing. It is important to note that the Society has campaigned equally vigorously to prevent the use of drugs that do not work or cause harm. An example of this is the Society’s campaign against the use of neuroleptics/antipsychotic medication for people with dementia.

5.5. Despite our caution, the Society has welcomed support from the pharmaceutical industry. Although we have turned down many opportunities offered by pharmaceutical companies, there have been specific strategic alliances which we feel had a positive benefit for people with dementia and their carers. Most recently we have been engaged in the development of a funding consortium involving all the companies that have drugs licensed for the treatment of dementia. We hope that this way of working will be successful and enable us to reach more people affected by dementia. This is a pilot project and will be carefully evaluated in terms of its success in improving our ability to reach people affected by dementia, as well as being a viable way of partnership working for the future. The Society’s trustees are closely scrutinising this pilot project.

6. Conclusion

6.1. The pharmaceutical industry has developed four drugs for Alzheimer’s disease that have made a huge difference to the quality of life of many people with dementia and their carers. However, as outlined above, commercial pressures mean that the benefits of drug development are available to a restricted group and that research funded by the pharmaceutical industry lacks transparency, which has serious implications for evidence based healthcare.

6.2. Closer working between the pharmaceutical industry and patient groups would have benefits for both parties in terms of development of drugs which really meet people’s needs. The Society is eager to find a way of doing this that does not compromise the independence and reputation of patient organisations.

References

REVIEW OF THE GUIDELINES ON WORKING WITH PHARMACEUTICAL COMPANIES

1. INTRODUCTION

The existing policy on working with pharmaceutical companies has served the Society well. It has enabled Society to have open and transparent discussions with pharmaceutical partners in a field that is changing fast. Indeed, the Society was praised for its transparency in a recent Which? report which found that out of 125 patient groups, only two—the Alzheimer’s Society and Diabetes UK—had an accessible, clear policy.

We now have four major drugs on the market for the treatment of dementia. In addition, people with dementia are significant users of a number of antipsychotic drugs and most pharmaceutical companies have at least one drug for the treatment of Alzheimer’s under development.

Partnerships between pharmaceutical companies and voluntary organisations are very tightly regulated by the industry. They cannot, for example, promote their product to members of the general public. It is for this reason that many would welcome the opportunity of funding our work to a much greater extent, including awareness raising, information provision and increasingly service delivery.

One of the current policy’s strengths is its flexibility. This is also one of its greatest weaknesses. It has enabled the Society to both accept and turn down partnerships without justification or additional explanation. However, it has led to increasing confusion and a lack of clarity over what is and isn’t permitted within the policy—especially at a branch level.

There are two significant reasons why the policy should be examined now:

— Lack of consistency between policy at national and branch level.
— Lack of strategic direction in developing partnerships.

I have also recommended that this policy is revised in tandem with a review of sponsorship more broadly. There is a lack of clarity on this issue at both a national and a local level.

During discussions with staff, it is clear that there is some dispute over what the Society’s policy should be. I have highlighted a number of scenarios which the Society has been faced with over the past few months. The aim is to develop a stronger consensus and shared understanding. Which partnerships would you permit?

2. SCENARIOS

Q1 During Alzheimer’s Awareness Week a branch wants to organise a meeting targeted at GPs. It wants to seek financial support from a drug company for the cost of lunch, speaker expenses and hire of hall. Do you think they should be able to do this?

Within the existing guidelines, the branch can accept an educational, unrestricted grant/donation towards the cost of the conference. This donation has to be publicly acknowledged, but the drug company logo must not appear alongside the Alzheimer’s Society logo. Nor must the company have any control over the conference programme or the participants invited to attend. The drug company will often have a public presence at the event such as a stand. This does not count as “sponsorship”. It is often recommend that the branch works with the PCT to put on a joint event.

— Q1A If you accept support for the above branch meeting do you think that national office should accept unrestricted grants from drug companies for its conferences, eg younger people with dementia/national AAW event?
Q2 A branch is desperate to obtain funding to enable them to continue to provide a very successful early intervention project for people with early stage dementia. The PCT says that there is no money to continue funding a very effective project. The branch know that a drug company is prepared to support the project. The drug company says that it doesn’t need to have its name mentioned on any of the information leaflets about the service. Can the branch accept the money?

We are currently saying no. Instead, we suggested that the PCT, which is supportive, acts as a broker.

Q3 The Society has developed an excellent training workshop package for primary care staff on early diagnosis. It is working with a private training provider in order to deliver the training to GPs. This provider is seeking sponsorship from drug companies for the training. Even though the Society has secured endorsement from the Department of Health and the Royal College of GPs, and we provide the materials and the speakers our logo (and hence our name) will not appear on the conference flyer. Some of the drug companies find it hard to see how this opportunity fits within our guidelines. Do you think we’re missing an excellent opportunity?

— Q3A Would you be happy if branches approached drug companies in a similar manner in order to put on much needed training?

Q4 A branch receives a donation from drug company for a laptop and projector. Is this ok?

Q5 A branch wants to approach a drug company that does not have any Alzheimer’s drugs on the market. Who should be responsible for advising them on this?

Q6 The public affairs team is asked to comment on a market research proposal for the development of a new drug. Should it help?

Currently we say no. The existing guidelines say that we will help with information etc. However, we have an unwritten policy that we only deal directly with a pharmaceutical company. We also have an unwritten policy that if they can’t tell us who it is they are working for, we can’t help. This is based on a policy of being as honest and transparent as possible (it is also a really quick way of getting people off the phone!). We do however offer advice on how to write patient information leaflets etc—sometimes we get a donation for this work.

We also facilitate carers/people with dementia speaking to drug sales teams. Branches sometimes receive a donation for this work. The public affairs and information and education teams have worked closely with several agencies on the launch of products and press releases.

Q7 A drug company wants to pay the Society £5 for every questionnaire returned by an old age psychiatrist and to use this as an incentive to increase returns. Should we accept?

We say no. A branch did however say yes to a similar offer and received £600.

Q8 A drug company wants to buy and distribute 20,000 copies of “I’m told I’ve got dementia” and also sends our posters and information to all GP practices during Alzheimer’s Awareness Week. Is this ok?

Q9 Both a branch and national office want to approach a drug company for prizes for raffle. Is this allowed?

Q10 A national memory clinic website supported by a drug company under the name of “Dementia Link” wants to give the Society a prominent link. Alzheimer’s Scotland have their logo/link on the front page. This could be an important link for many people wanting to find out about memory clinics. Should we have our logo added?

We ended up putting our name (in house style yellow) but not our logo on this site. We later ask for it to be removed because of concerns about site and the way in which this is presented as the Society’s endorsement.

Q11 The Society is offered editorial and advertising space on a supplement in Pulse magazine (for GPs) which is sponsored by a drug company. This is a target audience for the Society. Should we take the space?

We decide to accept even though this does mean that logos appear on same publication (though not on same page). We insist that our piece is moved to a page with no product endorsement.
3. PROPOSED RECOMMENDATIONS

Depending on feedback from discussion on the above scenarios, I suggest that minor amendments are made to the existing policy:

1. Include a definition of what we mean by sponsorship. Suggest that sponsorship is defined as an event where a sponsor’s logo is used, and the wording/credit acknowledged might be part of the sponsorship negotiation. Sponsorship is different from an unrestricted donation for an event — this requires a one line credit, logos are not used and the Society controls the wording, position of credit and all activities associated with organising the event.

2. Include a new clause stating where possible, we favour the use of funding consortia composed of two or more companies from the same industry.

In addition, there are a number of other suggestions that are worth considering:

3. Should there be a limit to the percentage of income/project that may be funded by a drug company? At the moment it is about 1% at national level. Do we think that is about right? We have no idea about the amount given to branches.

4. The current policy says that all contact should be made through the Head of public affairs. It is appropriate that there is a central contact, but the current policy does not work well. Suggest that the regional teams act as a first point of contact for branch enquiries. There is good co-ordination between public affairs and regional teams on this issue.

5. There is also a need to be more strategic in our partnerships with pharmaceutical companies. The Society tends to wait to be offered opportunities rather than actively seeking agreements to work on a joint project. Notable exceptions to this include the support of the production of the Working Together Video by Pfizer and a grant from Novartis for research on the use of drugs.

6. I also recommend that this policy is revised in tandem with a review of sponsorship more broadly. There is a lack of clarity on this issue at both a national and a local level.

   — This requires a broader review and needs to include sponsorship of publications and newsletters. Who do we want sponsoring information/advice sheets or the Carers Handbook for example?

   — Also, some branch newsletters for example carry advertisements for local care homes and solicitors. Should this be allowed?

4. SUMMARY

The scenarios highlight the varied nature of our partnerships with pharmaceutical companies. On the whole, the Society has positive relationships with the pharmaceutical companies and the agencies that they use.

There have been many strategic alliances and information about the Society is now included on all patient and carer booklets that are distributed with the drugs. As a result, the Society has received new members, particularly from people with dementia. However, it is essential that the Society is, and is perceived as being, an independent provider of accurate information.

April 2003

APPENDIX 15

Memorandum by the General Medical Council (PI 43)

THE ROLE OF THE GENERAL MEDICAL COUNCIL

The objective of the GMC is to protect, promote and maintain the health and safety of the public.

We do this by the exercise of our functions in:

(a) Establishing standards of good medical practice, which reflect what society, and the profession, expect of doctors.
(b) Assuring the quality of basic medical education in the UK and co-ordinating all stages of medical education.
(c) Setting and administering fair systems for entry to and remaining on the medical register.
(d) Dealing firmly and fairly with doctors whose fitness to practise is questioned. The “fitness to practise” procedures are the legal processes which the GMC applies to cases where a doctor’s continued right to registration is called into question because of alleged serious deficiencies in their fitness to practise, that is, their conduct, health or performance.
The GMC was established under the Medical Act 1858. The GMC’s duties and powers continue to be conferred and regulated by primary and secondary legislation. The current powers derive from the Medical Act 1983, as amended.

The GMC is committed to promoting equality and valuing diversity and to operating processes and procedures that are fair, objective, transparent and free from discrimination.

In June 2001 the Charity Commission announced that it had decided on 2 April 2001 to recognise the GMC’s charitable status. On 9 November 2001 the GMC was formally registered as a charity.

**Impact of the Pharmaceutical Industry on Medical Practice**

The GMC does not regulate the pharmaceutical industry and has not researched, or developed a corporate policy on, the industry’s impact on medical practice.

Our guidance on professional standards covers both the therapeutic use of medicines and medical research. We give general guidance in our core booklet *Good Medical Practice* and more specific advice in *Research: the role and responsibilities of doctors*. Copies of both booklets are enclosed.

*Good Medical Practice* establishes the principles which should underpin all doctors’ professional work. This includes putting patients’ interests first, including when prescribing, keeping up to date, and reporting any adverse drug reaction. (See paragraphs 3 and 10–11). *Good Medical Practice* also warns doctors against involvement in any relationships with pharmaceutical or other companies which could raise, or be seen to raise, a conflict of interests (see paragraph 55). This is intended to cover matters such as accepting hospitality or gifts from pharmaceutical companies, other than those which are trivial. Our guidance does not, of course, operate in isolation, but is just part of the regulation of this area of practice. The Medicines (Advertising) Regulations 1994 and the Code of Practice issued to the pharmaceutical industry provide further controls over the hospitality or gifts which may be offered to doctors by pharmaceutical companies.

*Good Medical Practice* also makes clear that doctors must be honest and open about any financial or commercial interests they have in pharmaceutical companies and ensure that those interests do not affect their independent judgement in providing and arranging patient care (paragraphs 56–57).

We give more detailed guidance on how the principles established in *Good Medical Practice* apply in research in our booklet *Research: the role and responsibilities of doctors*. You may be interested to note in particular the statement of principles set out in paragraph 5 of the booklet, and the paragraph on conflicts of interest in paragraph 13.

The booklet also emphasises the need for openness and honesty in all financial and commercial matters, and in particular the obligation to make clear to research ethics committees, and participants in research, how research is funded and the fees or other payment or rewards to be made to researchers.

It is unusual for the GMC to receive complaints about doctors asking for or accepting inappropriate fees or hospitality from pharmaceutical companies. However, cases relating to the honesty of doctors involved in clinical drugs trials are more frequent, and many lead to the doctor being struck off, or suspended from the register. Such cases often involve doctors inventing patients and data relating to their care, or involving “real” patients in clinical trials without consent. Our concerns are with these actions in themselves and with their effect on research data available to other practitioners, rather than whether, for example, the methods of payment for such work, have an influence on, or affect, doctors’ conduct.

Alongside its role in setting standards for medical practice, the GMC issues guidance and sets outcomes for medical education and training. We ensure that the outcomes are met through our programme of Quality Assurance of Basic Medical Education which includes visits to medical schools. *Tomorrow’s Doctors* sets out the competencies required for graduation and admission to the provisional register. We have been revising our guidance on the Pre-Registration House Officer year that follows graduation and aim to publish a new edition of *The New Doctor* later this year. This will set out the competencies required to complete PRHO training and achieve full registration. We have recently published new guidance on *Continuing Professional Development*, which is often funded by the pharmaceutical industry. Our website includes a list of organisations that can help doctors to undertake appropriate CPD. Throughout our educational guidance we stress the importance of clinical competence alongside probity and patient-centredness in medical practice and research.

Some doctors do fail to maintain the standards that we expect. We work closely with the NHS and the National Clinical Assessment Authority, and with other organisations, to ensure that problems are dealt with at the appropriate level in the best interests of patients. Where necessary we can take action on doctors’ registration. We summarise the results of fitness to practise cases in *GMC News*, which is distributed to all doctors on the medical register. Our fitness to practise work contributes to the environment in which we develop our guidance on standards of medical practice and the outcomes required of those undertaking medical education and training.

While acting within our statutory role and functions, we can therefore promote medical practice which puts patients first and is not compromised by external pressures or financial incentives.
APPENDIX 16

Memorandum by PharmacyHealthLink (PI 44)

ABOUT PHARMACYHEALTHLINK

PharmacyHealthLink (PHLink) is a registered charity set up to improve the health of the public by conducting research, providing training and information, and developing the skills of pharmacists to promote the health of the public and educate them in matters affecting their health. The beneficiaries of the charity are the UK general public and specifically those who use pharmacies or obtain pharmacy advice.

AN OVERVIEW OF OUR APPROACH TO IMPROVING THE PUBLIC’S HEALTH

PHLink is dedicated to improving the public’s health by improving their access to high quality and effective healthcare advice and provision of services through pharmacies in all settings, but mainly community, hospital and primary care. The Charity relies on reviews of published evidence and the opinion of experts, pharmacy staff and the public to help inform its work.

THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY ON PRESCRIBING PRACTICE: EXAMPLES FROM THE FIELD OF SMOKING CESSATION

Background

Our main evidence in this submission comes from our experience of the field of smoking cessation. Reducing the prevalence of adult smoking remains one of the Government’s key priorities for improving health21 and PHLink have been working closely with the Department of Health, the NHS and other organisations to help them meet one of the key public health targets22—specifically “800,000 smokers from all groups successfully quitting at the four week stage by 2006”.

Since 1997 a number of policy initiatives have been implemented to help reduce smoking prevalence. One was to increase access to effective smoking cessation treatments—specifically, bupropion hydrochloride (Zyban®) and nicotine replacement therapy (NRT)—by making them available on NHS prescription. This happened in June 2000 for bupropion and in April 2001 for all NRT products. Many NRT products were already available to the public before that time either as Pharmacy-Only (P) or as General Sales List (GSL) medicines.

PHLink responded to the original consultations from the (then) Medicines Control Agency (MCA) on these issues and supported the proposal to make NRT reimbursable on the NHS as well as the reclassification of certain NRT products to GSL status. PHLink also submitted evidence into the technology appraisal of smoking cessation treatments23 run by the National Institute for Clinical Evidence (NICE). Since then it has been working with a range of healthcare organisations to improve access to smoking cessation treatments on the NHS through pharmacies, GP surgeries and other premises—this has been primarily achieved through writing and distributing template Patient Group Directions for Smoking Cessation Therapies.24

Issues arising from the supply of smoking cessation therapies on the NHS

The main issues arising of relevance to the Committee’s Inquiry are as follows:

1. The influence that the pharmaceutical industry has on prescribing practice in the NHS—via the decisions individual companies make when applying for a licence for its products, specifically:
   (a) In deciding what category a medicine should be placed in when applying for a licence (Prescription Only—POM; Pharmacy Only—P; or General Sales List—GSL).
   (b) In deciding what research to undertake, and with which groups of individuals or patients, in determining which medicines category to apply for a licence.
   (c) In deciding, on the outcomes of the above, which groups of individual or patients should be included/excluded from the licensed supply of the product.

2. The role of the Medicines and Healthcare products Regulatory Agency (MHRA) in “safeguarding public health.”

http://www.hm-treasury.gov.uk/media/70320/sr04—psa—ch3.pdf
http://www.dh.gov.uk/assetRoot/04/08/60/58/04086058.pdf
A brief outline only of each of these issues will be made in the next few pages. PHLink is willing to submit more evidence, either oral or written, in support of these statements on request.

1. The Influence that the Pharmaceutical Industry has on Prescribing Practice in the NHS—via the Decisions Individual Companies Make When Applying for a Licence for its Products

As the Committee will no doubt be aware, some of the most important decisions made in relation to the supply of medicines on the NHS are made by individual pharmaceutical companies during the process of submitting an application for a product to be licensed by the Medicines and Healthcare products Regulatory Agency (MHRA). These decisions affect key factors, such as the category of medicine that the product is supplied under (which has a huge influence on access to supply), the research that is conducted to determine its safety and efficacy (and for which groups of individuals/patients), and also the specific licensed “indication” of the product which ultimately determines its use and purpose.

Whilst PHLink accepts that strict confidentiality is needed for commercial purposes by the pharmaceutical industry when new products are being submitted for licence, the Charity believes, that after an agreed period of time post-licensing, or when competitor products have already been licensed for similar purposes, there should be much greater scope for the advice of external organisations, such as the NHS and health-related charities, to influence subsequent revisions of the product licences. This would further enhance patient safety as well as reduce bureaucracy and cost in providing medicines on the NHS, particularly where unnecessary licence restrictions are in place.

Using the example of smoking cessation treatments, there are over 20 licensed NRT products currently available for essentially the same licensed indication “the relief of nicotine withdrawal symptoms as an aid to smoking cessation”25. Despite having some differences in method of delivery26 of the active agent (nicotine) these products are very similar in terms of their pharmacological properties and physiological effects. However, their Summary of Product Characteristics (SPCs) vary in content, specifically with regards to contra-indications, cautions, dosage, maximum length of use and other characteristics. As a result, many health professionals are confused about product safety and efficacy in certain patient groups and consequently advise using NRT far more cautiously than clinically necessary or is desirable to be effective. The Charity, and other healthcare organisations, have made a number of (so far unsuccessful) approaches to individual pharmaceutical companies and the MHRA to:

(a) remove unnecessary restrictions on existing product licences (eg supply of NRT to under 18 year olds);

(b) to extend the range of “therapeutic indications” that NRT products are licensed for (eg to cover temporary abstinence—not just treatment of dependence or relief from withdrawal symptoms);

(c) to ensure consistency between existing product licences (eg having similar contra-indications and recommendations on maximum daily dosage).

Appendix 127 to this submission illustrates this point in more detail by comparing a “typical” SPC for a 2 mg nicotine gum with the proposed revisions for an SPC that would both “harmonise” existing SPCs as well as provide more accurate information on risk posed by these products to both patients and health professionals.

Appendix 228 to this submission illustrates the administrative “hoops” that NHS organisations currently have to negotiate if they are to increase access to supply of NRT on the NHS through professionals other than doctors (Improving Access to Smoking Cessation Therapies on the NHS through Patient Group Directions, PHLink, 2003). The extra administration is primarily required as a result of having to circumvent existing licence restrictions.

2. The Role of the MHRA in “Safeguarding Public Health”

Despite the huge public health gains that could be achieved with more smokers using effective smoking cessation treatments as an aid to quitting, current attempts by NHS professionals to persuade smokers to use NRT29 in cessation attempts are hindered by unnecessary licence restrictions, which are beyond the power of the NHS to remove, but lie with the relevant pharmaceutical companies and MHRA.

25 A few products (eg Nicotinell transdermal patches) state “the treatment of nicotine dependence” as their therapeutic indication.

26 There are currently six different forms of NRT licensed for use: chewing gum, transdermal patch, inhalator, nasal spray, lozenge and sub-lingual tablet.

27 The use of NRT in cessation attempts is known to double the success rate in quitting. Higher rates of success can be achieved if the patient also receives specialist behavioural support during their attempts to quit.


29 “Safeguarding public health” is the strapline of the logo of the MHRA.
An outline of the role of the pharmaceutical industry in submitting applications for product licensing to the MHRA has already been made. However, the picture would be skewed without also outlining the role of the MHRA in approving product licences.

The area of smoking cessation is possibly a unique area for the MHRA in that the “agreed approach” they use in assessing the safety and efficacy of a medicine is rendered inappropriate in this instance by the presence of a parallel “nicotine market” in tobacco. Unfortunately the delivery mechanisms for nicotine via tobacco use are much less regulated but also “dirtier” (ie they contain recognised and regulated toxins30) than delivery of nicotine through medicinal products. In order to “safeguard public health”31 the MHRA needs to recognise the existence of this parallel “nicotine market” and to adapt its regulatory approach to reflect the real risks being posed to the public from these different nicotine delivery devices. Unfortunately the MHRA has historically shown very little interest in adapting its approach to deal with either the existing inconsistencies in the regulation of nicotine products, or the risks posed by new nicotine delivery devices entering the tobacco market.

CONCLUSION

The role of the pharmaceutical industry and (inseparably) its association with the MHRA has a major influence on the supply and use of medicines within the NHS.

At present, the relationship between the two players (from the outside at least) appears to be symbiotic in that confidentiality over product licence applications and their revision is maintained and there appears to be very little room for external parties to influence proceedings (other than for “required consultations”, for example, the reclassification of a medicine). Whilst this is fully understandable for applications for new product licences, it appears to be less appropriate for established markets where relatively minor changes to product licences to better suit the NHS and patients could be justifiably made.

In addition, the role of the MHRA in smoking cessation does not appear to sit easily with its current approach to licensing medicines. If the MHRA was to change its approach to better reflect its stated aim of “safeguarding public health” then it might be appropriate for its role in regulating product licences for smoking cessation to continue. Without that change, however, it is likely to be more in the public’s interest for the regulation of nicotine and tobacco products to sit within a different framework, which might be more concordant with the approach of another regulatory body.

PharmacyHealthLink believes that the time is right for a thorough (external) review of the methodology that is currently used for licensing pharmaceutical products and the degree of scrutiny that the process is currently subject to. In our view, in line with developments in UK regulation elsewhere,32 there should be room for wider public and professional involvement, particularly at the post-licensing stage. PHLink believes the Health Select Committee Inquiry is ideally placed to conduct such a review and make recommendations on how this process could be “modernised” in line with other social and healthcare developments.

APPENDIX 17

Memorandum by the Scottish Association for Mental Health (PI 46)

INTRODUCTION

1. The Scottish Association for Mental Health (SAMH) is the largest voluntary sector organisation in its field in Scotland providing accommodation, support, information, training, employment and day care opportunities for people with mental health and related problems. In addition, we operate an information service, offering general mental health information and specialist legal and benefits advice. SAMH campaigns on a wide range of mental health issues, and works to challenge the stigma and discrimination suffered by people who live with mental health problems, influence policy and improve care services in Scotland.

2. SAMH has a policy of not accepting sponsorship or grants from the pharmaceutical industry.

3. In April 2004 SAMH published a report entitled All You Need to Know? A Scottish Survey of People’s Experiences of Psychiatric Drugs. This reported on the results of a survey conducted with people who had received a new or different prescription for their mental health problem within the last three years, together with discussion in four focus groups throughout Scotland. A total of 756 individual responses were analysed. The aim of the survey was to supplement information gained from RCTs by providing user based information on the performance of medicines and to adopt an inclusive approach to ensure views were sought from people who are often discounted from RCTs. Overall 61% of respondents described their drugs

31 Not printed.
32 Not printed.
as either “helpful” or “very helpful”—this percentage varied according to the type of drug. For some drugs this figure was nearly 80%. However, at the same time we found that many experienced unwanted effects, with 61% experiencing unwanted effects when taking the drugs, and 42% experienced unwanted effects when stopping. Some of these unwanted effects were very severe, including suicidal feelings, sleep deprivation, weight gain, paranoia, incontinence and sexual difficulties.

**Impact of the Drug Industry on Drug Innovation**

4. The pharmaceutical industry has successfully tested and marketed many drugs, particularly in the last 50 years. However, the dominance of the industry, particularly in the research field, has meant that other therapeutic approaches have been neglected. Some alternatives, such as Cognitive Behavioural Therapy, are well evidenced by research, but the same cannot be said for nutritional approaches to mental health problems, psycho-social interventions and complimentary therapies many of which are highly rated by service users. It is not wrong that money is spent on research into pharmaceutical products, but the sheer amount of resources going into this one area has led to an imbalance in the range of interventions available.

**Conduct of Medical Research**

5. The vast majority of drug trials are funded by the pharmaceutical industry. SAMH has serious concerns that the lack of independence of those responsible for conducting RCTs results in biased information reaching the public domain. For example, one study has indicated that trials funded by the pharmaceutical industry are four times more likely to have results favourable to their own drugs. SAMH strongly recommends the establishment of an independent body to perform clinical trials. Funding for this body should come from fees paid by pharmaceutical companies. Payment of these fees should be mandatory prior to issuing a drug license. This would have obvious benefits in terms of rigour, impartiality and credibility. It is our view that simply trying to force companies to be open and transparent regarding RCTs, whilst an improvement, would not be sufficient to ensure full impartiality and accuracy of results.

6. There are clear reasons for the methodological necessity of testing drugs in controlled environments. However this sort of evidence is based on establishing efficacy as opposed to effectiveness. In order to test for effectiveness drugs need to be tested in more natural settings. This would provide evidence on the performance of medicines in a more realistic setting and would provide consumers with information more useful to their own situation.

7. There is also a need for more longitudinal research into the effects of drugs. Most clinical trials are over a fairly short term, but many people with mental health problems will take psychiatric drugs for many years of their life.

8. Drug research should also be conducted using combinations of drugs. In our survey 756 respondents received 1,538 drugs. Often the implications of the interaction between these drugs is not well known and the additional side effects that can be caused by them is not well understood. The prescription of additional drugs to combat side effects is also a cause for concern as this can sometimes mask the ineffectiveness of the original drug.

**The Provision of Drug Information and Promotion, and Professional and Patient Education**

9. Decision making on prescription of medicines should be based on full information and informed consent and should be a joint decision between physician and consumer. Consumers who are not being given full information are being treated without their informed consent. Our survey showed that although in many cases consumers were happy with the input they were offered, some would have liked to have had more say in the decision. 70% of respondents were not offered a choice of drug at the time of prescription. 30% did not feel able to ask questions, 20% were either fairly or very unhappy that their prescription was a joint decision, and 61% had concerns about their drug after they started taking it.

10. This needs to be rectified by adequate training, impartial testing of drugs, the provision of information to consumers in accessible language, and the establishment and monitoring of clinical standards which have had meaningful user influence in their formulation.

11. Consumers are often experts in psychiatric drugs, especially those who have experienced mental ill health for prolonged periods of time. More weight needs to be given to research which reflects the views of those who use the drugs.

12. SAMH recommends the introduction of good practice guidelines on the prescription of psychiatric drugs to ensure that each time a new or different psychiatric drug is prescribed there is a full and frank discussion on all relevant aspects of the drug.

13. There is a general perception, widely shared by service users, carers and professionals, that the pharmaceutical industry spends a lot of money in promoting its products to the NHS, through the provision of conferences, (with free places and foreign travel) and other merchandising benefits. Some doctors have

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publicly raised concerns eg through the No Free Lunch Campaign. There needs to be more scrutiny and stricter regulation of the marketing and merchandising activities of the pharmaceutical sector. However, health professionals also need to take more responsibility over their relationship with the pharmaceutical industry.

**Regulatory Review of Drug Safety and Efficacy**

14. Although we understand changes are in progress in the system for reporting of side effects it is important that people are able to report their own side effects directly to an independent monitor. Systems should be developed to ensure health professionals take account of these reports.

15. Methods of administering drugs should also be subject to a high level of scrutiny and should be subject to constant review. Depot antipsychotics performed badly in our survey, suggesting the need for greater legal protections surrounding their use.

**Product Evaluation, Including Assessments of Value for Money**

16. Budgetary considerations should not prevent consumers from accessing the drugs they find most helpful. Given the very individual nature of a response to medication a wide a choice as possible is needed, to ensure that people find the medication that works best for them. Leaving aside the issue of fairness, trying to economise by only offering cheaper drugs probably costs the health service more in the long run, with increased admission to hospital and/or other demands placed on services as a result of ill-health.

*16 August 2004*

**APPENDIX 18**

*Memorandum by Professor Les Toop and Dr Dee Richards (PI 49)*

**Contents**

- Summary of Recommendations
- Background
- Drug Innovation
- The Conduct of Medical Research
- The Provision of Drug Information and Promotion
- Professional and Patient Education
- Regulatory Review of Drug Safety and Efficacy
- Product Evaluation
- Conclusion

**Recommendations**

1. Incentives need to re-aligned to encourage innovation in areas of public health need (eg newer antibiotics) rather than in areas of consumer want and company profit (eg anti-ageing and lifestyle).

2. Any and all clinical RCTs involving a new product should be registered with a central agency. Failure to register an RCT prior to it starting would rule its findings inadmissible as evidence in a subsequent licensing or funding application.

3. Marketing of products under the guise of post marketing phase 4 research should be much more closely scrutinised by ethics committees as an explicit part of their brief.

4. Trials that are industry-funded and which have not gone through an independent peer review process should have independent and rigorous scientific scrutiny to be judged ethically sound.

5. Direct to consumer advertising of prescription medicines should continue to be banned and regulation of disease awareness promotion strengthened and enforced.

6. Funding should be provided for an independent consumer medicine and health information service free of commercial interest.

7. Rational use of medicines should be promoted though provision of high quality, balanced and independent information coupled with feedback to prescribers on utilisation and be matched with meaningful incentives to change behaviour.
8. Provision of free samples by pharmaceutical companies should be banned and instead a mechanism provided for prescribers to provide a short trial courses of medicines.

9. Funding of licensing bodies should not be directly linked to the number of user pays applications in order to minimise perverse incentives.

10. The organisation charged with determining medicine subsidisation from public funds needs to be separated from political and industry influence.

11. Conflicting and competing interests of members of these committees should be made more transparent and explicit rules to ensure independence.

12. Licensing criteria should be strengthened with consideration of rigorous criteria of fast track licensing, explicit consideration of added therapeutic value in licensing and subsidisation decisions and facilitation of generic introduction.

13. Drug safety should be centrally managed and preferably at arms length from the licensing body. A more robust system for pharmaco-vigilance needs to be developed which includes facilitation of a process for patient self-report.

BACKGROUND

1. The influence of the pharmaceutical industry on health systems occurs at multiple levels. Over recent years this influence has become increasingly pervasive and has seen a trend to the “pharmaceuticalisation” of health in the developed world. These influences act in the following broad areas:

Licensing

2. Current user pays arrangements in many developed countries mean that the pharmaceutical industry is effectively the main funder and therefore the “client” of licensing agencies. Requirements for licensing do not encourage balanced disclosure of research allowing proper assessment of safety and efficacy.

Direct to doctor promotion

3. This is very effective at influencing prescriber behaviour and increasing sales. This promotional activity includes visits, gifts and other inducements, subsidisation of conference attendance, free samples etc.

Education

4. Pharmaceutical companies provide significant funds for sponsorship and have undue influence on the content of continuing education for prescribers. This takes the form of meeting sponsorship, the provision of “free lunches” through to initiation of education meetings with “expert speakers” discussing the benefits of company products.

Direct to patient promotion

5. This also takes many forms and in addition to brand advertising includes disease awareness advertising, thinly disguised brand advertising, funding of disease specific consumer groups, patient education and sophisticated campaigns run by public relations companies. It also includes high profile media coverage of “important breakthrough treatments” or “diseases” with “patients” and interviews with company sponsored “experts”.

Research

6. Pharmaceutical companies are a major funding source for research. This creates conflicts of interest for investigators, skewing of research towards pharmaceutical treatments and publication bias resulting in a relative decrease in research into non-pharmaceutical and preventative treatments.

DRUG INNOVATION

7. True innovations in pharmaceutical development do occur. However, they are the exception rather than the rule.

8. It is not well understood that the way in which medicines are developed means there is no reason to suppose that a New Chemical Entity (NCE) will be automatically better than older medicines in the treatments of common chronic conditions. There is good evidence from systematic reviews of the last 20 years of innovation carried out by separate groups in France and Canada that less than 10% of all new products coming to market represent significant advance on currently available therapy.\textsuperscript{1,2} The pharmaceutical industry has demonstrated a tendency to ignore and hide evidence of non-superiority
choosing instead to invest heavily in promoting newer patented “me toos” and lifestyle drugs. This has resulted in prescription choices being driven by commercial rather than by rational prescribing principles.

An excellent individual and recent example is the ALLHAT study,\(^3\) which examined older and newer treatments for hypertension. It found that the older (and very, very much cheaper) medicines were more effective than newer heavily promoted products at preventing the serious long-term complications of raised blood pressure. This is not just of fiscal concern. Of necessity, long term safety data, (particularly of rare and serious or fatal adverse reactions) cannot be known in the early life of medicines. Over recent decades as many as 13% of new medicines have subsequently been withdrawn or had serious safety caveats imposed on their use.\(^4\) Prudent and rational prescribing would dictate that newer agents are used cautiously and conservatively only when it is likely that there will be truly significant added clinical benefit for the patient. Such listings should be monitored by publicly funded and independent pharmaco-vigilance. This rarely happens. Instead newer medicines are often heavily promoted and prescribed with unwarranted enthusiasm and little proactive monitoring.

9. The majority of true innovation occurs in state funded and usually small private research institutions. In the opinion of many, pharmaceutical companies have become little more than sophisticated marketing organisations. Despite claims to the contrary, in our opinion it appears that in many instances the high prices of branded patented medicines (largely paid for by the taxpayer) are more likely to sustain expensive marketing and PR campaigns and shareholder profit, than be used for reinvestment into research and development of medicines addressing areas of public health need. Limiting marketing excesses and reducing prices with purchasing strategies such as reference pricing would free up resource for more publicly funded innovative research targeted to areas of health need, and provide incentive for pharmaceutical companies to channel their efforts and profits into development of truly innovative drugs. The public money saved would also pay for robust independent consumer health information to counter the covert (and not so covert) direct to consumer promotion which is gaining momentum in the guise of disease awareness advertising and funding of patient groups.

**Recommendation**

10. Incentives need to be re-aligned to encourage innovation in areas of public health need (eg newer antibiotics) rather than in areas of consumer want and company profit (eg anti-ageing and lifestyle). This will never be achieved using conventional “market forces.”

**Conduct of Medical Research**

11. The majority of clinical trials (and therefore the agenda and often the research design) are now funded by the pharmaceutical industry. They are naturally very adept at designing studies to show their products in a good light. Space precludes fuller detail—many editorials in august journals have highlighted some of the greater excesses. Most forms of scientific half-truth and fraud have been uncovered and published in recent years, and a variety of dubious research practices are cause for ongoing concern. Companies do not use placebo controls or appropriate comparator drugs for their trials—comparator drugs tend to be those least likely to be efficacious and most likely to provoke adverse effects, rather than being the current most effective treatment. Doses chosen for the comparator drug are frequently not equivalent to those of the new drug. These practices result in overestimation of efficacy and safety of the newer drug. Other common practices include non-publication of trial data showing negative effects. Partial publication of data with suppression of negative data, and selection of large numbers of outcomes of dubious clinical significance which, with a currently accepted “statistical significance” level of \(p = 0.05\), results in at least one in 20 showing improved outcomes by chance alone.

12. One of the most flagrant lawful abuses of the scientific method relates to the selective minimum evidence accepted as evidence of efficacy by licensing authorities. Consider a company with a new product (perhaps an antidepressant) which it wishes to license. It commissions several trials, only two of which show any statistically significant efficacy against placebo, indeed one or two actually show the drug may have no effect or even negative effects. Only the two positive trials are put forward for publication and for subsequent proof of efficacy. In this way a product which may have almost no efficacy gains a license. With heavy promotion it may even become a blockbuster!

**Recommendations**

13. Any and all clinical RCTs involving a new product should be registered with a central agency (as indeed they already are locally to obtain ethical consent). Failure to register an RCT prior to it starting would rule its findings inadmissible as evidence in a subsequent licensing or funding application.

One of the easiest ways this could be achieved would be through ethical committees. Data from all registered trials, even those that were either not completed or remain unpublished, would have to be submitted (in a predetermined format) at the time of any licensing application, together with a statement signed by each of the investigators explaining why any studies were abandoned or remain unpublished. This process should not slow down the normal processing of applications, which already take several months to
complete. The stakes are high—blocking the licensing of a single ineffective drug could save taxpayers hundreds of millions of pounds/dollars. A model for such a global clinical trial’s register is already available in the Cochrane Collaboration trials register.

14. Marketing of products under the guise of post marketing phase 4 research should be much more closely scrutinised by ethics committees as an explicit part of their brief.

“Studies” which are no more than marketing exercises for newer “me-too” drugs should not receive ethics approval. Information sheets in pharmaceutical trials should include details of the amount of money the investigators will receive per patient enrolled and/or donations to their research trust funds and “unrestricted education grants”.

15. Those trials that are industry funded and which have not gone through an independent peer review process (which public grant funded research bodies use) should have independent and rigorous scientific scrutiny to be judged ethically sound.

Many of these poor quality studies offer little hope of producing useful new knowledge and are in fact no more than cheap promotional exercises for companies and money gathering exercises for the multitude of investigators. Adequately funded and independent pharmaco-vigilance would provide better data at less cost.

THE PROVISION OF DRUG INFORMATION AND PROMOTION, PROFESSIONAL AND PATIENT EDUCATION

16. There is intense pressure to allow direct to consumer communication or advertising by pharmaceutical companies under the guise of “information”. The concept of “public—private partnerships which superficially appear attractive, carry very real risks and provide further opportunities for industry capture. Undoubtedly industry will claim that direct to consumer disease awareness promotion is both educational and useful. However, there is no demonstrable benefit for population health and there are potential harms. There is no doubt that disease awareness promotion results in increased use of particular products in the same way as branded DTCA. For the reasons outlined above (see innovations section) the heavy promotion of products still under patent is least likely to result in cost effective health gains. Allowing advertising by permissive legislation, lack of enforcement or (as in the case of the US and NZ) by default, constitutes a public health intervention. As with any public health intervention, there should be evidence that benefits outweigh harms before implementation. We have argued that advertising of prescription medicines directly to the public is of net harm to the public health. The evidence for this is clearly detailed in our report.

17. Non-enforcement of legislation by governments, as a soft way of managing the pressure from industry, is widespread—this occurs in the USA Canada and Australia. A government’s failure to enforce a ban of advertising by allowing loopholes to permit advertising when a conscious decision has been made that DTCA is of net harm is arguably inconsistent with democratic principles. It is unclear whether this is deliberate policy to encourage industry or whether it represents an inability or unwillingness to take on the pharmaceutical industry in costly and time consuming legal battles.

18. Our report (and update) on direct to consumer advertising of prescription medicines in New Zealand has already been made available to the inquiry. The main points to note regarding regulation are that the New Zealand experience shows that complaint driven self regulation of either brand or disease awareness DTCA does not work. If the public is not to be misled, technical (ie scientific) pre-vetting for accuracy and fair balance is essential together with proactive monitoring. Central regulation is not working in the US as it is reported that the FDA have been instructed adopt a liberal attitude to enforcement by the current administration who have been extensively and effectively lobbied by industry.

Changes in Medicine Status to “Over the Counter” (OTC)

19. The licensing for provision of some prescription drugs for sale “Over the Counter” has implications for advertising in the UK. If a medicine is available OTC it can then be advertised. It will not take long for consumers to realise that it can be obtained more cheaply on prescription and for the pressure on general practitioners to prescribe to begin. This process may already have begun in the UK following the move of statins to OTC status. There is evidence from the US and New Zealand that GPs prescribe drugs they would not otherwise choose as a result of patient demand driven by advertising. This is not surprising given the “patient centred” model promoted as best practice for doctor patient decision making. Commercial drivers should not be allowed to intrude on this important therapeutic alliance.
RECOMMENDATIONS

20. That direct to consumer advertising of prescription medicines should continue to be banned and regulations around disease awareness should be strengthened and enforced.

21. Funding should be provided for independent medicine and health information service free of commercial interest.

Drug information for prescribers

22. The rules on promotion and sampling to physicians are regularly broken and it is time once again to revisit the relationship between the medical profession and the pharmaceutical industry. This promotion takes many forms; visits, inducements, gifts, funding for conference attendance, travel and provision of free samples. The influence of industry on research and medical education at all levels is very significant and ultimately driven by the need to increase sales of individual products. Despite what individual doctors feel about the influence of industry on their practice, there is no doubt that as a group, prescriber’s clinical practice is influenced by this promotional activity. To some extent this situation has arisen as the industry had picked up the shortfall from reduced central funding for both research and education (particularly continuing medical education). The irony is that allowing or indeed encouraging this influence in the end costs the taxpayer more than appropriately funding these activities centrally.

RECOMMENDATIONS

23. The keys to rational use of medicines are threefold. The provision of high quality, balanced and independent information coupled with feedback to prescribers on utilisation must be matched with meaningful incentives to change behaviour. There is research showing these are effective ways of promoting rational prescribing. The most appropriate incentive in our view is to involve prescribers in budget management with the autonomy and ability to use savings to improve patient care locally.

24. Provision of free samples by pharmaceutical companies should be banned and instead a mechanism provided for prescribers to provide a short trial course for patients of any licensed medication for a chronic condition.

REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY

25. Many countries have adopted a user (manufacturer) pays approach to licensing. This leads to a system with processes and importantly attitudes that accommodate industry as the principal client, rather than acting principally as servants of the public. Funding of licensing bodies should not be directly linked to the number of user pays applications in order to minimise perverse incentives.

26. Conflicting and competing interests of members of licensing committees should be made more transparent and explicit rules to ensure independence.

27. New drugs carry added risks and criteria for fast track licensing need to be rigorous and only implemented in unusual circumstances—for example a vaccine in an outbreak situation or where there is urgent and clear health benefit likely to accrue to a large number of users.

28. Licensing of new drugs should include consideration of the ability of a manufacturer to provide evidence of clinically significant added therapeutic value over existing therapies. This would minimise the money wasted on large numbers of heavily promoted “me too” products offering little if any health gain at increased cost.

29. Licensing of generic drugs should be facilitated. Loopholes, which allow extension of patents (“evergreening”), are a significant barrier to generic introduction.

30. The same comments apply to decisions around the state subsidisation of new drugs. The organisation charged with determining medicine subsidisation from public funds needs to be separated from political and industry influence. In this way politicians are provided with some insulation from industry when decisions are not commercially favourable.

31. Recent examples demonstrate that the pharmaceutical industry cannot be relied on to responsibly report safety concerns in a timely manner. Drug safety should be centrally managed and preferably at arms length from the licensing body. A more robust system for pharmaco-vigilance needs to be developed. This should include the facilitation of patient self-report, which is likely to be the most effective early warning system of problems.
RECOMMENDATIONS

32. Funding of licensing bodies should not be directly linked to the number of user pays applications in order to minimise perverse incentives.

33. The organisation charged with determining medicine subsidisation from public funds needs to be separated from political and industry influence.

34. Conflicting and competing interests of members of these committees should be made more transparent and explicit rules to ensure independence.

35. Licensing criteria should be strengthened with consideration of rigorous criteria of fast track licensing, explicit consideration of added therapeutic value in licensing and subsidisation decisions and facilitation of generic introduction.

36. Drug safety should be centrally managed and preferably at arms length from the licensing body. A more robust system for pharmaco-vigilance needs to be developed which includes facilitation of a process for patient self-report.

PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY

37. We suggest the committee look closely at the functioning and effectiveness of the PBS in Australia and PHARMAC in New Zealand. Value for money remains largely subjective. Pharmacoeconomics is a young and still very imprecise science. Different economists can and do make very different assumptions and predictions on the same data sets. Many of the variables, particularly opportunity costs, cannot be easily quantified. In our view there is no obvious reason why the costs of medicines should increase any more than general inflation. Compare the price of innovation in the computer industry where with time we expect more power, more memory and more data storage at a cheaper price. The prices demanded (and paid) for many new medicines cannot be justified on the basis of value added over existing products, nor on the argument of research and development costs. In many cases they do not represent good value for money. Prioritisation frameworks for organisations which evaluate products (eg NICE) should include public health needs in their prioritisation for reviews to guard against a tendency to use these evaluations solely as a counter to industry skewing the focus towards new chemical entities.

RECOMMENDATIONS

38. We suggest the committee look closely at the functioning and effectiveness of the PBS in Australia and PHARMAC in New Zealand.

39. Prioritisation frameworks for organisations that evaluate products (eg NICE) should include public health needs.

CONCLUSION

40. There is intense pressure on politicians and policy makers in all countries from powerful pharmaceutical lobbyists. The common themes of this lobbying include:
   — decreasing times to licensing;
   — more liberal rules on advertising directly to consumers;
   — increase in patent protection times;
   — increased barriers to introduction of cheaper generic drugs through intellectual property and patent protection; and
   — limit access to data used to license drugs on the grounds of “commercial sensitivity”.

41. Drug company arguments for special commercial consideration in these areas include the importance of their industry and the high costs of research and development. There is no other industry that receives commercial protection at such a high level. Third party insurers (often the state) largely underwrite their profits. In general the industry have not shown the extra responsibility that would be expected to be associated with such a privileged position. Indeed some would say they have abused this privilege. Arguments, which promote high research and development costs as a threat to viability of the industry, are not sustained by evidence. The pharmaceutical industry globally is currently among the most profitable. This does not suggest they are struggling with R&D costs or that additional concessions should be considered.

42. Medicines generally are of enormous value to the health of populations when used appropriately. The pharmaceutical industry will understandably push the boundaries as far as regulatory frameworks allow in order to maximise profits for their shareholders. Many have observed that the pendulum has swung too far in favour of the pharmaceutical industry. Governments and regulatory authorities have a responsibility to enhance and protect the health of the public, ensuring safe and effective medicines are available whilst using taxpayers money wisely. To achieve these aims incentives must be aligned to ensure that the pharmaceutical industry serves the population and not the other way around.
REFERENCES


APPENDIX 19

Memorandum by Dr Peter R Mansfield on behalf of Healthy Skepticism Inc (PI 50)

HEALTHY SKEPTICISM ABOUT DRUG PROMOTION

INTRODUCTION

This memorandum will focus on the provision of drug information and promotion but will provide brief comments relevant to all the other terms of reference for the inquiry.

We are currently working on a detailed policy discussion paper for Australia titled: “Pharmaceutical policy: Proposals for getting better value for money.” The current draft is available on request. To keep this memorandum short and relevant to the UK the focus here will be on key concepts rather than details. We understand that there are plans for the inquiry to visit Australia. Members of Healthy Skepticism Inc. including myself would be happy to discuss our suggestions in more detail then.

This memorandum includes:
— Introduction to Healthy Skepticism Inc
— Introduction to the author
— The provision of drug information and promotion
   — Understanding the problems
   — Possible solutions
— Professional and patient education
— Drug innovation and the conduct of medical research
— Regulatory review of drug safety and efficacy
— Product evaluation, including assessment of value for money

INTRODUCTION TO HEALTHY SKEPTICISM INC

Healthy Skepticism is an international non-profit organisation for health professionals and everyone with an interest in improving health. Most members are doctors or pharmacists. Our main aim is to improve health by reducing harm from misleading drug promotion. Our strategy includes three approaches: research, education and advocacy. One of our activities that brings all three approaches together is Healthy Skepticism AdWatch.

AdWatch is a monthly webpage designed to help doctors, pharmacists and the public defend ourselves from misleading drug promotion. AdWatch illuminates the logical, psychological and pharmacological techniques used in drug advertisements. AdWatch also provides practical recommendations for optimal medical care. Everyone is invited to participate by providing feedback to the AdWatch team and to the companies responsible for the advertisement.

We are based in Australia but have many supporters in the UK. We have published many articles in the BMJ (British Medical Journal) and The Lancet. One of these articles is a review of the evidence about antidepressant drugs for children published in the BMJ in April 2004. We concluded that the magnitude of benefit from antidepressant drugs for children is unlikely to be sufficient to justify the risks of harm. We also reported that “authors of all of the four larger studies have exaggerated the benefits, downplayed the harms, or both.” Our article received extensive coverage in newspapers around the world.

A second opinion about Healthy Skepticism Inc:

“A small group known as Healthy Skepticism . . . has consistently and insistently drawn the attention of producers to promotional malpractice, calling for (and often securing) correction. These organisations [Healthy Skepticism, Médecins Sans Frontières and Health Action International] are
small, but they are capable; they bear malice towards no one, and they are honest. If industry is indeed persuaded to face up to its social responsibilities in the coming years it may well be because of these associations and others like them.”—Graham Dukes (Professor of Drug Policy Studies, University of Oslo, Norway)34

INTRODUCTION TO THE AUTHOR

The author of this Memorandum is Dr Peter R Mansfield, General Practitioner, Director of Healthy Skepticism Inc. and Research Fellow, Department of General Practice, University of Adelaide. Peter’s research is supported by (Australian) National Health and Medical Research Council Public Health Postgraduate Scholarship 250465. In 2004 Peter was awarded Flinders University’s highest award for graduates: The Convocation Medal “for outstanding leadership in the advancement of professional practice and service to the community in the safe use of pharmaceutical drugs.”

THE PROVISION OF DRUG INFORMATION AND PROMOTION

UNDERSTANDING THE PROBLEMS

1. Currently drug promotion does more harm than good

All of the studies, that we are aware of, that measure the impact of exposure to and attitudes towards drug company information on the quality of medicines use support the same conclusion. The more doctors depend on drug company information, the more medically inappropriate and expensive their prescribing.35,36,37,38,39,40,41,42,43,44,45,46

It is likely that drug promotion can be beneficial when the following conditions are met:

— the information used is reliable, balanced and relevant without significant omissions.
— that drug has a superior ratio of benefits over harms and costs compared to current treatments for a specific indication.
— the drug is currently under used for that specific indication.
— the promotion is targeted at increasing the use of a drug for the specific indication to appropriate levels and not beyond.

However, those conditions are rarely met. The percentage of new drugs that have any medical advantage over older cheaper drugs has been assessed as only 23% during 1989–2000 in the USA and only 10.5% during 1980–2003 in France.47,48

A major economic study of drug promotion in The Netherlands concluded that the “average effect of drug marketing on price elasticities is unambiguously welfare-negative. This is because the effect we see is an effect after correcting for quality differences and this allows us to interpret the lower sensitivity to prices as brand loyalty not supported by product characteristics. This is socially undesirable.”

We conclude that drug promotion is an effective tool that can be used for good or ill. However, currently drug promotion does more harm than good.

2. Doctors are susceptible to influence

Doctors have mostly been trained to memorise and apply medical information but few have much expertise in critical appraisal of scientific evidence or in the psychology and informal logic of decision making. Doctors are intelligent but nevertheless are often vulnerable to being influenced by the same advertising methods that influence many other people. For example, even small gifts lead to unintended bias. Many doctors are aware that other doctors are influenced by drug promotion but deny that they are influenced themselves. That “illusion of unique invulnerability” makes people more vulnerable.

We conclude that doctors are more vulnerable to misleading drug promotion than they think. This probably also applies to everyone else.

3. Drug companies seek profits

Drug companies do what they are paid to do. Regardless of the level of good intentions, companies have little choice but to do what works to maximise profit. Otherwise they risk being overtaken or taken over by more aggressive competitors. If the probability and magnitude of gains from misleading promotion exceed the risk of penalties then misleading promotion should be expected. Drug company staff may be genuinely misled by their own propaganda because of groupthink or they may comply with what works because of “golden handcuffs” (the fear of losing jobs that pay more than they could get elsewhere).

Current systems, in all the countries that we know about, pay drug companies most for doing what works to increase the price and sales of new patent monopoly protected drugs regardless of the impact on health. Drug companies know a great deal about what works for influencing doctors and have huge resources for promotion.

We conclude that drug companies currently use misleading drug promotion because it is profitable. If they could make more profit using reliable promotion, they would.

4. We have a system problem

Currently doctors and drug companies are locked together in a flawed system where both groups encourage the other to do the wrong thing in a vicious cycle. If companies over-promote their drugs effectively, doctors reward them via higher drug sales. If doctors over-prescribe drugs, companies have more money for gifts and for promotion reinforcing doctors’ beliefs that they are doing the right thing.

We conclude that, because doctors are vulnerable to misleading promotion, the system currently rewards drug companies for promotion that is distorted towards increasing sales regardless of the impact on health.

POTENTIAL SOLUTIONS

There are four main approaches that if used in combination could unlock the system problem described above:

1. Increased regulation of drug promotion.
2. Improve medical decision making.
3. Redesign the incentives for doctors.
4. Redesign the incentives for drug companies.

50 Smith R. Doctors are not scientists. BMJ 2004;328 http://bmj.bmjournals.com/cgi/content/full/328/7454/0-h
1. *Increased regulation of drug promotion*

Because drug promotion currently does more harm than good, ideally it should be completely banned. We understand that this recommendation may seem extreme but it does follow logically. If banning drug promotion is not achievable then the more it can be limited the more health care is likely to be improved. Whatever promotion is allowed should be regulated up to the point of diminishing returns.

Evaluation of drug promotion requires skills in many fields including: clinical pharmacology and pharmaco-epidemiology, health economics, marketing, psychology, semiotics and informal logic. Healthy Skepticism Inc. has a track record in medical education and training for organisations such as the Australian Health Insurance Commission. We would be willing and able to develop training in evaluation of drug promotion for regulators.

We recommend using a regulatory pyramid approach as elucidated by Ayres and Braithwaite (1994). This involves developing the capacity to use a wide range of sanctions with the understanding that if problems are not resolved with easy sanctions then the regulator will move to using progressively more onerous sanctions.

Easy sanctions should include appeals to social responsibility. Healthy Skepticism Inc. has over 20 years of experience with such appeals, sometimes with significant success.

Medium level sanctions should include appeals to the desire for profit. The probability and magnitude of fines need to be greater than the probability and magnitude of profit from misleading promotion.

Ideally regulatory pyramids should include removal from the market as an achievable final sanction. This is because some companies don’t respond appropriately to lower level sanctions. It is accepted in most countries that regulation of health professionals should include the capacity to remove them from the market. However removing a large pharmaceutical company from the market would cause significant harm if it is a monopoly supplier of essential drugs. Consequently, it is important to develop other incapacitating sanctions. One option is to have the capacity to revoke licences to promote specific drugs for specified periods. Another option is to develop professional regulation systems for individual staff of pharmaceutical companies so that individuals can be removed from the market. However it is important to remember that the cause of the problems is at the system level so blaming individuals alone will not solve the problem. If the system is not changed the staff who replace those who have been removed are like to behave in similar ways to their predecessors.

Developing regulatory capacity is not enough without appropriate implementation. Implementation is often undermined by the normal process known as regulatory capture. Ayres and Braithwaite (1994) have made a detailed argument for avoiding regulatory capture by using a combination of (a) regulation by government staff with (b) industry self regulation and (c) delegation of regulatory powers to non-profit public interest groups. We agree with their conclusions. Healthy Skepticism Inc. would consider serving in the way Ayres and Braithwaite suggest if the opportunity arose.

Without the capacity to remove whole companies from the market, regulation alone will not be enough to solve all the problems so regulation should be combined with the other approaches below.

2. *Improve medical decision making*

Medical decision making can best be improved via education for doctors, pharmacists and consumers so that all are empowered to play their part better. Healthy Skepticism Inc. has expertise in education for medical decision making particularly via the *AdWatch* section of our website. We are willing and able to share our expertise.

If doctors were helped to become better decision makers then prescribing could improve. Such improvement could occur in part via reduced vulnerability to misleading drug promotion. Drug companies could reduce that improvement by using more subtle misleading techniques, but it is also possible that they might adapt to improved decision making by providing more reliable information. The fact that doctors have human vulnerabilities limits the extent of improvement that can be achieved by improving medical decision making alone. However worthwhile improvements may be achieved if improved decision making capacity is supported by incentives as is discussed below.

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59 Mansfield PR. MaLAM, a medical lobby for appropriate marketing of pharmaceuticals. Med J Aust 1997; 167: 590–592

3. Redesign the incentives for doctors

Ideally doctors should be prohibited from receiving any incentives from drug companies because even small gifts lead to unintended bias.61, 62 This may seem an extreme position but the available evidence suggests that no other policy would be effective for reducing adverse influence. If prohibiting gifts is not achievable, another option would be to make all gifts taxable. As an example, if doctors were invited to a meeting and served a meal then the drug company would be obliged to issue them with a form giving the value of the meal. At tax time doctors would have to declare, and pay tax, on all gifts that they received from drug companies.

We are aware that the UK is about to experiment with expanded direct incentives for achieving performance targets.63 Such incentives may be beneficial in their own right and may have a beneficial side effect of motivating doctors to be more wary of drug promotion that conflicts with the achievement of quality targets. This hope is supported somewhat by experience in New Zealand where giving GPs a period of budget management responsibly is thought to have led to a significant increase in the level of scepticism about drug promotion.64

We conclude that removing incentives for bad practice and increasing incentives for good practice will contribute to reducing the adverse influence of drug promotion. We use the concept of direct incentives for achieving performance targets as a model for part of our proposals of redesigning incentives for drug companies below.

4. Redesign the incentives for drug companies

Drug companies are currently paid according to drug sales volumes at prices that are much higher than manufacturing costs. They use the surplus for multiple functions including research, education and promotion. We recommend that these separate functions be paid for separately by splitting the government funds currently paid to drug companies into separate payment sources for each function: research, education, promotion etc. Each payment source would invite organisations (including drug companies) to submit proposals for funding by competitive tender.

For example, the promotion payment source could put out to tender contracts for promotion of activities given priority according to health need. These priority activities could include pharmaceutical issues (eg increasing the use of underused drugs or decreasing the use of overused drugs) and also non-pharmaceutical issues (eg increasing physical activity levels). These contracts could include direct incentives for achieving performance targets. Drug company marketing departments could compete against, or form consortia with, other organisations (eg universities and non-government organisations) to win these contracts.

Such tendering could produce significant improvements with minimal disruption to pharmaceutical companies because they already subcontract many of these activities to other organisations, eg advertising agencies, university researchers and medical education providers.

Total payments from government to drug companies could be kept the same. The separate payments for promotion would be funded from savings achieved by lowering drug prices towards manufacturing costs without the large surpluses that are currently used to pay for other functions such as research, education and promotion etc. These functions would be paid for separately. The lower prices would reduce the funds available for misleading promotion and reduce the profits to be gained from it.

Another proposal that is compatible with our first proposal is to pay for drug sales with a blended combination of the traditional payments per sales volume (but at lower prices) supplemented with bonus payments for achieving performance targets. These targets could include measures of appropriate utilization across postcodes in proportion to need and measures of appropriate prescribing by doctors. Such direct incentives for achieving performance targets would reward appropriate promotion.

A third proposal that is compatible with our other proposals is to use price volume agreements and risk sharing agreements as have been used in Australia65 or capped annual contracts as have been used in New Zealand.66 Under price volume agreements the price paid per drug pack gradually decreases as the sales volume increases so that the incentive to over-promote is reduced. By contrast fixed prices reward over-promotion because of economies of scale over fixed costs lead to higher marginal profits at higher sales volumes. Capped annual contracts are similar except that once a pre-specified sales target (calculated to match national needs) has been reached then the price paid for additional sales drops to zero. This gives drug companies an incentive to de-promote their drug if it is being overuse so as to maximise their profit by maintaining sales volumes at the target.

64 Personal communication. Prof Les Toop.
Political achievability of these proposals would be enhanced by ensuring that drug companies continued to receive good returns on investment as long as they were efficient and effective at achieving the new performance targets. The main difference would be a shift from paying drug companies to do the wrong thing (over-promoting drugs) to paying them more according to their contributions to improving health. In the long run giving drug companies a more valuable role plus economic gains from improved health would enable and justify countries to pay drug companies more money than otherwise. Drug company staff who are unhappy about the status quo may be more productive if enabled to work more for the common good than currently.

**Protagonists and Patient Education**

Similar tendering systems as suggested above for promotion could be used as a better way to fund continuing education for health professionals, patients and the wider public.

Last week the BMJ accepted a commissioned editorial written by Peter Mansfield and experts in Canada and New Zealand about the conflicting pressures on policy about direct to consumer promotion of prescription drugs that. We concluded that “the potential awareness raising benefits of direct to consumer advertising could be better targeted and sustained at lower cost with less harm through publicly funded and accountable drug information services and health campaigns.”

**Drug Innovation and the Conduct of Medical Research**

Rather than aiming at greatest medical need, current systems for paying drug companies reward research and development of “me too drugs” for chronic conditions of people who have the greatest capacity to pay. The industry is spending increasing amounts on that type of research with diminishing returns. The large pharmaceutical companies are increasingly outsourcing research and development to smaller organisations that are more innovative and efficient.

Drug company funding of medical research is associated with systematic bias.

Similar tendering systems as suggested above for promotion could be used as a better way to fund drug research and also development of drugs that currently would not be developed by drug companies because they are judged unlikely to be very profitable.

**Regulatory Review of Drug Safety and Efficacy**

Our comments above about the problem of regulatory capture in relation to regulation of promotion also apply to regulation of safety and efficacy, so we will repeat them here:

Developing regulatory capacity alone is not enough. Regulators must use their capacities appropriately. This is often undermined by the normal process know as regulatory capture. Ayres and Braithwaite (1994) have made a detailed argument for avoiding regulatory capture by using a combination of (a) regulation by government staff with (b) industry self regulation and (c) delegation of regulatory powers to non-profit public interest groups. We agree with their conclusions. Healthy Skepticism Inc. would consider serving in the way Ayres and Braithwaite suggest if the opportunity arose.

**Product Evaluation, Including Assessment of Value for Money**

Evaluation of drugs includes evaluation of the claims that drug companies make about their drugs. This requires similar skills to those required for evaluation of drug promotion including: clinical pharmacology and pharmaco-epidemiology, health economics, marketing, psychology, semiotics and informal logic. Healthy Skepticism Inc. has a track record in medical education and training for organisations such as the Australian Health Insurance Commission. We would be willing and able to develop training in evaluation of claims about drugs for drug evaluators.

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68 Davis L. BIO conference shows biotech partnering is still key to big pharma growth. SCRIP—World Pharmaceutical News 23 June 2004.
ACKNOWLEDGEMENTS

I thank A/Prof Joel Lexchin of the School of Health Policy and Management at York University, Canada, Ms Melissa Raven of the Department of Public Health, Flinders University, Australia, Prof David Menkes of the Psychological Medicine Academic Unit, University of Wales, UK and Dr Staffan Svensson of the Department of Clinical Pharmacology, Sahlgren’s University Hospital, Gothenburg, Sweden for helpful comments.

APPENDIX 20

Memorandum submitted by the Joint Task Force on Medicines Partnership (PI 58)

1. INTRODUCTION

1.1 The Task Force on Medicines Partnership is a Department of Health funded programme which aims to help patients to get the most out of medicines by implementing the principles of concordance. Concordance is a process of successful prescribing and medicine taking where health professionals and patients work together as partners to agree on diagnosis and treatment, and patients are supported in medicine taking.

1.2 Medicines Partnership was set up at the start of 2002 under Pharmacy in the Future, part of the NHS Plan. It consists of a 30 member Task Force, supported by the Medicines Partnership centre, hosted by the Royal Pharmaceutical Society (RPSGP), under the Directorship of Joanne Shaw. Medicines Partnership has a unique perspective on how to enable patients to get the most out for their medicines, because the Task Force represents a unique collaboration between the NHS, health professionals, patient groups, academics and the pharmaceutical industry.

1.3 The experience of the Medicines Partnership programme demonstrates the following:

— It is possible for the NHS to work closely with the pharmaceutical industry for the benefit of patients and collaborating partners. Through its programme, Medicines Partnership has worked successfully with industry, harnessed industry resources and influenced industry to work differently in many of its projects. The key prerequisite for a successful joint project is transparency of objectives at the start.

— In order to make informed choices and get the most benefit from medicines, patients need much better information and support at the time of the prescribing decision and when they come to use medicines. There is currently a lack of clear, accessible information for patients which accurately presents the possible risks and likely benefits of different treatment options. Pharmaceutical companies are well placed to contribute to this information because of their unique resources and knowledge of their own products. Regulatory constraints, and fears about pharmaceutical company influence limit the extent to which companies use their resources in this way. A number of Medicines Partnership projects illustrate how this can be done effectively.

2. MEDICINES PARTNERSHIP’S WORKING RELATIONSHIP WITH INDUSTRY

2.1 The Task Force has been a partnership with industry from the outset. In 1995, Merck Sharp and Dohme and the Royal Pharmaceutical Society of Great Britain established a joint commission on the causes and consequences of non-compliance. Research suggested that 50% of medicines prescribed for long-term conditions are not taken as intended. This represents a huge cost: to patients (in avoidable ill health and premature death), to the NHS (in wasted medicines and avoidable hospitalisation); to society (in avoidable sickness absence and social support)), and to the pharmaceutical industry (in lost revenues and mistaken perceptions about efficacy).

2.2 The programme has five objectives:

— To encourage and enable professionals to involve patients as partners in prescribing decisions;

— To ensure that medicines concordance is incorporated in public and private sector policies;

— To facilitate model practice projects and demonstrate results;

— To influence patient and public expectations;

— To enlarge and disseminate the knowledge base about concordance.

2.3 The programme breaks new ground by recognising the mutual interest of both the public and private providers of health services in improving medicines’ use, and seeking innovative and transparent ways to allow the two to work together within current guidelines.

2.4 Examples of projects where Medicines Partnership has worked jointly with industry include the following:
— We are building on the learning of Roche, Biogen and Schering-Plough who are all providing proactive nurse-led telephone support programmes for patients taking specific medications. We are assisting these companies in evaluating their services and making them more sensitive to the needs of patients. We hope to use the results to inform a randomised controlled trial of telephone support for people taking statins, and use this to build a case for much greater provision of these services where they are shown to be effective, possibly offered through NHS Direct.

— We collaborated with a range of companies and other stakeholders to deliver Ask about Medicines Week 2003, a campaign intended to encourage the public to be more proactive in finding out about their medicines. Planning is now well in hand for a second Ask about Medicines Week in November 2004.

— We are collaborating with the ABPI and individual companies to develop a new structured source of medicines information which will be available through NHS Direct Online and other media. This is the subject of a separate submission to the Committee from the Medicines Information Project itself.

— With Merck Sharp and Dohme and MORI, in 2003 we commissioned a major survey of patient attitudes to medicines and medicines information, to access success to date with the national agenda. This will form a baseline against which repeats of the survey will be compared in this and future years.

— We have received a major unrestricted educational grant from Pfizer to pilot a community pharmacy service for patients with Parkinson’s Disease and are working collaboratively with them and other stakeholders on implementation.

— We have worked with Bristol Myers Squibb to develop a guide for health professionals on setting up medication review services for people with schizophrenia.

— We have collaborated with Sanofi Synthelabo and a consortium of interested organisations, including the Muslim Council of Britain and a rabbinical authority and advisor to the Board of Deputies of British Jews, to produce a guide to drugs of porcine origin and their clinical alternatives, with information on culturally sensitive prescribing.

2.5 Throughout these projects, two important principles have guided the way in which we work with industry and made it possible for all parties to benefit.

2.6 Firstly, there has been transparency of objectives on all sides at the outset. The recent ABPI and NHS Alliance guidance on the NHS and Pharmaceutical Industry working together suggests that industry and the NHS should agree joint objectives at the outset of projects. Whilst this is important, we also believe that in addition, there must be a recognition that the different parties involved have different goals and reasons for participating, and these need to be clearly understood by all to avoid misunderstanding and mistrust.

2.7 Secondly, in all of our projects, three parties are involved: the NHS (including prescribing professionals), patients and patient organisations, and industry. This coalition of interests and expertise provides an effective check on any potential undue pharmaceutical company influence: prescribing professionals are usually able to provide a fact-based, unbiased perspective on the evidence for different treatment options and patient groups provide an important user-perspective.

3. The Need for Improved Medicines Information and Support, and the Pharmaceutical Industry’s Role

3.1 Concordance requires patients to have sufficient information about treatment options, in a style and format that meets their needs, to enable them to make informed choices about treatment in collaboration with a health professional. A newly published study confirms the findings of many before it: after around four weeks, a large proportion of patients starting out on new medicine for a chronic condition are no longer taking the medicine—most intentionally so—and most expressed a substantial and sustained need for more information about their medicine.

3.2 The pharmaceutical industry is well placed to play an active role in providing enhanced information about medicines. Companies have unrivalled access to information about the risk and benefit profile of individual medicines through both trial data and reported incidence of adverse reactions after product launch. They also have access to substantial resources to enable them to deliver information and support, and also a significant interest in doing so. The Medicines Partnership projects outlined above show that, with the right checks and balances in place, industry can play a valuable role in this area to the benefit of patients.

3.3 There are a number of regulatory and other barriers to industry playing this role to the full. For example:

Regulations limit the usefulness of the patient information leaflet which each product must carry, and result in many patients reporting that the leaflets are too general, too narrow, too negative and too late to meet their needs.\textsuperscript{75}

Direct to consumer advertising controls, and the ABPI code of conduct, have led to confusion about whether it is legitimate for companies to inform patients prescribed with their products about the availability of support and information services offered. Therefore, for example, the Motivation, Advice and Proactive Support (MAP) telephone service offered by Roche to patients taking Orlistat (Xenical\textsuperscript{\textregistered}) for obesity, is not advertised on the product packaging, and patients can only find out about it from a health professional.

In our experience, fear of pharmaceutical company influence can prevent local health services working collaboratively with industry at an organisational level, leaving relationships with companies to individual health professionals, where problems can occur.

4. CONCLUSIONS AND RECOMMENDATIONS

There are good reasons why pharmaceutical industry influence on the NHS needs to be considered very carefully. Industry can play a valuable role, particularly in providing information and support to patients taking medicines to facilitate shared decision-making with health professionals. Medicines Partnership has shown how industry collaboration can work well, both through individual Medicines Partnership projects and also through the Medicines Partnership programme as a whole, which has been an open collaboration with industry from the start. Based on this experience, we believe that mistrust of pharmaceutical companies prevents industry from playing its potential role to the full, and that patients and the NHS would benefit from more open, transparent, multi-lateral working relationships with industry.

\textit{Joanne Shaw}

Director

APPENDIX 21

\textbf{Memorandum by APRIL (Adverse Psychiatric Reactions Information Link) (PI 60)}

\textbf{SUMMARY}

The charity collects and collates information from health professionals, the public and from medical literature about psychiatric and neuropsychiatric adverse drug reactions (ADRs), and alerts doctors and professors to inquiries such as this one.

The chair Mrs Millie Kieve who, as part of a Millennium Award in 2000, studied suicide prevention and attended meetings and conferences in the UK and the USA. Many leading specialists in the field of ADRs support the charity by speaking at conferences and offering advice and information. All the information in this submission is from knowledge and information gained since Karen Kieve died following a series of adverse reactions to a variety of medicines and anaesthetics in 1995.

The charity held a major conference in 2001 and will hold one 4 November 2004.

Meetings are planned at the House of Commons and the Royal Society of Medicine. All this work is done with little funding and no paid staff.

1. DRUG INNOVATION

(a) The pharmaceutical industry had a higher than expected trade surplus of £3.6 billion in 2003 (ABPI Press Release 19 May 2004) The industry spends very little of their profits on new drug development.

(b) A great deal of money is spent on producing what are known as “Me Too” drugs to break into the market of competitors. Ingredients of established drugs may be altered or just the name changed. Sometimes old drugs may be directed at new conditions not included in the original licence application. For example Duloxetine was used for urinary tract infection and will be marketed as an antidepressant. Prozac became Sarafem and Wellbutrin became Zyban.

\textit{Recommendation for action by the Government}

(a) There should be a mandatory obligation for the industry to spend a designated proportion of profits on research for treating rare disease and finding cures for iatrogenic disease and other long-term medical conditions.

\textsuperscript{75} Raynor, DKT, British Pharmaceutical Conference, 2003.
(b) New licences could be restricted to drugs proven in clinical trials to be more effective or safer than similar drugs already on the market. Only drugs with improved efficacy or safety in comparison with existing licensed drugs, at equivalent doses, should be considered.

2. The Conduct of Medical Research

(a) Favourable results of clinical trials have been selectively published and unfavourable results suppressed.

(b) Serious adverse drug events (SAEs) during clinical trials are not disclosed.

The SAEs that occur during the clinical trials are the confidential information of the pharmaceutical company. James Wright, Professor of therapeutics and pharmacology at the UBC Canada presented some startling information from clinical trial data that he has researched for Zyban, cox 2 inhibitors and statins. I have his presentation and he has given me permission to share this information so it could be viewed by the Health Committee.

Information about the agitation suffered by people withdrawing from Seroxat in a pre licence trial, was not disclosed by GSK in pre licensing data. Dr David Healy found this evidence in the GSK files in their premises, during his research when he was allowed access for legal reasons.

(c) There is no research into why adverse drug reactions (ADRs) occur and no research to discover the causes of iatrogenic disease.

(d) There are no NHS clinics offering specialised help for iatrogenic illness or support for medication withdrawal. Such clinics could run research trials into ADR causes. NECA was the only dedicated withdrawal clinic run by Professor Heather Ashton to support people withdrawing from benzodiazepines.

(e) Too little research is carried out in the area pharmacogenetics.

Recommendation for action by the Government

(a) All clinical trials should be pre-registered and ALL results given to the regulators. All clinical trial data should be in the public domain. Freedom of information should apply. Undisclosed information leading to harm of patients should lead to legal proceedings.

(b) Serious Adverse Events (SAEs) should be disclosed to the regulators.

(c) Research into ADRs should be mandatory.

(d) Clinics for medication withdrawal support and for monitoring sufferers of iatrogenic disease should be government funded. Information and data from these clinics could provide valuable research material.

Professor Heather Ashton estimates 200,000 involuntary benzodiazepine addicts in the UK. Many people need support to withdraw from SSRI antidepressants.

(e) Enzyme deficiencies lead to ADRs and death, yet the “one size fits all” method of drug prescribing is costing the NHS a great deal of money due to the damage to health of thousands of patients. Patients suffering ADRs could be tested for enzyme deficiencies. Preventative initiatives could include enzyme and endocrine tests, which could possibly identify groups liable to suffer ADRs.

The Nuffield Bioethics Pharmacogenetics consultation results should be studied.
http://www.nuffieldbioethics.org/pharmacogenetics/latestnews.asp

The network of genetic centres in which the Government has invested, to investigate disease, should not just be to facilitate tests for genetic disease as at present. They could test patients for enzyme deficiencies to assess drug tolerance.

3. The Provision of Drug Information and Promotion

(a) Information

I. Patient Information Leaflets (PILs) do not contain enough information and are often unclear with ADRs being hidden in the small print. The fact that a drug may cause depression or suicidal ideation is often not stated.

II. Consent forms would ensure that the prescribing clinician explained the risk benefit to a patient, and the advisable safeguards for taking and withdrawing from medication.

III. Newly discovered ADRs from Yellow Card signals or Prescription Event Monitoring (PEM) studies are not put on the PILs, for many years or not at all in some cases.

IV. Drugs dispensed from bulk supply are often given to the patient in a brown bottle without a PIL. Hospital patients are seldom given information.
V. PILs do not disclose previous names under which the same drug was marketed.

VI. Hospital libraries have been found from personal research to lack vital ADR manuals and books. Even small publications such as the Consumer Assn Drug and Therapeutics Bulletin and the CSM Latest problems in pharmacovigilance are unavailable to most medical and nursing students.

VII. There is currently no system to keep coroners regularly informed about new ADR alerts or lists of drugs which affect a person’s driving ability.

VIII. Patients receiving dental treatment are not given PILs for drugs used during treatment.

Recommendation for action by the government

I. PILs from all manufacturers for the same or similar products, should be compiled and approved by independent scientists and not by sales people. Information and class warnings should be standardised, with nothing missed out that could be detrimental to the patient’s health. If a drug may cause suicidal feelings the PIL should state this. If a drug causes depression it should state this. “Tell your doctor if you have ever suffered from the following” does not explain that a drug can CAUSE the following . . .

The PILs should be reviewed by patient groups as well as specialists. The colour and size of print should be readable. It should be available in different languages, with a clear heading “POSSIBLE ADVERSE EFFECTS” on every PIL.

WARNINGS ABOUT THE RISK OF ALCOHOL with medicines should be put on PILs, in the box and also on the outside of the box. Any food or fruit juice that is contraindicated should be shown on the box and marked clearly on the PIL.

PILS should include the need to drink a full glass of water at least with medicines. The reason for this should be given which is to prevent damage to the oesophagus or kidneys and help prevent blood disorders.

II. The provision of consent forms in several languages should be considered for all long term medication. People are still informing APRIL of the fact that they have been taking cortico-steroids having received no warning about the risk of osteoporosis or the risk of suddenly stopping steroids. Mental depression caused by medication is being regularly treated with antidepressants without patients being informed their depression is medication induced. Depression is a serious condition and often triggered by medication ADRs. APRIL can provide testimony from hundreds of patients who in most cases failed to persuade their doctors to send in Yellow Card reports. Many of whom were prescribed antidepressants without having the original drug stopped. (Zoton and Dianette are often named as drugs causing depression, which lifts once the drug is stopped.

Marketing departments change the wording on PILs and adverts, without consulting the medical staff, I was informed by an MP who used to work for an advertising agency and by a pharmacist working for pharmaceutical companies.

III. Prescription Event Monitoring Studies (PEMs) ignored by MHRA and the manufacturer.

The Pharmacovigilance of Mirtazapine: results of the DSRU prescription event monitoring (PEM) study on 13,554 patients in England. This showed evidence of serious ADRs which are still not on the drug information or included in the CSM bulletin “Current Problems in Pharmacovigilance”. The following results: Agitation (73), aggression (70), rash (20), hallucinations (13) and abnormal dreams (31), were all unlabelled AES. The Drug Safety Research Unit (DSRU) PEM Journal of Psychopharmacology 2003;17(1):121-126. http://www.dsru.org/

Doctors should be informed individually by the pharmaceutical companies of such information as found in the DSRU PEM study and in other studies highlighting ADRs.

The Committee on Safety of Medicines (CSM) should include signals of unlabelled ADRs information from DSRU PEM studies in their publication “Current problems in pharmacovigilance”.

The MHRA should have mandatory power to add information to Patient Information data and PILs, the ADRs reported in studies, or on Yellow Cards reporting forms. Dr June Raine told me that the initiative has to come from the pharmaceutical company and this is not a satisfactory arrangement.

IV. Bulk supplies leads to many drugs being dispensed and given to the patients without advice or information due to lack of PILs being supplied by the manufacturer.

Pharmaceutical companies should supply enough PILs for every patient to receive one with their prescription from bulk supply dispensing.

Hospitals should provide the patients or their families with information about the drugs they intend to prescribe. Patients should always be provided with PILs to take home from the hospital.
V. Zyban also known as bupropion and wellbutrin has been documented for years as a drug that may cause seizures. Anyone prescribed this drug as an anti-smoking aid, in England would not necessarily know they were being given a well know antidepressant known as wellbutrin. This information is not on the patient information leaflet (PIL).

Prozac being re licensed for PMT under the name Sarafem may be given inadvertently to someone who should not be given SSRIs. All names that the drugs were previously marketed under should be on the PIL.

VI. The Government should make it a requirement by law that all available information on ADRs should be in every hospital library and kept up to date. Libraries should be inspected, possibly by patient volunteers who could be given a list of books to look for. Medical and nursing students should have easy access to the information available.

VII. Coroners should have access to information and independent advice about the role medication may have played in a sudden death. This charity APRIL is a resource but there should be an official resource for all coroners, many of whom have no medical knowledge.

VIII. A coroner informed me of a dental death where the fact that dental treatment was involved, was not even put on the death certificate. All dentists should be informed that patients are entitled to a PIL by law.

(b) Promotion

I. The Royal Institution of Great Britain has been holding a series of talks and meetings sponsored by Novartis at 21 Albermarle St London W1 aimed at audiences consisting of the general public, since 2001. These are still continuing, so must be of benefit to Novartis. The publicity for the talks may not mention specific drug promotion, or the fact that Novartis are sponsoring the talk, but the picture in the lecture theatre my be different.

I attended one of the Novartis meetings on 24 May 2001 titled “Schizophrenia”. At the side of the speakers was a large promotional poster.

The meeting was promoting early diagnosis, early drugging and specifically was singing the praise of Clozapine, the Novartis blockbuster drug for schizophrenia.

I heard Dr Adreanne Reveley state that Clozapine has no side effects. I also heard her state that the earlier you administer drugs the better the outcome. The emphasis was on finding evidence of schizophrenia in children and starting Clozapine as early intervention. She said there is a better outcome the earlier you administer the drugs. Professor Robin Murray was there to support her statements.

I was with psychologist Rufus May and will be willing to give oral evidence of the content of this meeting which was blatant drug promotion to the masses. Novartis had intended to use a film of the meeting as promotional material, on the internet but this intention was apparently thwarted by the close detailed questioning by Rufus May and myself.

II. “Europe’s premier forum for marketing and communications professionals in the pharmaceutical industry” was held in London on 10 and 11 May 2004.

The Forum brochure was quite disturbing and illuminating about the marketing tactics of the pharmaceutical industry and gives a hint of how unscrupulous the industry is in promoting drugs and disease awareness.

On Day One talk titles included:

10.20 “PATIENT RELATIONSHIP MARKETING-” The new DTC?
   * Understanding and segmenting patient populations.
   * Building profitable long term patient relationships etc

12.00 “DEVELOPING DISEASE AWARENESS AND PRODUCT CAMPAIGNS”
   * Do we really want disease awareness campaigns?
   * Have they got a future? etc

13.45 “MARKETING TO LOWER SOCIO ECONOMIC GROUPS”
   * Why your marketing to consumers needs to be trashy, have a reading age of 9, lots of bold colours and still be legal.

On Day Two Tuesday talk titles included:

11.20 “THE POWER OF STRONG BRANDING IN LIFE CYCLE MANAGEMENT”
   * Brands as business assets; brand development and its role in the pharma industry
   * The Zantac-Tagamet example: optimisation of a blockbuster etc

14.20 “WORKING TOWARDS SYNERGY BETWEEN PROFESSIONALS AND PATIENT GROUPS” (themed luncheon discussion)

A profile for speaker Philip Atkinson International Consumer Marketing Manager for Roche Pharmaceuticals, Switzerland it states at the end of the paragraph. “Philip’s specific interest is how to drive patient demand for healthcare products.”
(You can download the pdf brochure at http://www.pmc.access-events.com then click on Programme and when the programme page shows the participants, click on the small blue arrow which states “click here to download brochure as a pdf.”)

III. FREE HOLIDAYS AND ENTERTAINMENT are provided and doctors feel obliged to order expensive products from their host. Direct promotion of drugs to health professionals is a reason for the provision of perks in the way of free food, entertainment, holidays in luxury hotels and trips abroad. This is still happening yet well hidden.

IV. PATIENT SUPPORT GROUPS are sometimes set up by pharmaceutical companies and others are financially supported by them. This leads to the promotion of drugs in the groups journal and meetings where the drugs are promoted and little attention paid to warnings about ADRs. On a web site of a leading charity dealing with anxiety and supported by two pharmaceutical companies, there is a list of drugs used to treat the condition, no link to discussions about risk benefit or ADRs. Named doctors and professors on the anxiety site I viewed are known declare that they receive income from pharmaceutical companies.

V. CME SEMINARS AND MEETINGS sponsored by pharmaceutical companies should be reviewed. Clinicians are sometimes paid to promote drugs in meetings and conferences.

VI. CONFERENCES are so heavily sponsored by the pharmaceutical industry and the representatives are everywhere promoting and standing around looking at the doctors who, I believe feel intimidated and therefore do not ask relevant questions about ADRs during conference sessions. Very little discussion of risk benefit or ADRs took place at the British Association of Psychopharmacology annual conference, I attended. In a talk about suicide and antidepressants, I was the only person to ask about incidents of akathisia (drug induced physical and mental agitation that often leads to suicide).

VII. FREE FOOD IN THE GP PRACTICE
The provision of free lunch for GP practice staff in return for listening to information about a drug still goes on I am told by a local health professional.

VIII.DRUG PROMOTION to POLITICIANS and using politicians
Pharmaceutical companies employ lobbyists to influence politicians for the purpose of selling their products to the NHS.

One example of FREE FOOD AND DRUG PROMOTION IN THE HOUSE OF COMMONS

Conservative Party Mental Health Summit
Wednesday 29 October 2003
Portcullis House, Palace of Westminster
FOOD PROVIDED BY ELI LILLY

I attended a recent Conservative Mental Health Summit meeting at the House of Commons, the lunch was provided by Eli Lilly. The Mental Health Bill will promote the use of drugs and yet Tim Loughton MP or Liam Fox MP could not see this compromised the meeting at which Eli Lilly representatives were present.

DRUG PROMOTION at the meeting by a speaker.

At the same meeting, a person, ostensibly chosen as a patient spokesperson, promoted a drug in an obvious way during his talk. At the moment he said the name of the drug which he said had “helped his condition” I saw the Lilly reps of the look at each other smiling. The talk being about his experience as a mental health patient had no reason to include a drug name co-incidentally manufactured by Eli Lilly.

IX. The Promotion to and influence on the NHS
THE NATIONAL SUICIDE PREVENTION STRATEGY FOR ENGLAND contains no reference to medication induced suicide or akathisia. The risk of suicide is 2.2 times greater for those taking SSRIs antidepressants (stats from all clinical trials in the UK and USA Dr David Healy)

THE NATIONAL SERVICE FRAMEWORK FOR DEPRESSION THE ELDERLY AND MENTAL HEALTH promotes the discovery of depression yet contains no reference to medication induced depression.

ABPI Framework Will Help NHS And Pharmaceutical Industry To Work In Partnership To Help Patients
Thursday, 15 July 2004
A framework to guide joint working arrangements between the pharmaceutical industry and the NHS to benefit patients has been launched today by the Association of the British Pharmaceutical Industry (ABPI) in association with the NHS Alliance.
The announcement comes as a survey shows that more than half of Primary Care Organisations (PCOs) now work in partnership with the pharmaceutical industry, rating medicines management projects as the most helpful area of working. Other top-rated areas are in team building and communication skills, implementing NICE guidelines and national service frameworks, and the training of nurses.

“This survey shows how timely the issue of the framework guidelines is,” said Dr Trevor Jones, Director General of the ABPI. “The NHS Plan and other recent publications from the Department of Health all point to the benefits that can come from a constructive engagement with the private sector.

“In the spirit of this developing relationship, the ABPI has produced this document to introduce NHS managers and decision-makers to the benefits of partnership with the pharmaceutical industry”

An NHS Confederation Diary for 2005 has on the front cover the words “supported by Wyeth”

Within the diary it states “The confederation aims to bring industry and the NHS closer and to share expertise”

The delegate pack for the NHS Confederation conference June 2004 is also sponsored.

RECOMMENDATION FOR ACTION by the Government

I. The film of the Novartis meeting should be available and the Health Committee could review the film. The Royal Institution and other such “respected” bodies should be informed of their ethical duty to protect the public from blatant drug promotion by Novartis. A person I spoke to in the events department said they could not exist without Novartis and was not aware of the content of the meeting I attended. The government should provide funds to cover the cost of independent meetings at the Royal Institution so that a balance could be provided for the members and the public who attend RI meetings.

Such promotional conduct should be carefully monitored and government representatives should attend all meetings sponsored by pharmaceutical companies to hear and see the blatant promotion of drugs to innocent audiences. Clozapine causes serious blood disorders, far from having “no side effects” as stated by Dr Revel, the patient has to have regular blood tests while on Clozapine. The drugs cause diabetes, obesity and heart problems and a young person may be helped by counselling and may not need long-term medication.

The Government should look at the school curriculum which could include time to help children learn how to deal with life events and teach about life style, healthy living, the importance of healthy diet etc. Relaxation techniques and perhaps good breathing techniques and yoga could help people cope with life events.

Politicians concerned about the breakdown of values and decent behaviour in society should look towards the top of industry and in particular to the pharmaceutical industry where such bad examples trickle down into society as a whole.

The Government should halt the medicalisation of society. The promotion of disease should be stopped. New diseases such as “social phobia” are promoted to create a market for drugs.

II. Such conferences should be monitored by government “watch dog” representatives. The fact that no one hesitates to put such a blatantly crude marketing brochure on the Internet is a reflection of the complacency of the industry. The medicalisation of society is costing society in huge sales of medication and huge bills to pay for the damage they cause.

The cost of ADRs may be up to 70,000 deaths a year in hospitals according to the NPSA. The cost runs into billions for extra bed days and no one has estimated the cost to society of ADRs in Primary Care.

III. DRUG PROMOTION TO DOCTORS DURING LUXURY BREAKS & FREE TRIPS

I have been told by one entertainer that the provision of his services was furtively hidden in fake invoicing for lighting and other such needs for so called “therapy” weekends where 120 people, GPs and their partners or practice nurses were feted in the best luxury hotels, given free drink and top class entertainment.

The GPS had to attend one 10 or 15 minute talk on a topic such as asthma or migraine and had to sign a form saying that they had attended a “therapy weekend”.

The pharmaceutical company sales reps told my contact that they always got orders for the product the following week as the GPs could hardly refuse after being plied with food, as much drink as they could take and entertainment. For a few days.

The products being promoted were very expensive as in the case of an inhaler for asthma costing £22 as compared to the NHS blue one at £1.96.

The entertainer was told not to invoice the pharmaceutical companies but to invoice a small lighting company.
The pharmaceutical companies were providing so many luxury trips that the lighting company originally doing the invoicing to the pharm company, as lighting, then paying the entertainers, could not cope. So this entertainer was actually put on the books of the pharmaceutical company and was provided with a supply number for the invoices.

This stopped about six years ago and he knows that now the way the companies continue to entertain the doctors, is by employing professional entertainers with some kind of medical or health qualification such as therapist.

So a person with a background in entertainment now ostensibly employed as a therapist/speaker but who, if you attend a therapy weekend will be found doing stand up or some other entertainment for far longer than the actual 10 or 15 minute listed therapy talk. The fees are substantial for such entertainers with medical qualifications.

My source, has the same fear that so many in the medical profession and businesses have, that if he is identified, his current livelihood could be affected. He would be willing to be interviewed and produce evidence, if his identity could remain anonymous.

IV. Patient Groups should be told to display how much they receive from the pharmaceutical industry on their literature. A “health warning” should be mandatory to go on all literature from such groups as Depression Alliance who receive support from the industry.

V. The CME and other educational courses should be removed from the influence of the industry.

VI. The Government should develop guidelines for ethical management of professional organisations and the Royal colleges.

VII. The practice of promoting drugs in GP practices could be stopped.

VIII. The government will have to find ways of halting the influence of the industry. It should be illegal for politicians to accept free food, entertainment or money from the pharmaceutical industry, either for themselves, for meetings they organise or for party funds. Tony Blair had breakfast with Paul Drayson (now a life peer). His company, Powderject, made an estimated £20 million. The Government purchased a smallpox vaccine from them. Drayson apparently gave a second £50,000 donation to the Labour party while the Government was deciding who should be handed the contract.

Link to an article: http://politics.guardian.co.uk/foi/story/0,9061,1249440,00.html

IX. The National Suicide Prevention Strategy and the National Service Framework have failed in not mentioning that depression and suicide may result from ADRs. The Government should establish how and why these omissions occurred.

The close partnership with the ABPI and the NHS will result in greater than ever drug promotion. The Government should make sure that the education of medical students, nurses and health professionals balances the immense influence of the industry in every sphere of their lives.

Chairs at universities in Drug adverse effects and Toxicology should give an opportunity to medical and other students to specialise. Education which currently rarely included even and exam in pharmacology and therapeutics, let alone toxicology and ADRs, should include the subject in all curricula.

4. Professional and Patient Education

Professional Education

A very worrying fact is that few medical schools include any exam specifically in how drugs work, or how to prevent, recognise or treat ADRs.

Southampton University has just dispensed with their 12 days of pharmacology and therapeutics and replaced this with alternative medicine. According to Professor Saad Shakir of the DSRU.

The GMC produce guidelines on medical education “Tomorrows Doctors” and only added a reference for the need to include ADRs when I had pointed out their omission. They thanked me for drawing their attention to this. Dr John Halliday drew my attention to this and told me of the concerns of others like himself who were teaching pharmacology in universities.

Patient Education is often biased as it stems from support groups and disease campaigns funded by the industry, as happens at the Royal Institution.

The refusal of the Dean of UCL to display a flyer for a conference offering free places to medical students to hear leading experts in ADRs in 2001 was a shocking reality. He did not want to jeopardise his funding, he was reported to have told the member of the students union who asked permission for the flyer to be displayed.
Recommendation for Action by the Government

Government funding for medical education should be increased to reduce reliance on the pharmaceutical industry. All the universities where no specific pharmacology or ADR education takes place should be warned not to let their major source of funding be an industry that influences the standard of education.

5. REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY

The regulatory agency (MHRA) is also promoting the pharmaceutical industry and therefore cannot be viewed by the public as truly working in the interests of the patients.

It is known that drug licences are rushed through and that pharmaceutical companies may be selective in providing results of favourable clinical trials while withholding unfavourable results. Clinical trials do not currently have to include a cross section of population using varied age, gender and ethnic origin. Withdrawal period is excluded from clinical trials and reviews of patients, following cessation of drug, are not mandatory.

Recommendation for Action by the Government

Efficacy should be assessed on the basis of comparison with similar drugs using equivalent dosage and for the age group that may be prescribed the drug.

Results of all the clinical trials should be reviewed before licensing. No trial results should be hidden and it should be a criminal offence if trial data is hidden or altered.

ADR statistics should be centralised and information from such as the Royal College of Anaesthetists should be pooled centrally on an independent data base. Not, as now, retained solely for their own purposes.

The collating and analysing of ADR data should be funded by the government and should include data from medical records of patients who suffer sudden unexpected death due to organ failure, accident or suspected suicide. This data could be analysed and interesting statistics could emerge without recourse to expensive toxicity tests which fail to show all the drug deposits that may be in the tissues or otherwise dispersed from the blood soon after death.

The benefit to the Government would be to win back the respect of the public and the savings for the NHS would more than cover the cost in the long run.

6. PRODUCT EVALUATION, INCLUDING ASSESSMENTS OF VALUE FOR MONEY

Not applicable to APRIL

APPENDIX 22

Memorandum from the King’s Fund (PI 81)

The King’s Fund is an independent health charity. In our report Getting the Right Medicines, published in December 2003, the Fund argued that the interests of the pharmaceutical industry had too great an influence on the NHS, mainly because the mechanisms for asserting the public interest in the development of medicines was too weak. We argued that new forms of public/private partnership were required in which the public interest would be given greater weight and that the Department of Health should aim to create a level playing field, by appropriate research commissioning policies, between drugs and other forms of treatment.

In this memorandum, we develop this argument by focusing on a particular type of health need, those with chronic conditions. Patients with chronic conditions represent the ideal market for the pharmaceutical industry, but the nature of their interest means that only certain fields are investigated and that innovation is biased towards new drugs rather than a search for preventive measures and pays too little regard for other issues such as the long term impacts of specific drug regimes, interactions between drugs for multiple conditions, drug safety, adverse drug reactions, and alternatives to drugs such as diet or other behavioural modification (unless these are considered to be achievable by drug regimes). This bias stems directly from the fact that the companies are focused on only one part of the potential therapy spectrum.
Furthermore not all long-term conditions are commercially attractive either because the markets they represent are too small or the scope for new drugs is limited for scientific reasons.

The following comments relate to the headings set out in the Committee’s request for evidence.

**Drug Innovation**

*The conduct of medical research*

These can be taken together. The key issue here is the selection of topics for investigation. As noted above, there are many areas which are not of interest to the industry. Unless the public health interest is clearly articulated and appropriate action taken, these will continue to be neglected.

**The provision of drug information and promotion**

*Professional and patient education*

These two areas can be taken together. The central issue is the balance and objectivity of the information available to the patient and the professional. As things presently stand, the resources available for promoting commercially profitable drugs are much greater than those available for promoting alternatives—ie out of patent or generic drugs or other forms of treatment including cognitive and behavioural therapies.

The NHS has made significant strides in redressing the balance through local formularies, NHS direct online, support for systematic reviews, establishment of NICE etc. But it has not given substantive support to establishing the effective use of pharmaceuticals in practice within the populations to which they are actually applied which may be very different from those within which they have been trialled or evaluated.\(^{76}\)

In the absence of such research, both professionals and patients will remain poorly informed about the consequences of some of their decisions to redress this situation would require trials of drugs in use as opposed to the artificial circumstances of the trials conducted for regulatory purposes. The point also applies to the current policy of encouraging a switch of drugs such as statins from prescription only status to P or GSL status, the long-term consequences of which may or may not be beneficial.

**Regulatory review of drug safety and efficacy**

*Product evaluation*

These two areas can be taken together. Ensuring safe and effective treatment of chronic disease requires a long term monitoring and evaluation regime.

The existing requirement for licensing drugs do not entail a requirement that they should be shown to be more cost-effective than existing drugs nor that their long-term effects should be monitored by those seeking the licences. The recently extended yellow card system provides an important source of information, but this is not adequate for detecting all effects of this kind in a systematic way.

To overcome this deficiency requires a fundamental re-assessment of the role of the regulatory system, designed to place greater emphasis on its role after licensing. Recent changes to the yellow card scheme represent a first step in that direction, but this needs to be supplemented by more systematic long-term monitoring and evaluation. The recently reported study\(^{77}\) of hospital admissions arising from adverse drug reactions makes the point that drugs can be dangerous to health whatever their regulatory status.

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\(^{76}\) *BMJ* 2004 nmaid.

\(^{77}\) *BMJ* 2004 329 15.
**Policy Recommendations**

The basis for any policy recommendations must be an agreed view of how the drug development process should work in the public interest. We propose it should be part of what we term a therapy development process, which in outline would look like the following:

1. **All needs**
2. **Prioritisation between Needs**
3. **Initial identification of preventive and/or therapeutic options**
4. **Commissioning of research**
5. **Testing and Trialling: assessment on competitive basis**
6. **Selection of some options/addition of new options**
7. **Further testing/trialling**
8. **Selection for use with patients**
9. **Monitoring use**

The diagram has been deliberately drawn in a simplified form but it is sufficient to bring out some key points:

First, some needs including the needs of particular patient groups, are not identified and there is no systematic mechanism for identifying them.

Second, there is no mechanism for considering the balance of research effort over the whole health field. This would require not only the capacity to survey what research is or is not being done but also the capacity to commission work in areas found to be neglected.

Third, the current set of arrangements do not ensure a level playing field between different research and treatment options. The full range of options is not considered because the private sector is restricted by profit considerations and the public sector does not systematically seek to complement it.

Fourth, the current system is front loaded i.e. the balance of resources is heavily biased towards the new, rather than the effective use of the existing. The resources going in the later stages, particularly the final one, are small relative to those going into research into new therapeutic options and then subsequently into marketing them to health professionals and individuals. Therefore investment doesn’t necessarily match potential health benefit.

Within the framework suggested by the diagram, there is scope for different divisions of work. The industry could continue to work as now and the public interest could be pursued in a variety of ways, depending on what kind of partnerships can be developed between government and industry. Alternatively
the role of the industry could be modified through the introduction of an expanded regulatory and monitoring regime designed to deal with the issues raised above about effective and safe drug usage and the alternatives to drug regimes.

We do not wish to propose any particular kind of partnership or new regulatory regime. What we do recommend is the Department of Health acknowledges that the existing set of arrangements do not work as well as they might in the public interest. The recent announcement of a research collaborative\(^\text{78}\) is a step in the right direction as is the recognition, in the announcement, that there are important gaps in existing public and private research programmes. The next step is for the Department to lead a substantive study of what we have termed the therapy development process of which the drug development process forms part.

We would like to see the new Director of R&D set out a broad strategy as to what the role and use of NHS R&D funds should be, based on what we see as the failures of the health research economy on the one hand and NHS principles on the other. This should consider the need to apply a set of criteria which are not simply based on the major diseases but which take into account a wider range of considerations including equity, the potential for improved quality of life and the scope for patients to take care of their own condition(s), with or without the use of drugs.

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**APPENDIX 23**

**Memorandum by The Wellcome Trust (PI 93)**

The Wellcome Trust is pleased to respond to this inquiry into the influence of the pharmaceutical industry. The Trust is a major funder of biomedical research, with a mission “to foster and promote research with the aim of improving human and animal health”. Biomedical research funders cannot work in isolation: we see the pharmaceutical industry as a key partner in the process of translating research into healthcare benefits.

The Wellcome Trust aims to support the translation process by providing “pump-priming” funding for promising early-stage projects, and access to key advice on intellectual property and product development. The aim of this support is to maximise the likelihood that an invention will be suitable for further development by either a start-up company or the pharmaceutical industry. We therefore see our role as funding basic research and supporting the development of this research to a point where it will be taken up by industry or by venture capitalists (VCs). This is mainly achieved through our translation funding programmes\(^\text{79}\) and support for international public private partnerships such as the Medicines for Malaria Venture (MMV).\(^\text{80}\) This response concentrates on the influence of the pharmaceutical industry on the conduct of medical research and on the development of new drugs, as this is our main area of experience. It is in this context that The Trust suggests that as part of its inquiry the Committee should consider a number of issues which I have set out below.

**Market failure**

*It is well documented that for a large number of diseases there is little or no commercial research and development being undertaken.* These so-called orphan diseases include those that are the biggest killers in the developing world such as malaria and tuberculosis. It is clear that the market fails to provide the pharmaceutical industry with the necessary environment, predominantly financial return, to become involved with developing drugs for these orphan and developing world diseases. The Trust considers that it would be interesting to explore whether there are aspects of the regulatory environment which could be adapted so that it is more “fit for purpose” and as such reduce the financial burden in developing drugs for these areas. There have already been a number of other initiatives, such as tax incentives, to encourage greater commercial R&D in these areas but the Trust is not aware if the effectiveness of these schemes has been evaluated as yet and the Committee could usefully explore with the pharmaceutical industry what their minimum requirements are to invest in a particular area.

**Is there a widening gap between basic research and industry take up?**

The Lambert Review of Business-University Collaboration (published December 2003)\(^\text{81}\) illustrated that there has been a *general decline in industrial investment in UK R&D over the last 20 years.* Whilst the pharmaceutical industry, and particularly new biotechnologies do better than other areas, the Trust feels there is an increasing trend for the pharmaceutical industry to licence research in, either from academia or more commonly from spinout companies, rather than develop in-house basic research. It might well be unlikely and in fact inappropriate for academic research to be drawn further along the product development

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\(^{78}\) Department of Health PR2004/XXX.

\(^{79}\) Further details about Technology Transfer at the Wellcome Trust can be found at [http://www.wellcome.ac.uk/en/1/biottd.html](http://www.wellcome.ac.uk/en/1/biottd.html)

\(^{80}\) Further details about MMV can be found at [http://www.mmv.org/pages/page–main.htm](http://www.mmv.org/pages/page–main.htm)

pipeline in an attempt to fill this requirement. Eventually a gap may develop between what academia can deliver and what the pharmaceutical industry is prepared to invest or licence-in. It would be very useful if the Committee could explore whether this is an apparent or real trend.

Private Public Partnerships

Public private partnership are a new, but as yet unproven, model for bringing together public, charitable and industry money to both share risk and produce research which is mutually beneficial. This has been particularly successful in areas where the research creates pre-competitive information and the SNPs consortium is a very good example of this.

Product development public-private partnerships are one model trying to address the market failure in new drug and vaccine production particularly for those diseases most prevalent in the developing world. However, to date the Trust considers many of these PPPs have not been equal partnerships and particularly in international efforts such as MMV, the level of government support does not appear to match the commitment of the charitable foundations. PPPs will not be able to meet all future public health needs without significantly increased and equal levels of investment. It is worth noting that whilst these PPPs might improve the product development aspect of the pipeline there will still be many other areas such as product manufacture, marketing and distribution which will need addressing to eventually have an impact on the burden of disease itself. This will also require similar innovative ways of working between public and private stakeholders.

APPENDIX 24

Memorandum by the Proprietary Association of Great Britain (PI 94)

Introduction

1. The Proprietary Association of Great Britain (PAGB) is the trade association representing the manufacturers of over the counter medicines. Membership of the Association is limited to companies whose primary interest is the manufacture or marketing of branded non prescription (Over the Counter or OTC) products. Annex 1 describes the way medicines are classified as prescription sale, pharmacy sale or general sale and shows the market size. Some of the companies in PAGB membership also make prescription medicines and are members of the Association of the British Pharmaceutical Industry in respect of their prescription products. The interests of the generic industry are the responsibility of the British Generic Manufacturers Association.

2. PAGB was created 85 years ago to control the advertising of over the counter medicines through a self regulatory code of advertising practice and this is still a core activity for the association. It is a condition of membership that members send all their advertising to PAGB for scrutiny and approval by the PAGB secretariat before it is published. These days the PAGB code of practice sits within a regulatory framework which is overseen by the Medicines and Healthcare Products Regulatory Agency (MHRA) who are responsible for the regulations, deal with complaints and monitor advertising for compliance with the regulations.

3. In addition to this, PAGB provides general regulatory advice to members, sponsors research into self medication and primary care, organises stakeholder seminars and conferences, identifies areas of common interest where it is efficient for companies to work together and facilitates discussion and action. These areas are ingredient safety issues, communications about self-medication and food supplements and interaction with government bodies and those representing health professionals, especially doctors and pharmacists. PAGB is a member of the European Proprietary Medicines Association (“AESGP”) and though this we have interactions with the European Commission and Parliament and input into EU legislation.

4. The Association is consulted by government on aspects of regulation relevant to the industry and actively works with organisations with similar interests with a view to expanding the scope of self care and self medication. The major point of contact is with the MHRA through our involvement in working groups, regular liaison meetings and occasional meetings on specific regulations or ingredient matters.

The Government, Patients and Policy on Self Care and Self Medication

5. The National Health Services dominates and shapes healthcare in the UK. Before it came into being, self care and self medication was the family’s main way of managing illness, especially those who could not afford to see a doctor. For over 50 years, since the NHS started, everyone has had access to a general practitioner, free of charge. For many people going to the doctor is their automatic choice for treating a health problem. The OTC medicines market has therefore been limited to the pool of symptoms which people are prepared to treat by self-medication. This symptom pool is not as large as it could be, nor is it elastic, as many people prefer not to treat their symptoms at all.
6. One of PAGB’s long-term objectives is to help expand the scope of self medication in the UK through wider availability of OTC medicines and by encouraging people to manage illnesses themselves without the control of a health professional except where necessary.

7. This objective needs support from all stakeholders, government, health professionals and the public themselves. To engage their interest requires long-term thinking and over the past 20 years PAGB has sponsored research, held conferences and symposia and sought the champions for self care within the different stakeholder groups. The key stakeholders are government and the public.

Government

8. Until fairly recently it was not possible to point to any government document which mentioned self care or self medication much less spelt out a policy on it. The UK is not unusual in this. Around the world, most governments begin to take an interest in self medication as a way of reducing the drug bill. In the UK, two attempts have been made to do so, in 1985 with the introduction of the Selected List and its extension in 1993. The Selected List prohibits doctors from prescribing certain branded products in 17 therapeutic categories, mostly products in the self-medication sector. Other countries have gone down the same route but in almost every country people are charged for doctor visits. In the UK people can still see a doctor at no charge and in the majority of cases they will receive a prescription at the end of the consultation. There is no support from health professionals or the public for any major change in this system.

General Public

9. Consumer research sponsored by PAGB and others shows that the British public are cautious in their use of medicines, preferring not to take them unless it is absolutely necessary. Research in 1972, 1986 and 1996\(^2\) showed that people experience around five symptoms per person in any two week period but 50% of these symptoms are not treated at all or are managed with a home remedy, such as a hot toddy for a cold. Around a quarter of illnesses are taken to a doctor or treated with a prescription medicine, already in the home. Purchase of the product is often stimulated by the need to treat a person who is already sick, so there is a close relationship between the incidence of symptoms within the population, and the sales of medicines. It is most obvious at times of cold and flu epidemics when manufacturers can schedule production by monitoring the numbers of people reporting cols.

10. People seek professional advice when they are unsure about an illness or when it has gone on for longer than expected. They tend to see doctors as experts in illness and pharmacists as experts in medicines and they use both as appropriate to supplement their own knowledge and the advice they get from their family and friends and the media. Patients are clear that they want real empowerment and not to be passed from the control of one health professional to be dependent on another.

11. The level of satisfaction with OTC medicines is high with high levels of repeat purchasing. This means that people generally use the medicines based on their own experience and the information on the product label and leaflet. Research shows that people generally value the advice they get from a pharmacist and that pharmacists are trusted.

12. While PAGB member companies sponsor a great deal of consumer research on the products and therapeutic areas in which they are involved, it falls to PAGB to look at self care as a whole and to conduct research across the whole sector. We make this research available to anyone who wants to use it and it is published on the PAGB website.

Patient representative bodies

13. While people who are newly diagnosed with a chronic illness need a lot of medical support, those who have had an illness for some time become very competent at managing it. They view themselves as people whose illness is a part of their lives, not the whole of their lives. The people who represent patients in special interest groups are at the forefront of thinking about how illness should be managed and this is an area where industry learns from people who really know about medical conditions.

14. PAGB and its member companies have increasingly involved such people in stakeholder groups talking about switching ingredients from prescription control and their involvement has improved the quality of patient information and training support.

Self Care policy

15. The NHS has dominated health policy thinking since 1948. Since OTC medicines are self-purchased they were of little interest to policy makers. While policy proposals in the late 1980s and early '90s addressed the need for some secondary care interventions to be managed in GP surgeries the real changes can be tracked from the late '90s when initiatives such as NHS Direct showed over 30% of callers had a problem which could be managed by self care. At the opposite end of the spectrum the DoH Expert Patient Programme began to generate information which shows that people with chronic conditions become very good at managing them without much medical help.

16. In 2000, the NHS Plan set out an objective of making better use of pharmacists and moving more medicines from prescription control. This objective was picked up by the MHRA but there was still no overall strategy for self care and self medication within the NHS. For the first time the NHS Plan established self care as a level of care in the NHS, alongside primary, intermediate and secondary care.

17. Derek Wanless, in his reports in 2001 and 2002, stressed the need for self care to be promoted within an overall health policy and predicted that if people could not be persuaded to fully engage with self care programmes then the NHS would not be sustainable. This raised the profile of self care and in 2002 the Department of Health mapped out all the work programmes that had a self care element to them. This exercise showed that although there were many such programmes, they did not join up and opportunities for synergy were being missed. In October 2003 Sarah Mullally, Chief Nursing Officer, was appointed the first Director for Self Care with the task of ensuring that the role of self care was recognised in appropriate ways.

18. Research commissioned by the Department of Health in 2003 showed that around the country more and more primary care trusts are introducing minor ailment schemes where nurses or pharmacists are taking on the work of managing conditions which are now being taken to the GP or Accident and Emergency. The new GP contract specifically encourages doctors to try new ways of working and money has been set aside to develop the evidence base which these empirical schemes lack. It is now recognised that self care underpins healthcare in this country and the more people can safely do for themselves, the better the system will work.

19. Doctors used to be very dismissive of the role of pharmacists but are increasingly positive about their role in managing minor ailments and repeat prescriptions. All stakeholders qualify their support for more self medication by the caveat that it must not be a way of rationing access to the NHS which they want to see continue to be free at the point of demand. They are concerned about inequalities of access in that only those who can afford to buy OTC medicines really have a full choice but they do not think this should inhibit the widening of the scope of self care and self medication.

20. PAGB organises conferences which bring together Ministers of Health, regulatory officials, health professionals and patient representatives to discuss their experiences of self care and self medication. Consumer interests have been represented by charities such as the Kings Fund, the Pickering Institute and the Consumers Association. The BMA, RCGP, GPC, Doctor Patient Partnership and representatives of Health Authorities, primary care trusts and general practice have given their views. Reviewing the proceedings of these conferences it is notable that over the past 10 years patient representatives have become more questioning of health professionals, more confident in their own abilities and more demanding of the right to have access to medicines.

21. PAGB has supplied all of this information to parliamentarians, government, the NHS and the Department of Health in response to the various consultations on modernising the NHS and developing patient choice. The interest in self care and self medication is developing from changes in clinical practice and changes in the way people use health professionals. There is no overall government strategy that spells out where self care and primary care start and finish. Various research projects which are now going on in primary care trusts may generate the evidence base which will allow that strategy to be defined in the near future.

22. In the meantime, government is putting in place national standards and local action to measure self care in practice and to move towards improvements being made in these standards. There is increasingly explicit inclusion of self care in National Service Frameworks and in NICE guidelines.

Research and Innovation

23. PAGB and its companies have little direct involvement with research organisations or with the expert committees in the MHRA with the exception of the POM to P programme. Improving the process of reclassification and the climate for changing legal classification (so called switching) has been a major objective for PAGB. Member companies work with leading medical experts and pharmacists to develop switch dossiers and training materials.
Switches in legal status

24. The regulations which control medicines in Europe require that all new active substances shall be control as prescription only medicines when they are first marketed. This enables their safety to be established in a larger population of users after the preliminary evaluation before marketing. Medicines can move from prescription control when they are considered to be safe enough for people to use without medical supervision. Sometimes companies carry out additional clinical work to establish a new dosage form or a lower dose of ingredient but by and large the supporting data to reclassify a medicine is a safety-based evaluation.

25. In 1992, Medicines Control Agency (now the MHRA) introduced new guidelines and a transparent process for moving products from POM to P which was a stimulus to innovation. In practice, until that time, most manufacturers of OTC medicines had to formulate their products from a relatively small number of active ingredients. As a result of the new guidelines, developed by a working group led by the MHRA, involving PAGB and the Royal Pharmaceutical Society of Great Britain, over 40 ingredients have moved from prescription control since 1992.

26. The General Sales List was set up in the mid 1970s, and for over 20 years there were few significant changes in it. A guideline for switching products from Pharmacy Sale to General Sale was launched in 1997 and, in a similar way, began to stimulate P to GSL switching. Ibuprofen, Loperamide and Ranitidine are all ingredients which have changed legal classification from POM through P to GSL. A pattern is emerging of products moving from POM through P to GSL after a period in each category to evaluate their safety. In many cases the same products are available in P and GSL categories differentiated only by pack size.

27. The CSM has been cautious about allowing consumers access to medicines for indications if they think the indications would be better managed under a doctor’s supervision. It often takes two or more attempts to make a case that persuades the CSM. Hydrocortisone became available OTC in 1983 for insect bites and stings but it was only after 10 years’ experience as a pharmacy medicine that it could be promoted to the public for the treatment of eczema, a long established indication for the ingredient when it was a POM. However, over the last 15 years the products available for consumers to use in self-medication have changed considerably.

28. While all new chemical entities are prescription only medicines, and most remain so classified, the OTC market is now benefiting from the introduction of new ingredients, which were originally developed for use in prescription medicines. People are managing illnesses such as vaginal thrush, insomnia, irritable bowel syndrome, minor arthritic conditions without needing to visit a doctor every time. The OTC availability of emergency contraceptive tablets OTC a few years ago was a major change in approach and with the availability of nicotine replacement products and now statins for lowering cholesterol, people have new tools to help towards healthier lifestyles.

29. In response to the NHS Plan targets of wider access to OTC products the MHRA set up a new reclassification group in 2001 which developed further proposals to improve the process of switch, a new list of potential switch candidates and proposals for information and training which will be provided to pharmacists and the public. All of this information was subject to public consultation and is on the MHRA website. The list of switch products this time includes medicines for the management of more serious conditions and chronic illnesses. The list is not permission to develop an OTC product, ingredients will change legal status if an application is submitted and approved by the CSM. Some of the ingredients on that list are now beginning to be evaluated. Companies are assessing the safety of the ingredient and assessing whether consumers are ready to manage the relevant condition themselves.

30. Changing legal classification is not straightforward and requires time, resource, energy and long-term commitment on the part of the manufacturer. Many of the new molecules which are developed today have fewer side effects than the older ingredients but it is recognised that the newer indications bring a need for much better patient information and for training for pharmacists and their staff and the industry supplies this with input from professional bodies and the MHRA.

31. The PAGB input to the switch programme was to work with the other stakeholders to help develop the guidelines for standards for good consumer information and training for pharmacists and to industry to work to these standards. This was done with input from doctors, pharmacists and patients groups.

The Provision of Drug Information and Promotion

Drug Information

32. Drug information is not the same as promotion. Given the right information and support people can often manage their ailments themselves. For example, doctors are recognising that a patient with diabetes lives with it 365 days a year and sees a health professional for only a few hours of that year. Providing good information to patients and the health professionals who support them is vital. Research shows that people seek information from a variety of sources and their information requirements are different for different illnesses.
33. The information provided by the pharmaceutical industry is controlled by regulation. The Summary of Product Characteristics sets out the indications, dosage and side effects. This controls what is included in the product label and leaflet which have to be submitted and approved by the MHRA before a product can be marketed. In the near future new regulations will require that all patient leaflets be tested for readability and ease of use as a condition of getting a marketing authorisation.

34. As a contribution to safe use of medicines PAGB sponsors the Consumer Health Information Centre which has a panel of independent advisors who help develop materials to encourage people to use medicines sensibly. PAGB also provides a directory of OTC medicines to all GPs which has become the industry standard and is also available on line. (These can be accessed from www.pagb.co.uk)

35. Pharmacists and their staff are the first line of contact for consumers with questions about OTC medicines and manufacturers provide them with a lot of information, not only about their products but about the category they fit into and how different products work. This information is mainly provided in printed format and a joint industry/pharmacy working group has recently produced a guideline for the production of this material to encourage better separation of training and marketing materials.

Promotion

36. In communicating the value of self care and self treatment a balance needs to be struck between on the one hand, encouraging people to treat themselves but, on the other hand, the risk of encouraging over use. The regulations (The Medicines (Advertising) Regulations 1994, as amended 1999) governing the advertising of medicines in the UK recognise the need to moderate promotions of medicines to the public. Within an overall requirement that advertising should promote the rational use of medicines, there are specific prohibitions on promotional methods which could lead to unnecessary or excessive use of medicines.

37. Enforcement of the law and control of medicines advertising in the UK is the responsibility of the Medicines and Healthcare Products Regulatory Agency (“MHRA”) (which acts on behalf of the Ministers of Health who form the Licensing Authority in the UK). In addition Ofcom has responsibilities for broadcast advertising and the Advertising Standards Authority (which is a self-regulatory body for non-broadcast advertising) deals with complaints about medicines advertising.

38. The MHRA has primary responsibility for regulations and providing guidelines to their interpretation, but day to day advice to member companies on interpretation of the regulations, through vetting their advertising, is still a core activity of PAGB. The Association holds copies of the marketing authorisations for all the products supplied by its membership and checks all proposed advertising copy, for all media including websites, to ensure it complies with the terms of the marketing authorisation, the regulations and the Association’s Code of Practice.

39. PAGB has frequent interaction with the Medicines Control Agency (MHRA) on advertising and all other matters relating to the regulation of medicines. The Code of Practice was updated in 2004 with input from the MHRA and professional bodies. Training in compliance with the code of practice is provided by PAGB in monthly workshops.

Regulatory Review of Drug Safety and Efficacy

Efficacy

40. Most OTC medicines are based on ingredients which have been available for many years. There is no need to conduct new clinical trials to establish that a well known ingredient is effective. This concept was introduced in the 1980s across Europe to reduce unnecessary toxicology and pharmacological testing and to free up scarce clinical trial resources. It is still the approach today. A new directive for herbal medicines just adopted in Europe will allow herbal products to be registered on the basis that they have been on the market for 30 years and there is bibliographic data to show that there is a reasonable expectation that they will be effective.

41. When a new product based on established ingredients is developed and submitted for evaluation by the MHRA, it is usually examined by the MHRA assessors who rely on precedent and established medical opinion to approve the product for marketing. The CSM advice is sought in the case of medicines which contain ingredients which are currently prescription only where it is proposed that they should be available as pharmacy only medicines. If the CSM approves the proposal, the basis for approval is a public document and there is a period of public consultation and often a re-evaluation by the CSM or the Medicines Commission before regulations are changed to allow the wider access. Despite the prevalence of old ingredients, the OTC market is not a static one. In all the major categories today the brand leaders are based on ingredients which were originally developed as prescription products.

42. While single ingredient OTC products are generally licensed on the basis of well established medicinal use combination products containing two or more ingredients in a single product need to be supported by clinical research. Most combinations are put together to make it more convenient for consumers to take two

83 The Licensing Authority is the Ministers for Health for England, Scotland, Wales and Northern Ireland.
or more medicines but they can also lead to enhancement of efficacy if one ingredient boosts the effectiveness of another or prevents a side effect. Such combination products are not given marketing authorisations unless clinical studies have been carried out and the CSM is convinced that it is a rational treatment.

43. The Medicines Act requires each marketing authorisation to be judged individually and comparative efficacy may not be part of that assessment. Comparative safety can be taken into account and it routinely happens in the assessment of OTC products where a marketing authorisation will be refused if in the opinion of the CSM there are products available which offer efficacy with fewer side effects.

Safety

44. The safety review of OTC products is an ongoing process. Marketing authorisations are issued for five years and applications for renewal are submitted along with a review of adverse event reports which have arisen in that period. Companies are required by law to inform the MHRA of any adverse events reported to them to enable follow up and entry in the central database. As well as this, doctors, nurses and pharmacists can send reports of adverse reactions to the MHRA on “Yellow cards”—a scheme which has been operating for 40 years. This scheme is soon to be revised to allow the general public to report any problems directly to the MHRA.

45. OTC products share a relatively small number of ingredients and when problems arise it is common practice for the MHRA to undertake a full safety review and to apply the findings to all the products containing that ingredient. In the past few years this happened with aspirin where there was concern about the possibility of association with Reyes Syndrome. One of the first POM to P switches, terfenidine—a hayfever and allergy product, returned to POM status because new information showed that if taken with grapefruit juice it could cause heart problems in some people.

46. Research conducted by the National Audit Office confirmed that few people taking over the counter medicines experienced side effects. Those who did found they were minor and stopped when they stopped taking the product. On the other hand a recent report in the BMJ suggested that a significant number of people in hospital had suffered adverse reactions which were avoidable. Although the leaflets of medicines include information about adverse effects there has been some criticism that the language used is not understood by consumers. Over the next year or so, new guidelines will be introduced by the MHRA to improve the way the risks associated with the taking of a medicine are described.

47. All the advertisements for OTC medicines include a reminder to read the label and leaflet but this needs reinforcing. Since research shows that leaflet information is not consistently read by users, this improvement in information will have to be accompanied by a campaign to encourage people to read them. PAGB is working with other stakeholders to help achieve this objective.

Misuse of OTC Medicines

48. Any medicine with a potential for dependence is required to be restricted to prescription only status so by definition OTC medicines have a low potential for such problems. Research shows that most people are cautious in their use of medicines, preferring not to take them unless they really have to. In recent years concerns have been raised about over consumption of analgesics by some people. This is not related to wider availability of medicines, indeed the pack sizes of analgesics have been reduced in the last five years, but it may be linked to a condition called chronic daily headache. In order to understand this better work is going on with experts in the field and the hope is that in the near future pharmacists and doctors will be provided with materials to help them identify people with this problem and help them appropriately.

Product Evaluation, Including Assessments of Value for Money

49. Over the counter medicines are generally not prescribed under the NHS. Those which doctors prescribe are part of the PPRS scheme and their prices and profits are controlled in the same way as any other NHS medicine. The medicines which are bought over the counter by people are not price controlled at all. People have a choice of medicines to treat their symptoms. Some buy generics or pharmacy chain own labels, others prefer brands. Until a few years ago manufacturers were allowed to set the retail price which then had to be the price charged in every retail outlet. This is no longer the case and large grocery retailers and pharmacy chains routinely compete on price.

50. Resale price maintenance ended in 2002. An extensive review of the OTC pharmaceutical and its pricing and profits was conducted by the Office of Fair Trading in preparation for the court case. Having conducted the review the Director General of Fair Trading is on record as saying that it was no part of his case that the OTC industry made excessive profits.

September 2004
### MARKET DATA

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<td><strong>Smoking Cessation</strong></td>
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<td><strong>TOTAL OTC</strong></td>
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**LEGAL STATUS FOR SUPPLY CONTROLLING WHERE MEDICINES ARE SOLD**

UK medicines legislation provides for products to fall into one of three categories for the purpose of defining the route by which they may be sold or supplied to patients/consumers, (ie their legal status or classification):

- Prescription Only Medicines (“POM”) which is self explanatory.
- Pharmacy Sale medicines (“P”).
- General Sales List medicines (“GSL”).

The system for classifying medicines centres upon consideration of the active ingredient(s) and its safety *per se*. This takes into account the dose, which is considered to offer optimum benefit/risk balance and the maximum effective dose, which could be safely taken in one day. On top of that the indications for which the ingredient is to be used are considered. The formulation or way the ingredient is presented may also be relevant, as may the pack size.
OTC medicines fall into two of these legal categories controlling access

1. Authorised medicines available without prescription but legally confined to pharmacy distribution (“Pharmacy” or “P” medicines). The law requires that the sale of these medicines occur in a registered pharmacy under the supervision of a pharmacist. “Supervision” means that the pharmacist must be aware of the sale and in a position to intervene if necessary. There is no list defining which products are P medicines. This category consists of products, which have not been classified either as “GSL” or “POM”. Amongst the most significant P ingredients are codeine for pain relief, antihistamines for allergies, decongestants and a number of ingredients such as H2 antagonists and topical hydrocortisone which have moved from prescription control.

2. Authorised medicines legally saleable in any retail outlet (“General Sales List” or “GSL” medicines). These are defined as “medicines, which can with reasonable safety, be sold or supplied without the supervision of a pharmacist, and where wider availability would be a convenience.”

EU criteria define which products must be subject to prescription control (Directive 92/26/EEC Article 3). They include:

— the potential for abuse or misuse of the product;
— the possibility that the products could be toxic even if used correctly without medical supervision; and
— products containing substances requiring further investigation of side effects.
— All injectable products are prescription only.

New drugs are restricted to supply on prescription for the first five years of marketing. For the first three years, the company holding the marketing authorisation and the MHRA intensively monitor these POM products, during which time their safety profile is more fully established. The start of a switch dossier is an extensive review of the adverse reaction reports held by the company and by the MHRA, and reports worldwide, to establish that it is safe enough to use the product without medical supervision.

APPENDIX 25

Memorandum by Ray Moynihan (PI 98)

This brief submission will specifically address the terms of reference referring to industry’s impact on “drug information and promotion”, “patient education” and the industry’s influence on “the press and other media.”

SUBMISSION SUMMARY

1. The media is an important source of health information for the public, and as such, it is a key target of pharmaceutical industry public relations and marketing campaigns, promoting awareness of both drugs and diseases.

2. There is strong evidence from several countries that much media reporting tends to exaggerate drug benefits, play down drug harms and overlook important conflicts of interests of people quoted in stories.

3. Drug company “disease-awareness” campaigns routinely use “third-party” organisations including company-sponsored doctors and patients groups, to target the public via the media. The campaigns are ostensibly designed to “educate” the public about poorly understood conditions, but are often directly linked to company marketing strategies aimed primarily at expanding markets for medicines.

4. Health and medical journalists, and organisations representing them, have a role to play in encouraging better quality media reporting of both drugs and diseases, to help move medical reporting away from promotion and more towards journalism.

5. The quality of media reporting on medicine and health could be improved with much greater availability of accurate, reliable, and up-to-date information about drugs and diseases, from genuinely independent sources.
SUBMISSION

1. The media is an important source of health information for the public, and it is a key target of the pharmaceutical industry’s public relations and marketing campaigns, promoting awareness of drugs and diseases.

There is good evidence that media coverage of health and medicine can influence the attitudes and behaviours of clinicians and the public. A recent Cochrane review of the relevant evidence—while noting the limitations of existing studies—suggested that favourable publicity in the media was associated with higher rates of utilisation of health services. Media outlets are bombarded daily with promotional material from drug companies and their associated web of marketing and public relations firms, and there is little doubt many media stories are heavily influenced by those promotional strategies.

2. There is strong evidence from several countries that much media reporting tends to exaggerate drug benefits, play down drug harms and overlook important conflicts of interests of people quoted in stories.

A Harvard University-based study published in the New England Journal of Medicine examined five years worth of United States television and newspaper coverage of three medicines. It found that a majority of media stories used statistics in a way that exaggerated the benefits of the drug, a majority of media stories failed totally to mention the side effects of the drug, and more than 60% of media stories which quoted an expert with a conflict of interest, failed to disclose that conflict. Similar studies in Norway and Canada have found similar problems, and there is little reason to believe British media are different in this regard.

3. Drug company “disease-awareness” campaigns routinely use “third-party” organisations including company-sponsored doctors and patients groups, to target the public, via the media. The campaigns are ostensibly designed to “educate” the public about poorly understood conditions, but are often directly linked to company marketing strategies aimed primarily at expanding markets for medicines.

An article published in the British Medical Journal documented five case studies of what has been described as “Selling Sickness”, in which media organisations were used as part of drug company-funded “disease-awareness” campaigns. These case studies are part of a growing body of evidence demonstrating how drug companies work in alliance with sponsored professional and advocacy groups to help widen the boundaries of human illness, in order to expand markets for medicines. Sometimes the process is referred to as “disease-mongering”.

Pharmaceutical industry marketing literature explains that drug companies are actively engaged in “branding” medical conditions in ways that maximise drug sales.

“Branding” experts, who work with drug companies, have written about strategies used to “foster the creation” of conditions, and align those conditions with particular products. These strategies routinely involve working with advocacy and doctors’ groups to use the media to shape public perceptions about particular conditions.

One of the recent examples of the corporate sponsored creation of disease involves an emerging condition called Female Sexual Dysfunction. Highly inflated and misleading statistics about the prevalence of “FSD” are being promoted by some drug companies, and that misleading information is being reported in many media stories.

A forthcoming book, titled Selling Sickness, examines 10 case studies, including high cholesterol, depression, hypertension, menopause, irritable bowel syndrome, social anxiety disorder, osteoporosis, pre-menstrual dysphoric disorder and female sexual dysfunction. In each case, drug companies have worked with sponsored groups, using the media, to help change public perceptions about the nature and extent of the condition. In some cases drug companies have sponsored public relations campaigns to shift perceptions about an existing illness, and in some cases companies have sponsored and attended key medical meetings where the conditions are actually being defined. While acknowledging the importance of waging public health campaigns around heart disease and mental illness for example, the forthcoming book explores how
Some observers have suggested that industry funded “disease-awareness” campaigns are fundamentally changing our perception of what it means to be human.93

4. Health and medical journalists, and organizations representing them, have a role to play in encouraging better quality reporting of both drugs and diseases, to help move medical reporting away from promotion and more towards journalism.

Observers of media coverage of medicine suggest medical journalists are highly motivated to do a better job.94, 95 For example, the United States based Association of Health Care Journalists, among other groups, has become active in trying to improve the quality of medical reporting about medicines.96 13 Workshops introducing medical reporters to the basic principles of evidence-based healthcare, the importance of reporting on conflicts of interest, and the need to seek genuinely independent sources and information, have proved highly successful at annual conferences. Currently, different versions of these workshops are being devised for Latin America, in conjunction with members of the Cochrane Collaboration.

5. The quality of media reporting on medicine and health could be improved with much greater availability of accurate, reliable, and up-to-date information about drugs and diseases, from genuinely independent sources.

One of the side effects of the pharmaceutical industry’s enormous influence over the healthcare system is the difficulty for reporters in finding genuinely independent experts, patient advocates, or commentators. There is an urgent need for a greater availability of independent sources of information about drugs and diseases—including independent educational materials, independent medical researchers and independent patient advocates.

If the goal is a more informed and rational public debate about the appropriate use of medicines within health system, the availability of independent sources for the media—about both drugs and diseases—must be enhanced. Several organisations are now specialising in providing independent evidence-based information about medicines, (eg Cochrane Collaboration), though there are few genuinely independent sources of information about the nature and extent of medical conditions.

Enhanced public scrutiny of company funded “disease-awareness” campaigns and greater availability of independent sources of information about disease, are urgently needed.

ABOUT RAY MOYNIHAN

I am a medical writer and author who has been covering healthcare for almost a decade, with a strong interest in pharmaceutical marketing strategies. I write for outlets in several nations including Britain, Australia, the United States, and New Zealand. I have published extensively in print, radio and television, in the lay press and scientific journal.

I am the North American Visiting Editor and a regular contributor with the British Medical Journal, and I was a guest editor of the special 2003 theme issue of the BMJ titled, “Time to untangle doctors from drug companies.”97 That issue documented the extent of entanglement within health care,98 moves towards disentanglement,99 and suggested several simple steps to achieve less unhealthy drug company influence within health care.100

With colleagues at the Association of Health Care Journalists I am actively involved in trying to improve the quality of medical reporting.101 I have developed and delivered workshops that introduce medical reporters to the principles of evidence-based health care, which encourage more scepticism in reporting, and more rigorous investigation of drug company influence within healthcare.

I am currently co-authoring a book about the global pharmaceutical industry and medicalisation, working-title Selling Sickness, scheduled for publication in early 2005. A television documentary that I have co-created, Selling Sickness, is currently being screened in several nations, including Australia, Canada and France.

96 http://www.ahcj.umn.edu/
100 http://bmj.bmjournals.com/misc/doodrug.shtml
101 Tipsheet for reporting on drugs, devices and medical technologies http://www.cmwf.org/journalists/moynihan tipsheet.pdf
Evidence for Consideration for the House of Commons Committee Inquiry into the Influence of the Pharmaceutical Industry

Background

I was a Labour Member of the European Parliament from 1989–2004 and during that time served on the Industry Committee of the Parliament. I come from a trade union background and my union, now Amicus, represents a range of professional workers in the health service, and also has a substantial membership in the pharmaceutical and medical devices industries.

I attach a CV which will give the Committee some indication of the sort of work I’ve been involved in over the last 15 years. Since my retirement I have taken up two unpaid positions; President of the European Cervical Cancer Association (partly funded by the pharmaceutical industry) and Chairman of Health First Europe, an organisation newly set up by Eucomed, the umbrella organisation representing the medical devices industry.

I have been lobbied by the pharmaceutical industry over a range of issues during my time in the European Parliament. The most recent was the European Commission proposal concerning the placing on the market of pharmaceutical products. This was a major Commission proposal and generated a substantial interest both in the Parliament and in the various sections of the industry. I attach a list of organisations who lobbied me on this particular dossier. The reason for their lobby was that I drew up the Opinion (attached) for the Industry, Trade, Research & Energy Committee on the Commission proposal.

Normally, drawing up an Opinion is a comparatively minor matter and the Environment and Public Health Committee had the main responsibility for this dossier. However, because it was so important for the industry, what would normally be a comparatively minor piece of work was precisely the opposite. There was such an intense lobby on this matter that I had to make an early decision that I could only see each organisation once. There was just not time physically to see people for a second time. From 1999–2004 I represented the East Midlands which contains, among many other pharmaceutical interests, Astra Zeneca at Loughborough and Boots in Nottingham, for whom I therefore felt a special responsibility, and to whom I listened with particular care.

The issues were briefly these:

— The period concerning data exclusivity
— The balance between national and central (ie European) authorisations
— New proposals from the Commission concerning direct consumer advertising
— Parallel submissions concerning the placing on the market of veterinary medicines
— Introduction of a BOLAR provision

There have been other Directives over the years which interested the pharma industry over which there has been a vigorous lobby for example:

— patent rules
— Directives concerning advertising
— Directives concerning labelling of pharmaceutical products and patient information TRIPS
— Current WTO round
— Rare Diseases and Orphan Drugs Directive
— The Sixth Framework Research Programme
— REACH (proposals concerning the safety of chemicals)
— Cosmetics legislation

The way that the pharma industry has operated in the European Parliament has changed quite dramatically during my 15 years. Originally the lobby, as with many others, was broad ranging and took the form of a meeting or lunch or social event of some kind to which a large number of MEPs were invited. This changed very rapidly and the pharma industry soon realised that they needed to target particular MEPs who were either on the relevant Committees or had been appointed as Rapporteurs (where a particular MEP takes responsibility for steering a piece of legislation through its various stages). Pharma companies would contact a particular MEP, ask to visit them, produce a breakdown of a Commission proposal with an indication of how various parts of the proposal adversely or otherwise affected that particular section of the industry. These position papers are extremely useful—so much so that have declared them in my Declaration of Interest. The position paper which was presented would usually contain suggested draft new

102 Not printed.
amendments which were more to the taste of the industry. I must stress that this was all done properly and openly and I have had no experience of subterfuge or an organisation not making it absolutely clear who they were and how they were funded.

As well as this sections of the industry have held various functions over the years in the Parliament, usually, but not always, timed to coincide with the passing through of legislation relevant to the pharma industry. This would usually be sponsored by a particular MEP and indeed I have done this several times over the last years. For example a pharma company would book a room in the Parliament, organise a lunch and the lunch would be led with speakers, discussion, questions, comment, argument etc.

The Association of British Pharmaceuticals Industries used to hold a regular supper club in Strasbourg three or four times a year. This was most definitely not aimed at particular pieces of legislation but was designed to foster links between the industry and MEPs across the political spectrum and from the UK. These were well attended, and I found them useful and interesting. Of course the pharmaceutical industry is a major employer in the UK, and almost every MEP had a direct interest in fostering this relationship, as well as having strong links with universities and research establishments.

To revert to the most recent review, the issues between the in-patent section of the industry and the generics section revolved around data exclusivity and the BOLAR provisions. All sections of the industry were anxious to stress to us that there was a real issue surrounding the future location of the pharm industry and huge incentives (not always clearly spelled out) for the industry to gravitate towards to the United States of America. For all sorts of reasons I and many other MEPs feel very strongly that it is important to have the research sector of the pharma industry within the European Union and we listen very carefully to any question that proposals that the Commission come up with and or proposals that the Parliament come up with are detrimental to the final location of the industry.

There really is something of a Catch 22 situation with the pharma industry in the EU. They are for profit organisations whose profits come largely from the public purse, either directly or indirectly. There is little or no single market in the pharmaceutical industry and the price of products which have been authorised are not necessarily placed on the market at all in some EU countries. The differences in prices has meant the encouragement of parallel trading and indeed the parallel trade association was one which lobbied me. There was considerable irritation about the existence of parallel trade by the in-patent section of the pharma industry but in fact this did seem to me to be a legitimate business opportunity, whose legitimacy has been upheld by the ECJ and is indeed of considerable benefit to our own National Health Service. I have no data to substantiate this but my own experience and that of others indicates that hospital pharmacies are heavy users of parallel traded products. Unless we can create a climate where the research section of the pharma industry has incentives to invest money in new drugs then there will be no generic industry. Indeed this is the argument of the in-patent section, that the generic industry rides on the back of research funded by the in-patent section. However, the whole question of access to medicines which is shown at its most stark in the controversy between the drug companies and the Government in South Africa is an issue also in the European Union. The growth of e-pharmacies is an illustration of how we may get a single market by the backdoor as computer literate, usually middle-class patients, look to the internet for pharma products and other medical treatment. The Commission have recently come up with proposal about patient mobility which the European Parliament is soon to consider.

What was most interesting about the lobby on the recent review of authorisations was the controversy surrounding the Commission proposals on direct consumer advertising (the Commission were unhappy about it being described thus but in fact that’s what it was). The Commission in their proposal chose three diseases—asthma, diabetes and HIV/AIDS as pilots.

The argument was that these were three diseases for which it was unlikely that patients would choose to take drugs unless they were necessary ie they wouldn’t be encouraged by advertising to demand particular drugs. I was not entirely convinced by this argument but I could see some logic in it. In fact to allow a pilot over 10 years on just three diseases was extremely unlikely to help in deciding whether this form of patient information could be extended. I had many representations from patients’ organisations, all of them fully or partly funded by the pharmaceutical industry, saying that they approved of the Commission proposals and wanted to have more information available as patients. To be fair, the pharma industry did have an argument, as did the Commission, in saying that computer literate, English speaking patients already had access to information about pharmaceutical products. But the counter argument from the European Parliament went that if patients were to have information, it should not be just about one company’s pharmaceutical product but about a range and it should also be about providing information about other options (changes in lifestyle, doing nothing, surgery whatever). In the end, and I was instrumental in this, the Parliament voted to refer this whole matter back to the Commission to see whether the Commission could find ways to provide information and validate ways in which patients could get information. I would be happy to expand on this matter verbally if the Committee so require.

Overall, the pharma industry lobby is probably the most effective and professional on the Russell’s lobbying scene. I have no experience of any deceit or malpractice at all, indeed the industry is scrupulous about these matters. But this is not to conclude that this influence is entirely without flaw. The gap, and it
is a huge gap, is that the public health lobby has a tiny influence on policy, and that there is a conflict between the health objectives of the EU and the Internal Market objectives. If the way in which the pharma industry funds patients groups is factored in, then the gaps are even wider.

APPENDIX 27

Memorandum by Nuffield Council on Bioethics (PI 102)

Referring to the Term of Reference: the Provision of Drug Information and Promotion

1. In October 2002, the Nuffield Council on bioethics published a report on Genetics and human behaviour: the ethical context. It recommended that health service providers, and in particular the Department of Health, specifically charge a named agency with monitoring and, if necessary, controlling, the deliberate medicalising of normal populations. The Council noted that any discovery of biological mechanisms that influence behaviour, including genes, may aid the development of drugs which modify behaviour. The Council concluded that there is potential for the unhelpful widening of diagnostic categories, to encourage the use of medication by people who would not necessarily be thought of as exhibiting behavioural traits outside the normal range. This development could have deleterious effects, such as a shift in the boundary between normal variation and disorder further away form the extremes of variation, the reduction of social tolerance, the routine selection of genetic or medical interventions without adequate consideration being given to environmental interventions and other options, and unnecessary increased expenditure by the health service.

2. The relevant extract from the Report is Annexed.

Annex

Extract from the Nuffield Council on Bioethics Report Genetics and Human Behaviour: The Ethical Context

“Medicalising” Human Behaviour

13.13 Traits such as sexuality, aggression and intelligence have in the past been thought of as outcomes of inheritance, family background, socio-economic environment, individual choice and even divine intervention. If research in behavioural genetics identifies the influence of genes on such traits, they may mistakenly come to be thought of as being fundamentally determined by genetic factors and even as aspects of life which belong to one’s “fate” (see paragraphs 12.10–12.15). Indeed, being diagnosed as at risk of disease may have a tendency to make healthy people feel ill, or feel fatalistic about their chances of survival, despite the existence of diets, life-styles or treatments to avoid the development of disease. It is possible that information about genetic factors that indicate susceptibility to a disease may make people think that the unwanted outcome is inevitable.\footnote{Senior, V, Marteau, T M & Weinman, J (1999). Impact of genetic testing on causal models of heart disease and arthritis: an analogue study, Psychol. Health 14, 1077–88.}\footnote{Marteau, T M & Senior, V (1997). Illness representations after the human genome project: the perceived role of genes in causing illness. In Petrie, K J & Weinman, J A, editors. Perceptions of Health and Illness: Current Research and Applications. Reading, UK: Harwood Academic Publishers. pp 241–66.} With regard to behavioural traits, therefore, information about genetic susceptibility might engender similarly fatalist beliefs.

13.14 As the reviews of the evidence indicate, fatalism about genetics is a misconception. Even when behavioural traits are influenced by genes, there are always other influences, and the existence of genetic influences does not show that we are powerless to change or modify our character: “scientists may well identify an allele that causes a genetic predisposition to shyness, but such a discovery does not mean that shyness cannot be overcome.”\footnote{Rothstein, M A (2000). Genetics and the work force of the next hundred years. Columbia Bus. Law Rev. 2000 (3), 371–401 at p 383.} Nonetheless, this misconception is pervasive and gives rise to the anxiety that behavioural genetics will lead to the “medicalisation” of those who are found to be genetically predisposed to certain behavioural traits.

13.15 At the root of concerns about medicalisation is the idea that behavioural traits that have previously been regarded as “normal” will come to be viewed as “abnormal” or pathological. In addition, behavioural traits within the normal range may turn out to be amenable to influence by pharmacological interventions as a result of knowledge about the biological factors that affect them. Concerns about medicalisation have been expressed for many decades, for example in relation to the increasing number of psychiatric conditions
that are recognised, and in the increasing use of medicines. In the era of genetic research, the fear is that
the identification of the influences of genes will exacerbate this trend, encouraging the re-classification of
behavioural traits as within the realm of medicine.

13.16 In some cases genetic research may indicate that a behavioural trait is one for which medical
interventions are appropriate and welcome. Findings from research concerning the biological basis of
addiction to alcohol, and of autism, helped to liberate individuals and parents from the charges previously
laid against them of moral weakness and of neglecting their children respectively. In such cases, it should
be acknowledged that this “medicalising” tendency is beneficial: the research helps to confirm the view that
the individuals concerned should be perceived as ill, rather than bad, and in need of medical help, rather
than discipline and punishment.106

13.17 However, in other cases, medicalisation may have adverse effects. One such problem is that of
diagnostic spread, or the tendency for disorders to be broadly defined so that more and more individuals
are caught in the diagnostic net. This tendency may arise as a result of an erroneous assumption that once
a biological influence on a trait has been identified, the trait becomes the proper subject of medical
intervention. Or, it may be that if medicines are developed that have an effect on a trait, that trait will come
to be seen as a disorder, or something to be treated and altered.

13.18 An example of this latter phenomenon is the prescription of methylphenidate (Ritalin) to children
with Attention Deficit Hyperactivity Disorder (ADHD). This example is controversial because there are
undoubtedly some children who have serious behavioural problems and who benefit greatly from the drug.
It would be wrong to suggest that ADHD has been invented; indeed, the condition has been recognised for
many decades. However, the advent of medicines that are effective in improving concentration and reducing
hyperactivity is a fairly recent development. In 1999, the US National Association of State Boards of
Education estimated the number of children taking Ritalin on a daily basis at between 1.3 and 2 million. The
National Institutes of Health in the US has recently undertaken a study to examine prescribing practices.

13.19 Similarly, the producers of new “anti-shyness” drugs, such as Paxil and Luvox, have been accused
of applying to normal behaviour, interventions developed for pathological traits.107 Paxil is licensed in the
US for the treatment of depression, Social Anxiety Disorder (SAD), Generalised Anxiety Disorder
(GAD),108 Obsessive Compulsive Disorder, Panic Disorder and Post-traumatic Stress Disorder. The Paxil
website notes that approximately 10 million adults are diagnosed with GAD each year in the US.109 The
website encourages individuals to take an online “self-test” for GAD, which involves answering three
questions:

1. Do you worry excessively or are you anxious a lot of the time?
2. Are you often bothered by the following:
   — Feeling restless, keyed-up, or on edge?
   — Feeling tense?
   — Feeling tired, weak, or easily exhausted?
   — Having difficulty concentrating?
   — Feeling irritable?
   — Having difficulty sleeping?
3. Would you say your anxiety or worry interferes with your work, family or social life?

Answering “yes” to more than one of the complaints listed in question 2, even if the answers to questions
1 and 3 are negative, is sufficient to generate a response that says the results are inconclusive and suggests
discussing them further with a health professional.

13.20 A similar self-test can also be undertaken for SAD, the key symptoms of which are a persistent fear
of and an associated avoidance of social situations involving strangers. In an article in the New York Times
Magazine about SAD, one commentator observed:

“until recently, it was thought to be a rare disorder . . . Then in 1999, buoyed by the success of the
new psychotropic drugs, the pharmaceutical company SmithKline Beecham began marketing its
antidepressant Paxil as a treatment for social phobia . . . Experts cited alarming new statistics—
around 13% of us were socially phobic, for example—and magazines dished up the requisite

106 See for example Conrad, P & Schneider, J W (1992). Deviance and Medicalisation: From Badness to Sickness. Philadelphia:
Temple University Press.
107 See for example Koerner, B I (2002). First, you market the disease . . . then you push the pills to treat it. The Guardian,
(30 July). Taken from Koerner, B I Disorders made to order. Mother Jones magazine. July/August (2002).
108 GAD is psychiatric disorder which features in the two main classification systems for mental illness, the Diagnostic and
Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the ICD-10 Classification of Mental and Behavioural Disorders.
alarmist trend stories. A set of traits and behaviours, at least some of which were once regarded as neutral, or even desirable, re-emerged as a pathology—a function of brain chemistry, amenable to and indeed demanding pharmacological manipulation.110

13.21 These examples can be viewed as illustrations of diagnostic spread, the re-classification of behavioural traits, and the possibility of commercial and social pressure to make use of medical interventions. While these examples are not the result of findings in genetic research, they demonstrate the existence of a tendency towards medicalisation, and corresponding problems, to which findings in genetics may contribute.

13.22 A further potential problem related to medicalisation is the tendency to focus excessively on the biological factors that influence particular traits, rather than the social or economic factors. In paragraph 3.17, we observed that those factors that are described as the “cause” of a particular trait are often those by which one hopes to control or alter that trait. Thus, there is a risk that the role of genetic factors will be over-estimated, so that genetic and medical interventions can be provided, rather than focusing on the social and economic environments which are also likely to play a vital role. This may be so even though there is no scientific reason for assuming that if genetic influences on a trait are identified that trait will be easier to alter using medical or genetic interventions rather than other forms. Examples of this phenomenon include the risk that medicines may be prescribed for children who are disruptive but do not have a clinical diagnosis of hyperactivity, rather than investigating other approaches such as reducing class sizes, and that medication may be used rather than diet and exercise as strategies for dealing with hypertension or obesity.

13.23 Medicalisation is an issue that affects many areas of life, not just behavioural genetics. In the case of behavioural traits, since research into genetic influences is at an early stage, it is not possible to say whether medicalisation will be likely, or whether it will have, on balance, positive or negative implications. However, examples of the deleterious effects of medicalisation in other areas suggest the need for awareness of potential problems. We conclude that research in behavioural genetics has the potential to contribute to the existing phenomenon of medicalisation. Deleterious effects that should be borne in mind include shifting the boundary between normal variation and disorder further away from the extremes of variation; reducing social tolerance of previously “normal” behavioural traits; and the routine selection of genetic or medical interventions without adequate consideration being given to environmental interventions and other options.

13.24 Any discovery of biological mechanisms that influence behaviour, including genes, may aid in the development of drugs which modify behaviour. We consider that there is potential for the unhelpful widening of diagnostic categories, to encourage the use of medication by people who would not necessarily be thought of as exhibiting behavioural traits outside the normal range. In addition to the potentially harmful effects already listed, this could lead to unnecessary increased expenditure by the health service. We recommend that health service providers, and in particular the Department of Health, specifically charge a named agency with monitoring and, if necessary, controlling, this means of the deliberate medicalising of normal populations.

APPENDIX 28

Supplementary evidence by the Association of the British Pharmaceutical Industry (PI 35A)

As requested at the pharmaceutical industry’s oral evidence session on the 13 January, the ABPI would like to submit additional evidence in response to specific questions raised.

The additional evidence is focused on the following three areas:

(1) Statistics regarding chemistry teaching in schools and higher education, the basis of our concern with regard to the supply of key skills to the bio-pharmaceutical sector.

(2) The comparative cost of clinical trials in the UK, an area where we need to be globally competitive.

(3) Pharmaceutical industry employment figures, focused on the issues raised by the Committee—the balance between R & D and sales resources.

CHEMISTRY

Chemistry in Schools—GCSE Level

About 81% of students take a “double science” GCSE—studying biology, chemistry and physics. Some teachers and HE lecturers argue that this does not provide a suitable basis on which to study A-levels in science. About 11% of students follow only a single science course which is not regarded as a sufficient basis for going on to study any science subject at A-level.

Fewer than 10% of students study two or three separate science subjects at GCSE, with only 7.9% taking Chemistry GCSE in 2004.

Chemistry in Schools—A level

Both the number of entries in chemistry and the percentage of students have dropped in recent years. Just over 20 years ago, the number taking A-level chemistry was 47,792 but by 2004 had dropped to 37,254 (4.9% of total A level entries).

Chemistry teachers

The number of teachers employed to teach chemistry alone in secondary schools has more than halved since 1984. The vast majority of science teachers are also expected to teach biology and physics as part of a “combined” science course.

It is calculated that approximately 8350 chemistry teachers are required to cover teaching at GCSE and A-level, whereas only 4,680 teachers in maintained schools have a degree, PGCE or BEd in chemistry. The estimated shortfall of 3,670 teachers must mean that large numbers of students are being taught chemistry by teachers without a qualification in the subject.2.

Chemistry in Higher Education

Applications from UK students to study chemistry have been declining steadily over the past 10 years and the total number of graduates in chemistry has decreased from 4,144 in 1996 to 2,955 in 2003.

In the past 18 months, Kings College and Queen Mary in London, Swansea, Exeter and Anglia Polytechnic University have announced closure of their chemistry departments. Others are known to be contemplating closure. In addition, De Montfort University, Leicester admitted its last intake of students in 2002. A major factor in this trend is that if the chemistry department has a Research Assessment rating (RAE) below 5, then funding provided by the Higher Education Funding Council (HEFCE) to support research infrastructure is significantly reduced. At Exeter, the Vice Chancellor was reported to have said that the income per member of staff in the chemistry and biology departments was £20,900 per year, whereas in physics it was £46,200 per year.

In addition, the decision by HEFCE to reduce the funding multiplier paid to universities to support teaching in laboratory-based subjects has been reduced from twice the amount given for lecture based subjects to 1.7 times.

The pharmaceutical industry generally recruits graduates who have completed an MChem or MSci in the chemical sciences for their chemistry research and development departments. In 2002, there were 1150 such graduates. The geographical distribution of these courses is not uniform. In 2003, whereas 10 universities in the Midlands offered MChem/MSci courses in chemical sciences, in Eastern Counties and the South, only two did4. With the recently announced closure of Swansea’s chemistry department, Wales will also only have two institutions offering these courses.

BPI does not believe that allowing these random decisions to close chemistry departments, which result in large areas of the country with no high quality chemistry department, is in the national interest. We would welcome recommendations from the Committee to reverse this trend.

A policy is required, driven by Government and by HEFCE, that will lead to co-operation between universities to ensure an adequate supply of chemistry teachers, courses and graduates, in which regional needs are met within a national framework.

COST OF CONDUCTING CLINICAL TRIALS IN THE UK AND ELSEWHERE

The costs of phase II-III clinical research in the UK have increased since 1995, and significantly exceed those in competitor countries, although the rate of growth may now be slowing.

The following slides illustrate the average yearly cost increase for conducting clinical research in the UK, as well as comparative costs of Phase II-III studies across all therapeutic areas for selected European countries.

It will be clear from the above data that the UK is the most expensive country in Europe in which to conduct trials, and that overhead allocation is a major factor. The ABPI is calling for:

— Transparency in the pricing of general overheads.
— Elimination of charges for standard care.
— The NHS to comply with NHS costing initiatives (due to be launched 28 February 2005).

We would welcome recommendations from the Committee to ensure our continuing global competitiveness.
EMPLOYMENT WITHIN THE PHARMACEUTICAL INDUSTRY

In the Committee’s deliberations it was frequently stated or implied that the UK industry employs more people in selling than in researching and producing medicines. The opposite is the case. The most recent employment figure (2003) we have for the industry is 73,000. Of this figure, 29,000 work in R&D, and 20,000 are involved in the manufacturing process. By contrast, the industry has 8,000 medical representatives. The remaining 16,000 people perform a variety of functions including corporate affairs, finance, marketing, and human resources. Even adding a proportion of the figure for marketing to the number for sales representatives, this element of the workforce is substantially exceeded by scientific and technical personnel.

15 February 2005

APPENDIX 29

Letter from David Dickinson, to the Clerk of the Committee (PI 127)

MODEL OF ACCESSIBLE INFORMATION FOR PATIENTS

I am writing to you as Clerk of the Committee because my attention has been drawn to proceedings last year of the 3rd Health Committee session taking evidence on the influence of the pharmaceutical industry. Evidence about the quality of patient information leaflets and consent information sheets was given, and I understand that Mr Hinchliffe challenged witnesses to provide a leaflet so that it could be understood by all patients, suggesting that an example might be submitted at a later date.

I wanted to reassure the Committee that effort does go into making documents user-friendly; to show that there is some good practice in the UK (which leads Europe in this field); and to demonstrate that it is possible to produce information that puts complex truths in simple language and helps ordinary people to make sensible everyday judgements about risk.

We may not quite have achieved a universal leaflet, but I and my colleagues (in particular Suzy Gallina and Jane Teather) have worked hard over the last few years to make patient information more accessible, and I annex the resulting model of a patient-friendly patient information leaflet, based on aggregating more than 250 interviews with patients.

We are an information design consultancy, working with both patients and the pharmaceutical industry to improve the quality and user-friendliness of patient information. In fact it was we who worked with the British offshoot of Novartis, to modify their clinical trial information sheets—cited in evidence to the Committee by Dr Richard Nicholson—so that their consent documents are now something that patients want to read, and taken up by the regulators in their templates.

Although the model leaflet is recognisably similar to current leaflets, it is better designed, more clearly worded and closely focused on four areas which patients consistently express concern: what the medicine does, the dos and don’t of taking it, how to take it, and clear information on side effects (including how likely they are and how serious they are). It does not quite meet the regulatory requirements as they are currently drafted, since the relevant legal guidance does not quite allow such a conversational style.

7 February 2005
About Burofen

Burofen is for treating pain. It treats the pain caused by rheumatoid arthritis. It is also used for muscle pain, especially backache, neuralgia (neural pain), migraine, headache, tooth ache, period pains, feverishness, and symptoms of colds and flu. It's one of a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs for short).

What this medicine does
Burofen is not a cure for your condition, but it can make it easier to live with. Burofen and medicines like it are called anti-inflammatory drugs because they damp down the inflammation which is often the cause of pain or fever. They work by cutting down the body’s production of inflammatory substances called prostaglandins. You should notice that the pain becomes less intense. That should make it easier for you to live your life normally.

What arthritis is
Arthritis just means painful joints. Osteoarthritis is the more common type of wear-and-tear arthritis, which most often affects people over 60. Rheumatoid arthritis is a particularly painful type which most commonly affects people between the ages of 30 and 50.

Burofen Do’s and Don’ts

Don’t
- Don’t use Burofen at all...
  - If you have a stomach ulcer (peptic ulcer) or used to have one.
  - If you are allergic to any of the ingredients (see box, far left).
  - If you ever had an allergic reaction to ibuprofen, aspirin or other anti-inflammatory painkillers in the same family. Reactions may include wheezing, breathlessness or swollen lips.
  - If you react badly to milk or lactose (if you are lactose-intolerant).
  - If you are pregnant or planning to get pregnant.
  - After the expiry date on the box. If any of these applies to you, talk to your doctor or pharmacist.

Don’t give Burofen...
- To children under 12. Your doctor or pharmacist will suggest other medicines for younger children.

Don’t use Burofen without a doctor’s advice...
- If you have kidney, liver or heart problems (or if you used to). If you do have kidney problems and you have to take Burofen, your doctor may test your kidneys before and after.
- If you have asthma (or used to) Burofen can bring on an attack.
- If you are over 60. Older people are more at risk from the serious effects of any reactions. If you are over 60, take fewer tablets: just enough to make you feel better.
- For more than 3 days. If pain carries on for longer, talk to your doctor.
- At higher than the recommended dose: 2 tablets every four hours, and no more than 8 in 24 hours.
- If you are taking other medicines, especially medicines listed in the next section, Taking Burofen.

Do

Do use Burofen...
- exactly as your doctor told you to.

Do take Burofen...
- with a glass of water: swallow the tablets whole.
- with food: preferably after a meal.

You can use Burofen...
- if you drive or use machines. Burofen has no effect on your ability.
- if you are breastfeeding, you can still take Burofen. A little ibuprofen does get into breast milk, but it’s unlikely to do your child any harm.

Taking Burofen

How much to take...
- Adults: 2 tablets every four hours as needed. No more than 8 in 24 hours.
- Children 12-18 years: 1 tablet every four hours as needed. No more than 4 in 24 hours.
- Not for children under 12
- Don’t take too much...
  - Don’t take more than 8 tablets in 24 hours. See a doctor if you’re no better after 3 days.
  - If you take too many tablets, talk to a doctor as soon as you can.
  - If you miss a dose, don’t worry. Forget about the missed dose. Take the next tablet as usual, and carry on from there.

Taking Burofen with other medicines...
Make sure your doctor knows if you are taking a medicine listed here:
- Drugs that thin the blood (anti-coagulants). Burofen may make the blood thinner.
- Drugs for high blood pressure (anti-hypertensives). Burofen may work against them.
- Aspirin (or other other anti-inflammatory painkillers). If you take these at the same time, you are more likely to get side effects.
- Water tablets (diuretics). Burofen may work against these.

Side effects
Possible side effects of Burofen

⚠️ Serious effects: see a doctor at once
These are likely to affect less than 1 in every 100 people
- Severe stomach pain, which may be a sign of ulcers or bleeding
- Skin peeling or blisters
- Unusual or easy bruising, caused by shortage of platelets in the blood (thrombocytopaenia)
- Producing much less urine, which can be caused by kidney failure.

If you notice any of these, stop taking Burofen and tell a doctor at once.

⚠️ Less serious, but tell a doctor
These are likely to affect 1 or 2 in every 100 people
- Headaches
- Dizziness
- Flu-like illness
- Yellowish skin or eyes (jaundice)
- Signs of allergy - breathlessness, wheezing, swollen lips, feeling faint
- Unusual or easy bruising, caused by shortage of platelets in the blood (thrombocytopaenia)
- Producing much less urine, which can be caused by kidney failure.

If you find these are troubling you, talk to a doctor when you can.

⚠️ Minor effects: tell doctor or pharmacist
These are likely to affect 2 to 6 in every 100 people
- Indigestion
- Feeling sick
- Pain in the gut

If you find these are troubling you, talk to a doctor or pharmacist.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Some people get side effects when they take Burofen. Most people don’t. For most people, the benefits are much more likely than the side-effects.

Burofen does not cause drowsiness, so you can still drive or use machines when you’ve taken it.

Look out for any of the effects listed above, and if you notice them, or anything else unusual that you think is caused by Burofen, tell a doctor or pharmacist (chemist) as soon as you can.

More information

Storing Burofen
- Keep Burofen away from children – somewhere they can’t see it or reach it.
- Keep in a dry place at less than 25 ºC (77ºF).
- Don’t take the tablets after the expiry date printed on the box.

Other help with pain
- Many hospitals have pain clinics. If you are suffering from a lot of pain for a long time, there may be other treatments that can help. Ask your doctor for details.
- Self help and support groups can give advice on your condition and put you in touch with other people who have been through the same thing. Ask your local library for details.
- Makers Mark runs a helpline by phone and email which can put you in touch with specially trained advisers who can help you cope with pain.

Email: pain.care@makersmark.com
Freephone: 00800 123 4567.

You can get a larger print version of this leaflet. Call this free phone number:
Tel: 00800 123 4567.

This leaflet was last changed 10 January 2000.
APPENDIX 30

Letter from the President, Faculty of Pharmaceutical Medicine to the Chairman of the Committee (PI 120)

The Faculty of Pharmaceutical Medicine was established in 1989 as a Faculty of the three Royal Colleges of Physicians of the United Kingdom to ensure that appropriate standards are set, examined and maintained within this specialist field in order to best serve both patients and the public health.

The mission statement of the Faculty is as follows:

THE SETTING, MAINTENANCE AND IMPROVEMENT OF STANDARDS IN PHARMACEUTICAL MEDICINE

Pharmaceutical medicine is a discipline that involves the discovery, development, evaluation, registration, monitoring and ethical marketing of medicinal products and medical devices. The responsibility of the pharmaceutical physician within this process is to guard the interests of patients by working to standards which ensure that research studies are conducted according to Good Clinical Practice (GCP), that safety data are collected, acted upon and reported to the highest international standards and that all communication with medical professionals and patients is accurate and ethical.

I fear that some of the evidence that has been provided to you by those advising you and also some of the witnesses might be leaving you with some misunderstandings. Whilst your enquiry is into the influence of the pharmaceutical industry, and we do not and nor should we represent the industry, many of the claims and statements constitute general allegations against pharmaceutical physicians.

It is on this basis that I feel I ought to write to you.

Since the Faculty was formed we have continued to develop the examination system that was already in place so that it is now one of the most challenging of the Diploma examinations within the Royal Colleges. In addition we have developed a Higher Medical Training (HMT) programme similar in structure to those already in place for all other medical specialties. This has been operational for 2 years and over 100 physicians have already enrolled.

In addition we are working with the General Medical Council to ensure that pharmaceutical physicians not only have the opportunity to revalidate, but are encouraged to do so under the new arrangements being put in place by the GMC.

As I am sure you are aware all the protocols for clinical trials carried out by the pharmaceutical industry have to be approved both by the MHRA and an Ethics Committee. These studies are amongst the best designed of any that are undertaken in human subjects, are carried out under a great deal of scrutiny and quality control procedures and analysed according to strict statistical criteria.

To suggest that pharmaceutical physicians are not properly trained or not capable of doing their job to an adequate standard, as has been suggested by some of your witnesses, is disingenuous.

APPENDIX 31

Memorandum by the Medicines Commission (PI 112)

1. INTRODUCTION

1.1 The Medicines Commission is grateful for the opportunity to give its views on the “Influence of the Pharmaceutical Industry” to the Health Select Committee.

1.1.1 The Commission was established under Section 2 of the Medicines Act 1968. Its general function is to advise “the Ministers” (ie the Secretary of State and the Northern Ireland Departments for health and agriculture) “on matters relating to the execution of this Act or the exercise of any powers conferred by it, or otherwise relating to medicinal products, where either the Commission consider it expedient, or they are requested by the Minister or Ministers in question to do so”. The Commission is fundamental to the working of the Act, and in addition to its general function was established to provide advice to the “licensing authority” under section 6 of the Medicines Act 1968 (consisting of the Secretaries of State for Health and Environment, Food & Rural Affairs, and the Northern Ireland Departments for health & agriculture) on matters relating to the licensing of medicines.

The Commission also have a duty to make recommendations to the Ministers on the number and functions of committees to be set up under Section 4 of the Act, such as the Committee on Safety of Medicines (CSM) and the Veterinary Products Committee (VPC), and on suitable members of such committees.

1.1.2 An important additional function of the Commission is to act as an appellate body for human and veterinary use marketing authorisation applications that have been refused by the licensing authority on advice from the CSM and VPC. In such cases, applicants have a right to make representations to the
1.1.3 The Act requires that the Commission’s members should include at least one person with experience and capacity in each of the following: practice of medicine; practice of veterinary medicine; practice of pharmacy; chemistry other than pharmaceutical chemistry; and the pharmaceutical industry (currently two members). In its current constitution, the Commission has some 24 members with a broad range of expertise. It also includes lay members, complementary medicine practitioners, microbiologists, nurses, statisticians, and hospital, university, and primary care doctors. All Commissioners are appointed on the basis of their individual expertise and bring diverse perspectives. The Commission provides an independent overview and meets approximately five to six times per year; members are appointed for four-year terms.

1.2 At its November meeting the Commission considered in detail the Health Select Committee’s Inquiry on the “Influence of the Pharmaceutical Industry”. The Commission welcomed the inquiry and felt that this was an appropriate time to re-consider the roles and influences that pharmaceutical companies have on medicines, medicines innovation, and health care in general.

In making the following comments the Commission was conscious of the rapid changes in public and professional access to, and the use of, medicines, and the need to be imaginative and thoughtful about the potential for restructuring the relation between policy makers, industry and health professions. It has attempted to draw on the diverse views and expertise of Commissioners by stepping back from preconceptions of health and industry relations, and questioning where and why the imbalances between health policy objectives and industry occur, and what can be done to improve them for public benefit.

The Health Services and Pharmaceutical Industry

1.2.1 The Health Select Committee inquiry should be viewed positively, for its potential to provide advice on restructuring the relationship between policy makers, regulators, industry, consumers, and all health professionals. The range of consumers and health professionals directly involved in day to day medicines management has increased and will continue to do so as switches to over the counter (OTC) drugs continue, and nursing and allied health professionals are incorporated into prescribing and policy making activities.

1.2.2 There is a perceived imbalance between the objectives of the industry and those of health care. The Inquiry will want to look widely and constructively at what are considered to be the real issues, rather than mere perceptions. The extent to which the ultimate objectives of health services and industry are disparate need to be considered, and ways they may best work together need to be explored.

1.2.3 In the current changing climate it is imperative that accountability, openness, transparency, and public participation are promoted on both sides. It is critical that the development and planning of policies that are credible, fair, and practical should involve players who are independent of government, industry, and special interest groups.

1.2.4 All stakeholders in health care have vested interests. The influence of pharmaceutical companies needs to be seen alongside the interests of the state (to provide comprehensive health care while controlling costs), patient groups (to get their specific problem dealt with quickly and safely), professionals, news media, and politicians. All these interest groups exert an influence, which can sometimes be excessive, producing an unbalancing and possibly damaging effect. Transparency and balance are key.

1.2.5 The current problems with the influence of pharmaceutical companies are well recognised. They include, for example, the lack of transparency of research data, distortion from publication bias, excessive delays before responding to reports on adverse effects, and inaccessibility of information about patients who have taken part in clinical trials. The possible availability of information from a wide range of sources on the web means that restricting information on drugs would no longer be possible. A useful approach would be to create a trusted reliable kite mark for information that is well researched and evidence-based, to run alongside information from special interest groups and those promoting particular information.

— Creation of a reliable kite mark for evidence-based information.

1.2.6 In recognising the major issues, we also note that problems would be much worse without the current regulatory systems. Tackling these issues is not just about more regulation, but about changing the nature of regulation and other aspects to fit modern needs better. This includes identifying the wide range of health professions and researchers engaged in the processes more systematically, as well as the roles of consumers. For example, the increasingly important and welcome engagement of patient groups makes it essential to have a strategic approach to them. Consideration should be given to the setting up of an umbrella body to promote good practises in prescribing, supply, and administration of medicines, and to consider other aspects, such as funding arrangements.

— An umbrella body to promote good practises in prescribing, supply, and administration of medicines.
Definitions

1.3 The phrase “pharmaceutical industry” requires more precise definition. There are many different types of pharmaceutical companies, ranging from so-called “Big Pharma” at one end of the spectrum (eg large multinational companies) to small local generics companies at the other. Biotech companies and manufacturers of herbal and homoeopathic medicines form other distinct groups. Furthermore, within each company there is a range of activities that need to be carefully distinguished, from high quality science at one end of the spectrum to marketing activities at the other. A scientist in a company working at the academic end of drug innovation and therapy will have no influence over the marketing activities of the company. It is the activities of those working in the marketing divisions that determine how drugs are marketed and presented to health care workers and the public.

1.3.1 It will be important, whatever measures are recommended, to recognize the complexity of pharmaceutical companies, and to ensure that recommendations that are targeted at one sector of pharmaceutical activity will not damage another.

1.3.2 It will be particularly important not to threaten the continuance of basic scientific research that pharmaceutical companies foster, often associated with universities. An index of the success of industry research is that several Nobel Prize winners won their prizes for work that was carried out while they were working for pharmaceutical companies. Examples include: Gerhard Domagk, 1938, for discovering sulphonamides; Paul Miller, 1948, for discovering DDT; John Vane, 1982, for his work on prostaglandins and the mechanism of action of aspirin; James Black, 1988, for discovering beta-blockers (and, later, histamine antagonists); Gertrude Elion and George Hitchings, 1988, for their work on differences in the structures and actions of normal and abnormal cells).

2. Drug Innovation

2.1 As health service providers and consumers, we are in need of innovative drugs to treat new, as well as current diseases and to improve the quality of lives. It is notable that the influence of the pharmaceutical industry has been positive in the development of new products in a way that no state controlled system has been able to match. Over the years there have been numerous examples of this: ACE inhibitors and angiotensin receptor blockers in reducing mortality in heart failure, statins in preventing heart attacks and strokes, and sildenafil for erectile dysfunction.

We need new methods of encouraging the production of innovative drugs by both academe and pharmaceutical companies, both separately and also in concert. Mechanisms should be established in order to encourage this.

— Development of methods to encourage the production of innovative drugs.

2.1.1 Over the last few years there has been a dramatic reduction in the numbers of new molecular entities being submitted to licensing authorities. There has also been a reduction in the number of entities being awarded licences. Figures recently published by the US Food and Drug Administration (FDA) show that the numbers of new licence applications submitted to them fell from about 70 per year in 1993 to under 15 in 2003 [1]. The reasons are complex, but in their report the FDA point to the fact that “the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences”. They partly blame the way in which the reductionist approach, “knowledge at the gene, gene expression or pathway level” has been fostered at the expense of the systems approach, and they call for “strengthening and rebuilding [of] physiology, pharmacology, [and] clinical pharmacology”. In other words, research on the gene and genome, necessary though it is, has driven out research on the functioning of body systems, to the detriment of innovation in drug therapy.

2.1.2 In the UK, the Higher Education Funding Council’s University Research Assessment Exercise (RAE) has put more emphasis on reductionist research at the expense of systems research, and this may have fostered the decline. The increasing closure and contraction of some university science departments is possibly a sad reflection of this process. This imbalance needs to be redressed by fostering attitudes that value systems-based research and by earmarking funds for functional research and the revival of academic research in physiology and pharmacology.

2.1.3 Research performed in academic institutions has a profound effect on drug innovation by pharmaceutical companies. Although companies fund research in universities, for many years now governments have spent twice as much on scientific research as industrial companies. This was true in the 1960s [2] and is true today [3].

2.1.4 Pharmaceutical companies have benefited, and have been very effective, in using the results of research from all sectors working in drug development. Often UK-based companies fund research organisations abroad, where costs are cheaper. Companies should be encouraged to divert more money into academic research institutions in the UK than they currently do. Basic scientific research institutes in the UK, perhaps jointly funded by universities and pharmaceutical companies, should be developed, with appropriate regulatory functions to ensure public credibility in research findings and their applications.

— Development of basic scientific research institutes in the UK perhaps jointly funded by Universities and companies.
2.2 Funding for research into adverse drug reactions (ADRs), an extremely important aspect of drug therapy, has been impossible to find in the current research climate. Large grant-giving bodies (such as the Medical Research Council and the Wellcome Trust) do not fund such research, because it is not at the “cutting edge”. Equally, Universities tend not to fund such research, largely because of the pressures of the Research Assessment Exercise noted above. Pharmaceutical companies provide little funding for such research, because they do not perceive it as being in their interests to do so, although recent events surrounding Vioxx (rofecoxib) have highlighted this deficiency.

2.2.1 The early discovery of adverse drug effects would help a company in their decisions to proceed in the development of a drug and in planning better methods of making their drugs available with suitable monitoring. Early discovery of adverse effects also allows companies to develop coping strategies (as exemplified by the Clozaril-clozapine Monitoring Scheme [4]), potentially leading to enhanced usefulness of drugs that might otherwise be lost. Late discovery leads almost inevitably to the need to withdraw the drug, at great financial loss (eg Vioxx-rofecoxib).

— Companies should be encouraged to fund early research into the adverse effects of their drugs and ways of predicting or avoiding them.

Underdeveloped Areas

2.3 Encouragement should be given to appropriate drug development in areas that do not necessarily yield high financial returns. Recent UK and EU developments, promoting good practice, have provided incentives to research drugs for paediatric use. This is a good example of a previously under-developed but critical area of medicines research and use.

2.3.1 As a major purchaser of healthcare, the NHS has still to maximise its influence on industry prices and drug development. As we understand it, medicines in the UK are more costly than in many other European countries, despite the strength, centralisation, and negotiating ability of its public sector health delivery.

3. THE CONDUCT OF MEDICAL RESEARCH

3.1 Within industry, there is an imbalance between the over-powerful marketing divisions of pharmaceutical companies and their scientific and medical divisions. Short-term marketing plans concentrate on studies that will help to market products. This has the advantage of reaping immediate rewards and avoids the necessity of performing studies that may take time and have the potential of raising difficulties. This is neither in patients’ best interests, nor in companies’ own long-term interests if harmful effects of products go undetected.

— All medical research in pharmaceutical companies should follow the principles of research governance. There should be consistent standards of quality, appropriate methods, ethical review, and outside scrutiny.

3.1.1 There is a bias towards publishing only positive data. This has a consequence on other agencies, which must waste resources in repeating the same research.

— There should be a requirement to publish all data, backed up by the compulsory trials register that is due to be established in 2005. This should be at the heart of any new approach.

3.1.2 Industry has been accused of medicalising society, by promoting/creating new medical conditions with potential for a strong consumer demand, but which do not have an evidence base. This is likely to influence the drugs that are chosen for future development at the cost of investing in well-established needs.

— There should be careful scrutiny of the conditions for which drugs are promoted.

3.1.3 Pharmaceutical companies, amongst their other functions, support posts, grants and university departments. Without this support, many departments would not be able to conduct valuable research and would find it difficult to find funding elsewhere. If this is felt to undermine the credibility of medicines research then alternative sources of funding will have to be identified, as it is critical to good practice that such research should continue. However it must be recognised that the industry contributes approximately £6.7 billion per annum to Britain’s gross domestic product and also about £12 billion in exports.

3.1.4 Pharmaceutical companies have also played a significant role in funding conferences and in facilitating meetings and workshops. This source of funding should be encouraged, since consideration would need to be given to alternative sources of funding if this funding were not available. However, suitable controls should be exerted over the extent to which funding of this sort allows companies to promote their products covertly.

3.1.5 There are many helpful functions that the pharmaceutical industry performs for the improvement of healthcare and the impact of these beneficial effects should be recognised. For example, industry has played an important role in highlighting issues of fraud in medical research by pursuing cases through the General Medical Council.
3.1.6 The FDA in the USA audits pivotal registration studies. Recently a section of the Medicines and Healthcare products Regulatory Agency (MHRA) has undertaken studies of Good Clinical Practice (GCP) and audit; this had been highlighted in the Audit Commission’s report on the old Medicines Control Agency. Within most companies, there is a policy to audit clinical studies actively, as it is crucial to them that their data are robust. This is perhaps not as well developed in some academic institutions.

3.1.7 There is increasing recognition that drug use and medication management requires not only clinical research, but also research into social, behavioural, and economic factors. This would help inform best use of public investment into purchasing drugs and treatments. Growing collaboration between the Medical Research Council (MRC) and the Economic and Social Research Council (ESRC), underpins the importance of joint research.

— Social, behavioural, and economic research should be initiated and encouraged in order to inform on patterns of drug taking.

3.1.8 There is a need to invest in this “insight” research in order to (a) appreciate the reasons why consumers use OTC and prescribed medications; (b) consider how to improve prescribing practices (eg avoiding wasteful prescribing); (c) understand the power and influence of the different players in medication management at all levels (consumers, professions, regulators, industry, government).

4. Provision of Medicines Information and their Promotion

4.1 Commissioners recognise the diversity of sources from which information on medicines is now generated and received by the public; these include school curricula, electronic, broadcast, and written media, industry sponsored information, specialist user groups, and medical evidence websites. We note that any developments must take account of the full range of resources, and that the government has particular responsibility for ensuring that the public is given best advice on how to read and interpret such findings.

4.2 There are many ways in which drug information is provided. For statutory reasons, the Patient Information Leaflets (PILs) are provided with all medications dispensed to the public. However, these leaflets are often difficult to understand and excessively detailed. Information is also provided on the packages in which drugs are marketed, but this means of purveying information is not always used to best advantage.

— PILs should be made easier to understand, and regulations changed to enable this when necessary.
— Consideration should be given to the design and packaging of drugs.
— Patient information should be provided in a variety of ways.
— Controlled information should be made available on the internet, websites, and TV resources.
— These could be used to back up paper information.
— NHS Direct and other help lines should be used more for those not keen/able to use IT.

4.3 Pharmaceutical companies promote their products in many ways. They distribute drug information leaflets through the post and at meetings. These meetings are either sponsored (hospitality for scientific meetings) or promotional, and information is often given about a drug that the company produces. Conferences and workshops may be sponsored, and doctors can have their expenses paid for attending meetings at home and abroad. Even if there is no active publicity, there is a hidden incentive for health care workers who benefit from such meetings to prescribe the company’s products.

— There needs to be a more open and transparent approach to the marketing of drugs.
— Health care workers need to be educated on effective methods of evaluating information that a company provides.
— In respect of hospitality/sponsorship activities, pharmaceutical companies and health care professionals should work in partnership, to ensure that their members comply with current good practices.

4.3.1 There is a fine line to be drawn between education and advertising when a drug is being marketed. Basic scientific information on the development and production of drugs can be very educational. However, if this is related to the drug being promoted, it can act as an advertisement.

4.3.2 There is evidence that the distribution of gifts and grants to individuals for travel to attend conferences has an influence on their prescribing habits. There is a need to follow guidelines of good practice and to be open to scrutiny, audit, and transparency. There are several codes of practice (such as those formulated by the ABPI and the Royal College of Physicians) for healthcare workers and companies, which need to be followed. There is a need for greater transparency.

— Codes of Good Practice should be followed. Attempts to influence prescribing habits, for example by advertising, should be minimised, unless there is a good evidence base for the preference of a particular drug.
5. Professional and Patient Information

Multiple players are involved in the delivery of drug information to patients. With the extension of public choice in drug use (increased numbers of OTC formulations) and a greater range of direct professional involvement in day to day drug delivery, it is increasingly important that the public and professionals understand the role of industry in the development and marketing of drugs and the delivery of information. The Committee inquiry offers a timely opportunity to review how this may best be achieved.

5.2 The MHRA (or an equivalent independent body), needs to have responsibility for the strategic overview of medicines information. Policies should be developed with the active involvement of the public, in consultation with voluntary agencies such as the Long Term Medical Condition Alliance and other Consumer and Carer groups. The Department for Education and Skills (DFES) could be included, to ensure the engagement of school education as well as direct health consumers. Outcomes might include requirements for examining medicines use under the citizenship parts of secondary school curricula, to requiring pharmaceutical studies to be available for external scrutiny by consumers.

5.3 Professional education is currently divided across diverse structures, such as: medicines advisory bodies (eg NICE); regulatory agencies (the MHRA, including the CSM); companies (subsidy or payment for postgraduate short courses); the DH (including the Chief Nursing Officer for nurse prescribing); Professional Bodies (the GMC, the Royal Medical Colleges, the Royal Pharmaceutical Society, the Nursing and Midwifery Council); funding bodies (Workforce Confederations/SHAs), and last, but not least, Higher Education Institutions.

5.3.1 Specific information is given in the British National Formulary (BNF), which gives detailed information on drugs prescribable on the NHS, the Drug and Therapeutics Bulletin (DTB) published monthly, learned journals, and textbooks. These all provide alternative sources of information. Overall, this leads to a fragmented, ad hoc system, which does not best oversee and provide for the needs of consumers. It is recognised that there is a significant number of errors in prescribing, which range from wrong dosages to prescribing the wrong drugs.

5.3.2 It is critical that the above range of professional bodies should provide credible information. However, currently, because of their diversity, there is a lack of coherence of approach.

— In order to rationalise the prescription, supply, and administration of pharmaceutical products, a Council should be established to be responsible for the strategic development of a comprehensive, future-looking plan for undergraduate and postgraduate education development across the full range of health professionals.

— Better education in prescribing and adverse drug reactions and interactions should be provided throughout the careers of prescribers.

— Any education should include the understanding of the role of the pharmaceutical companies and an awareness of the potential impact of their activities on prescribing and research practice.

— Companies should be encouraged to develop ways of educating health professionals and the public (eg through informative websites). The nature of the information purveyed in this way needs to be scrutinized for bias.

5.4 The pharmaceutical industry provides substantial input to the education and training of pharmacologists and toxicologists in UK universities. This takes the form of providing guest lecturers, grants to enhance research projects, and providing training in integrated pharmacology and physiology for undergraduate and postgraduate students. This is often done in collaboration with the British Pharmacological Society and the Physiology Society.

In a recent survey the decline in teaching of integrative pharmacology/physiology in UK universities was highlighted suggesting that collaboration between industry and learned societies should be encouraged and supported by funding agencies. It is encouraging to note that a small number of MRC PhD studentships for whole animal pharmacology, physiology, and toxicology have already been ring-fenced to start in 2005.

5.5 Drug treatments can be very complex and there are few black and white issues. The needs of very ill people to get better treatments have to be constantly balanced against assessments of probable levels of risk. Over time, the UK will probably move to a culture in which people make more informed choices about the balance of benefits and harms of treatments. In this environment people will have a more healthy scepticism and more realistic expectations about any medical intervention. Public education on assessing the balance of benefits and harms is necessary.

6. Regulatory Review of the Quality, Efficacy, and Safety of Medicines

6.1 Drug regulation in the United Kingdom has developed a system that is often used as a model for other countries. This is largely due to the control that is provided by the Medicines and Healthcare products Regulatory Agency (MHRA). Commissioners welcomed the 2003 Audit Commission report on the work of the Medicines Control Agency, the predecessor of the MHRA, reporting on its strengths but also proposing changes that included better communication and public participation in decision-making.
6.2 However there are two potential areas of conflict of interest within the MHRA that should be considered. First, funding for the activities of the MHRA comes from the pharmaceutical industry itself, from fees for licensing. Secondly, the MHRA acts as the regulatory body for both the licensing of new medicines and the pharmacovigilance of new and established medicines, through a complexity of divisions and committees.

— There should be a transparent division between the two main functions of the MHRA (licensing and pharmacovigilance).
— Serious consideration should be given to providing government funding for the MHRA.

6.2.2 Checks and balances need to be made more explicit, more diverse, and more imaginative, in order to meet changing social expectations for influence, transparency, and accountability. The MHRA has a major role to play in communicating these changing requirements to a public that increasingly welcomes such information.

6.2.3 Pharmaceutical companies have both a legal and a moral obligation to report to the Regulatory Agencies any patient reports of adverse events that they receive. Companies also follow these up (with patient consent) with the patient’s General Practitioner, but the response rate by GPs to these follow-ups is extremely low.

— Doctors should be encouraged to take part in pharmaceutical company initiated reporting of adverse drug reactions and to report them themselves. Financial incentives should be considered.

6.2.4 The range of media from which public and professional information is collected should be recognised and use should be made of modern technologies for rapid response.

6.2.5 Serious consideration should be given to scrutiny by a range of interested parties, including the public, who pay for medicines directly, over the counter, and indirectly, through taxes, and those who prescribe, supply, and administer the products. This also relates to the point about active diversity in professional and public education.

6.2.6 A key target would be to shorten the delays in getting from early reports of problems to regulatory action. Patient organisations could play a valuable role, by picking up early signals and by working with regulators to conduct quick initial surveys to see if a full investigation is merited.

7. Product Evaluation, Including Assessments of Value for Money

7.1 There are many other sources of influence that interact in complex ways with the pharmaceutical industry; these should be made more transparent. Once a drug is licensed and available for prescription in the NHS, the price may be influenced by NICE decisions, decisions of drug and therapeutics committees (which influence local negotiations between Trusts’ purchasing departments and companies), possibilities of therapeutic substitutions (some of which may be limited by the need to conform with the Medicines Act), and possibilities for the importation of parallel drugs (although the use of such products is often offset in the UK by unintelligible patient information in different languages).

7.2 There would be potential savings to the NHS if there were central negotiations on behalf of Trusts/PCT consortia.

The mechanisms that companies use to profit from their products should be explicitly acknowledged and analysed, to explain why the same product can cost markedly different amounts in different parts of Europe and in different parts of the NHS.

8. Summary

The following are the main suggestions and recommendations of the Medicines Commission following its discussion on the “Influence of the Pharmaceutical Industry”:

— Creation of a reliable kite mark for evidence-based information on drugs and drug products.
— An umbrella body to promote good practices in prescribing, supply, and administration of medicines.
— Development of methods to encourage the production of innovative drugs.
— Development of basic scientific research institutes in the UK, perhaps jointly funded by Universities and companies.
— Companies should be encouraged to fund early research into the adverse effects of their drugs and ways of predicting or avoiding them.
— All medical research in pharmaceutical companies should follow the principles of research governance. There should be consistent standards of quality, appropriate methods, ethical review, and outside scrutiny.
— There should be a requirement to publish all data, backed up by the compulsory trials register.
— There should be careful scrutiny of the medical conditions for which drugs are promoted.
Social, behavioural, and economic research should be initiated and encouraged in order to inform on patterns of drug taking.

PILs should be made easier to understand, and regulations changed to enable this when necessary.

Consideration should be given to the design and packaging of drugs.

Patient information should be provided using a variety of ways.

Controlled information should be made available on the internet, websites, and TV resources. These could be used to back up paper information.

NHS Direct and other help facilities should be used more for those not keen/able to use IT.

There needs to be a more open and transparent approach to the marketing of drugs.

Health care workers need to be educated on methods of adequately evaluating information that a company provides.

In respect of hospitality/sponsorship activities, pharmaceutical companies and health care professionals should work in partnership, to ensure that their members comply with current good practices. Codes of Good Practice should be followed. Attempts to influence prescribing habits, for example by advertising, should be minimised, unless there is a good evidence base for the preference of a particular drug.

In order to rationalise the prescription, supply, and administration of pharmaceutical products, a Council should be established to be responsible for the strategic development of a comprehensive, future-looking plan for undergraduate and postgraduate education development across the full range of health professionals.

Better education in prescribing and adverse drug reactions and interactions should be provided throughout the careers of prescribers.

Any education should include the understanding of the role of the pharmaceutical companies and an awareness of the potential impact of their activities on prescribing and research practice.

Companies should be encouraged to develop ways of educating health professionals and the public (e.g. through informative websites). The nature of the information purveyed in this way needs to be scrutinised for bias.

There should be a transparent division between the two main functions of the MHRA (licensing and pharmacovigilance).

Serious consideration should be given to providing government funding for the MHRA.

Doctors should be encouraged to take part in pharmaceutical company initiated reporting of adverse drug reactions and to report them themselves. Financial incentives should be considered.

9. References


APPENDIX 32

Memorandum by Dr Julian Colledge (PI 113)

Introduction

I graduated in Medicine from Bristol University in 1972 and have gained post-graduate qualifications in psychiatry, general practice and obstetrics and gynaecology. During the past 25 years as a General Practitioner I have always had an interest in cost-effective prescribing. For eight years I was a manager of an out-of-hours co-operative for 300 doctors and was responsible for managing the medicines and dealing with the complaints.
HEALTH NEEDS AND NHS SPENDING

1. The priorities of NHS spending are distorted by overwhelming demands for medication. We are using too many drugs and too many expensive medicines with little certainty that they are benefiting our patients.

2. Massive financial savings could be made by cost-effective prescribing using a “Core National Formulary.”

3. There is no doubt that the pharmaceutical industry has produced some drugs which have been of immense benefit to humanity over the past 50 years. However, also it would be reasonable to say that many drugs have not been of benefit and definitely some have been harmful. Iatrogenic illness is a significant cause of morbidity and mortality.

4. Of the thousands of drugs available on the NHS very few save lives.

5. Pharmaceutical companies generate needs and markets.

A GP’S PERSPECTIVE

The role of the doctor should primarily be one of health education to prevent illness, support, and encouragement of self reliance in the management of disease. All of us should remember that the title of doctor is derived from the latin docere—to teach, and that one of the basic tenets of the Hippocratic Oath is—“first do no harm.” Unfortunately the provision of prescriptions has become institutionalised in modern health care—“the quick fix.”

Working at the coal face, I have seen so far, more than a quarter-of-a-million patients and yet only saved a few lives. Prompt administration of penicillin to patients with meningitis, and other inexpensive antibiotics to patients with overwhelming infections and early referral for surgery of patients who had life-threatening surgical conditions have been the main factors in saving lives in general practice. Of course, good management of chronic conditions, such as hypertension, does have an impact on morbidity and mortality, however again medication used does not have to be vastly expensive.

From the Black Report and other research you will know that poverty and ill-health are closely linked. Clean water, sanitation, employment, reduction of poverty, vaccination programmes, avoidance of environmental pollution are all major factors in the improved health of the nation. To promote individual versus state responsibility for health and endeavouring to prioritize and achieve the right balance of spending is immensely difficult.

The pharmaceutical industry is basically driven by the profit motive. 47% of my patients are on some form of repeat medication and 14% of my patients are on four or more repeat medicines. My Practice is fairly average for rates of prescribing. These statistics seem shocking and one has to question the health benefits (and financial implications) of such a large proportion of the population taking regular medication. My practice prescribing costs are 16% below the local average and 17% below the national average. The practice is meeting all the requirements of the new GMS Contract and is achieving the maximum number of points. The Practice makes less than average referrals to secondary care. Data confirming these figures is available upon request.

MISTAKES OF THE PAST—HARMING OR KILLING PATIENTS WITH DRUGS

As a junior doctor in the 1970’s working for a cardiologist I prescribed Practolol, a beta-blocker that was subsequently withdrawn as it caused retro-peritoneal fibrosis and death. Also, I also prescribed Clofibrate to lower cholesterol, which subsequently was withdrawn because it caused an increased rate of bowel cancer. In November 2004 Vioxx (Rofecoxib) used in arthritis was withdrawn from the market as it caused a significant increased rate of deaths from heart problems. For many years, I was convinced by the research data, general medical opinion and the information from pharmaceutical companies that HRT was good for my menopausal female patients. In the early 90’s many GPs had “Well Woman Clinics” and a very high proportion of menopausal women were put on HRT in the belief that it reduced their risk of heart disease and osteoporosis. These beliefs were supported by some very large trials from the USA. At the time, some of the media encouraged patients to think that HRT was the path to eternal youth. In an editorial article in the British Medical Journal about 18-months ago the conclusion was “That HRT is good for symptoms but bad for health”.

Initiatives such as NICE, working on evidence based medicine should reduce future risks. But serious mistakes continue to be made. Why does this still happen?

DRUG INNOVATION

From the general practice perspective over the past 30 years, the following categories of drugs have been major advances and made very positive impacts on health care:

— PPI’s (proton pump inhibitors) have dramatically reduced the mortality and morbidity from peptic ulceration.
— The low dose combined oral contraceptive Pill is effective, safe and inexpensive.
— Beta-blockers, statins and ACE-inhibitors and diuretics have all made major contributions in the
care of hypertension and cardiovascular disease.
— SSRI anti-depressants are safe in overdose and have been a major advance in the treatment of
depression.
— Many anticancer drugs have been enormously beneficial to humanity.

Within these categories there are now many off patent generic medicines which are inexpensive and very
cost-effective. However, there are many expensive “me-too” drugs which have no real benefit over the
ground breaking original drugs. All too often misleading research and advertising are used to boost drug
company profits. Eso. and des. molecular variations of former drugs are blatantly misleading and a method
of profiteering.

NICE and regulatory bodies should contribute towards identifying needs and approving research at a
national and international level.

Hopefully the mapping of the human genome and other advances in human biology will inspire and enrich
future unbiased research and then pharmaceutical innovation.

**THE CONDUCT OF MEDICAL RESEARCH**

Nowadays a very large amount of research is sponsored by drug companies and clearly is biased. Important negative findings are often withheld. These should be published, for example the manner in which the data was presented with regard to Cox-2 inhibitors. The British Medical Journal has expressed concerns about this over a period of several years (Abbasi K. Editors Choice. BMJ 204:329.27.11.04). Similar problems have arisen with the conduct of research and marketing of a group of drugs called A2-blockers, used in heart disease and hypertension (Verma S and Strauss M. Angiotensin Receptor Blockers and Myocardial Infarction, BMJ 329.27.11.04 Page 1248–1249). This article illustrates how confusing the research is relating to these particular drugs and how they may be positively harmful to patients. Currently the NHS spends vast sums of money on these drugs on an evidence base which is very shaky and will probably result in litigation. Twenty-five years ago the Medical Research Council undertook a large amount of pure research, the funds for the MRC were whittled down. Surely the NHS and universities should be undertaking non-sponsored pure research.

**THE PROVISION OF DRUG INFORMATION AND PROMOTION**

“There is no such thing as a free lunch”. Advertising works. With the best will in the world, accepting
educational grants, sponsorship or hospitality will inevitably compromise the prescribing of individual
doctors. My own opinions have been inappropriately swayed by pharmaceutical representatives and
promotional information.

Safe, unbiased and useful sources of information include medical journals such as the British Medical
Journal, Drugs and Therapeutics Bulletin and Current Problems published by the Committee of Safety of
Medicines. The Department of Health bulletins and other independent medical journals and locally
produced prescribing information. Many websites, such as the British Hypertension Society, produce
balanced and well-considered information about prescribing with appropriate evidence based links.

**REGULATORY REVIEW OF DRUG SAFETY AND EFFICACY**

The controversy surrounding many drugs, for example HRT (hormone replacement therapy), Cox-2
inhibitors (anti-inflammatory drugs for arthritis) and angiotensin receptor blockers (for raised blood
pressure, heart disease and prevention of renal disease in diabetics), illustrates the immense difficulties for
any regulatory authorities. The research is often very controversial and contradictory.

Vested interest and immense profits hinder truth. With respect to the most recent controversy, to quote
David Graham, the United States Food and Drug Administration Associate Director, “The dangers of
Rofecoxib were apparent eight years ago and not acted upon, the harms suppressed. What has now unfolded
may be the most serious example of regulatory failings about drug related harm since the thalidomide
scandal”. Please see Advisory Briefing of the Food and Drug Administration, NDA, 20-757(S-021),
www.fda.gov.
**PRODUCT EVALUATION, VALUE FOR MONEY**

Please see a GP’s perspective above and attached document entitled “Cost Effective Prescribing—Saving Millions for the NHS”.

**CONCLUSION**

- Enormous financial savings to the NHS could be made by adopting an evidence based “Core National Formulary” without compromising safety or efficacy.
- The positive and negative influences of the pharmaceutical industry should be recognised and constantly scrutinised.
- Pure academic research must be encouraged and adequately funded from unbiased sources.
- Negative research findings should be published.
- Health promotion and encouragement of personal responsibility for health must be encouraged.
- Please see separate document entitled “Cost Effective Prescribing—Saving Millions for the NHS.” for specific details of how to achieve significant financial savings.

**APPENDIX 33 (PI 125)**

**Memorandum by the University of Stirling**

*Dealing in Drugs: An Analysis of the Pharmaceutical Industry’s Marketing Documents*

1. **INTRODUCTION**

As part of their investigation into the conduct of the UK pharmaceutical industry, the House of Commons Health Select Committee obtained access to internal documents from various pharmaceutical companies relating to their marketing activity for specified products or programmes. The Institute for Social Marketing (ISM), at the University of Stirling and the Open University, was asked to analyse these documents and prepare a report.

The committee obtained documents from five pharmaceutical companies: GlaxoSmithKline, AstraZeneca, Pfizer, Eli Lilly and Wyeth. Each company was instructed to provide all promotional and product support material for specific brands or programmes (see Table 1 below). On the ISM’s advice, the Committee requested a range of documents, including: contact reports between clients and agency/agencies, client briefs, creative briefs, media briefs, market research reports, details of public relations activity and any other documents relating to promotion and product support. A total of 49 boxes were obtained.

**Table 1**

<table>
<thead>
<tr>
<th>Company</th>
<th>Product/Brand</th>
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<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>Seretide</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Nexuim, Crestor</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Celebrex, Bextra, Liptor</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>Zyprexa (Well being support programme), Cialis (36 hours of freedom)</td>
</tr>
<tr>
<td>Wyeth</td>
<td>Zoton FasTab</td>
</tr>
</tbody>
</table>

The Association of the British Pharmaceutical Industry (ABPI) Code of Practice, 2003, covers all forms of promotional activity by the UK pharmaceutical industry. Although the code itself is self-regulatory, it was designed to reflect the requirements of the Medicines Act and the European Advertising Directives, which are legally binding. The Code states that promotional activity by the pharmaceutical industry for prescription-only (PO) medicines should only target members of the health professions and not the general public, and in doing so should abide by the code in “both spirit and letter” and such promotion should be carried out “in a responsible, ethical and professional manner”. The documents obtained were analysed around four key themes taken from the Code of Practice.

- Targeting patients and general public.
- Servicing the emotional needs of health professionals and the use of branding.
— The use of public relations and building relationships to counteract negative publicity.
— Disguised marketing to the health professionals.

In each area, examples were found that contravened the spirit if not the letter of the Code of Practice. This is of particular concern because the analysis is based on a small number of documents as three of the five companies provided a very limited set of papers. For this reason the results have been anonymised.

2. FINDINGS

2.1 Targeting Patients and General Public

The Code of Practice states that as far as targeting patients and the general public is concerned:

“Medicines must not be advertised to the general public if they are prescription only medicines.”
Code of Practice, Clause 20.1

“Statements must not be made for the purpose of encouraging members of the general public to ask their doctors to prescribe a specific medicine.”
Code of Practice, Clause 20.2

“A company may conduct a disease awareness or public health campaign provided that the purpose is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine.”
Code of Practice, Clause 20.2

Thus, beyond the simple provision of information, the pharmaceutical industry is prohibited from targeting patients and the general public with marketing and promotional activity relating to prescription-only (PO) medicines. In many of the documents, however, patients and the general public emerge as key targets for direct and indirect communications that go beyond the simple provision of information. Detailed and continuous market research, for example, is conducted with the public to uncover their emotional drivers and motivations, which are then exploited to encourage presentation to the medical services. Public relations activity is also used to encourage media coverage with the clear intention of targeting patients, patient groups and the general public. This activity is then tied into specific brands and their performance in the market place.

Market Research

There is clear evidence that the industry is concerned with identifying populations who are not currently presenting to the medical services for diagnosis and prescription of medicines. This population, dubbed “the missing millions”, are estimated to include almost 2 million people in the UK:

“Through their strategic planning process, Company X have identified a population of patients . . . that do not currently present to their GP or take prescription medications.” . . . “This population provides a significant opportunity for Company X.”

Research is then conducted with the aim of understanding what barriers exist to prevent these people from presenting and to identify factors, both rational and emotional, that will overcome these barriers and encourage presentation:

“Overall aim:
To understand how to target these patients and overcome their barriers to presentation.

Specific aims:
To understand the segments of patients that do not currently present to GPs
To explore their rationale/belief systems that inhibit them from presenting
Identify hooks and drivers to encourage them to seek advice
—both emotional and rational.”

The documents make it clear that the pharmaceutical industry is concerned with using the results of such research to design strategies that are able to ‘target these customers’ and goes as far as identifying which of these customers will be most ‘receptive’ to their communications:

“Evaluate and communicate channels that could be used to target these customers. Identify which segments are likely to be most receptive.”

This demonstrates that the pharmaceutical industry are concerned with targeting members of the general public, particularly those who are most likely to respond to their messages—and the fact that they refer to them as customers suggests that this is not just motivated by an interest in public health.

The documents also demonstrate that the pharmaceutical industry employs sophisticated marketing principles, such as segmentation, targeting channel choice and source effects to maximise their success.
Thus, their research is used to segment the population into smaller, more homogenous groups, and targeting strategies are employed to meet the specific and unique needs of each group. In one research paper, for example, segmentation principles are employed to identify various patient types based on their involvement with the condition and the impact their condition has on their life, including segments called “endurers”, “sceptics” and “deniers”. Figure 1 overleaf outlines all the segments identified.

Figure 1: Segmentation of Patient Types
Qualitative Segments Based on Characteristics of Missing Millions

The research then goes on to identify the most appropriate ways in which to target these groups to encourage them to present to the medical services. Figure 2 below outlines how they propose to target one group: “hard working heroes”. This highlights that the main barrier to presentation for this group is a lack of perceived time and the research then suggests providing information on “how little time improvement requires” and suggests providing the incentive of prolonging their “working career” by taking medication.

Figure 2: Targeting strategies for ‘hard working heroes’
Belief Change Strategy - ‘Hard working Heroes’

→ Fewer hard working heroes around than endurers/resigned
   - however, important target group as likely to become endurers/resigned as get older.

The research also profiles all of the identified patient groups according to ease of targeting (see Figure 3 overleaf). The majority of the “missing millions” are identified as “easier targets” in terms of their “willingness to take medication”, although it is recognised that even this group “may still have reservations re prescribed ‘symptom relief’ that needs to be taken continuously”. “Prescribed symptom relief” can only be interpreted as prescription medicines.

1 Although all of the figures presented in this analysis have been taken from the pharmaceutical industry’s own documents some have been adapted slightly to ensure the findings remain anonymous.
Based mainly on willingness to take medication / active interest in condition and current impact of life, patient types appear to separate into two groups re ‘ease of reaching’
- although even those easier to reach may still have reservations re prescribed symptom relief that needs to be taken continuously

Given these reservations, a clear need is identified to “reframe perspectives” and “raise expectations re normality” among these “missing millions” and the documents highlight that “patients will need to be provided with hooks to make them ‘open to change beliefs’” and once belief patterns are changed, behaviour should follow suit”. Again this must refer to their willingness to take medication, and a desire to make them more favourably inclined to do so.

Research is also conducted with the general public which aims to “evaluate and communicate channels that could be used to target customers” and highlights more general communication principles the industry consider when targeting such general public groups. For example, the outcomes of the research suggest that the perceived source of the message is vital to the target audience’s receptiveness to the communication.

“Strong perception exists amongst missing millions that any communication or information provided needs to be from credible source, eg. GP, ‘medical organisation’, patient group—NOT outwardly a drug company—stigma attached to pharmaceutical companies that they’d just be doing it to sell drugs’, not seen to be patient focussed.”

Similarly, other more “credible” channels of communication are outlined:

“Patient leaflets left on the counter in pharmacies/GPs surgeries—perceived to be more ‘credible’ source than, eg at end of supermarket aisle.”

Advertising and Public Relations

There are also occasions within the documents when overt references are made to “direct consumer advertising” and again there is a desire that this advertising should be “not obviously from a pharmaceutical company”. Potential routes are outlined, including “PR activities” in the form of “articles in lay press”, “TV documentaries” and “soap operas”—which being indirect and unattributed are potentially more powerful than conventional advertising.

Furthermore, the campaign is clearly aimed at those who will be “most likely to take action” which suggests that the campaign is primarily concerned with those who are most likely to benefit the company rather than those who may arguably be more legitimate targets, but more resistant to change. In a similar vein, concerns are raised in the conclusions and recommendations that some of the target audience are presenting to pharmacies rather than GPs or hospitals which “results in fewer scripts”. This is clearly viewed as a threat and is described as “something to be monitored”. More specifically, calculations are made regarding the number of people who are prescribed the company’s brand. The clear aim of the campaign is to “be effective in attracting these people” which again makes it clear that the ultimate aim of the campaign is to increase sales of the company’s brand.

Public relations activity is also used to target “patients”, “patient groups”, “consumers” and “consumer journalists”.
“Increased understanding of the need to approach GPs.”
“To secure publication of three articles within the consumer media by end of March 2005.”

This PR activity aims, among other things, to promote awareness of specific diseases, the need to seek treatment and the benefits of specific brands.

“Create a positive media and press environment for brand X. “Positive articles on brand X generating a positive press environment.”
“Generate a positive risk: benefit of brand X.”
“Strengthen relationships with target journalists to ensure brand X possesses a greater share of voice in the future.”
“Utilisation of real-life data to demonstrate the critical role of brand X”.

The documents also provide examples of research being conducted with members of the general public to evaluate the effectiveness of an “advertising campaign run in the national press”. Although the Code of Practice allows pharmaceutical companies to run “disease awareness or public health campaigns”, these are only permitted if the goal is to “encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine”. However, the documents show that such campaigns are evaluated according to the impact on “future behaviour, information sought and treatments received” and there is a clear desire from the company who ran the advertising campaign to “provide a return on investment calculation”, rather than evaluate it in terms of changes in the target audience’s general knowledge, attitudes and behaviours concerning a specific condition.

In summary, this section shows that the public are the target for sophisticated promotional activity by pharmaceutical companies; that this activity exploits emotional drivers and marketing principles that go way beyond the simple provision of information and that its ultimate effectiveness is directly tied in to specific brands. In our view this breaches both the letter and the spirit of the code.

2.2 Servicing the Emotional Needs of Health Professionals and the Use of Branding

The Code of Practice states:

“Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly.”

Code of Practice, Clause 7.2

An important theme to emerge from many of the documents was the importance not only of creating products, but the creation of strong and powerful brands. An extract from one document describes brands as “existing only in the mind of consumers” and as something that the pharmaceutical industry “manipulate[d]”.

“What is a brand?

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is stripped of all its emotional baggage</td>
<td>What it becomes with all its emotional baggage intact</td>
</tr>
<tr>
<td>Constructed by manufacturing</td>
<td>Exits only in the mind of consumers—understood, measured and manipulated by us.”</td>
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Figure 4 overleaf outlines the equal importance attached by the pharmaceutical industry to the role of “rational” and “emotional” elements in the development of strong brands. For example, emotional elements such as “how does using the brand make the customer feel?” and “how would others view users of the brand?” appear to be given as much importance as “what are the physical features of the product?” and “how do the features benefit the customer?”.
This role of “emotion” is recognised as growing in importance given that there are “less clear rational differences” between different products within the pharmaceutical industry and therefore in order to “find further competitive advantage” products must be “differentiate [ed] on an emotional basis as well”. One-document estimates that this can lead to a “50% increase in sales”.

Consistently throughout the documents, brands are deliberately associated with attributes that can not be described as “objective” as required by the Code of Practice, such as “energetic”, “passionate”, “desirable”, “sexy”, “romantic”, “intimate”, “relaxed”, “effortless”, “freedom” and “fun”.

Not only are brands deliberately associated with such attributes and designed and marketed to satisfy emotional as well as rational benefits, but there is a clear desire by the industry to exploit health professional’s emotional needs and vulnerabilities. For example, the pressure GPs are under when prescribing and the difficulties they face on a daily basis including the pressure associated with prescribing the right medication, perceived difficulties in patient compliance and the risk of being judged by peers.

Brands and marketing activity are designed accordingly to tap into “customer insight of hassle of how difficult the patients will be to treat”, “likelihood of compliance” and to tap into their “emotional button of risk”. Another document demonstrates that campaigns are deliberately designed to “give the perception that brand X is a trusted brand” and to “give the customer the confidence to prescribe Brand X first line for new patients”. Similarly, marketing activity is designed to make GPs feel “unburdened, confident, no more heart sink moments, rebelling and responsible” by prescribing certain brands and to “provide reassurance that a large proportion of doctors are using brand X” and as a “decision beyond criticism”.

The documents go into detail about how best to communicate these messages, including the desired “tone of voice”. For example, one document describes it as “important to convey confidence, reassurance” through the “tone of voice” of the communication. Figure 5 below outlines diagrammatically how one company identified the “need” of prescribers and devised strategies such as “differentiate brand X” through the use of slogans in order to provide prescribers with the “confidence” to prescribe their brand and to “commit customer[s] to increase brand X prescribing from current level”.

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Figure 4: Brand Portrait

- **RATIONAL**
  - **Features**
    - What are the main physical features of the product?
  - **Customer Insight**
    - Fundamental truths that link our product to customer needs
  - **Physical Benefits**
    - How do the features benefit the customer?

- **EMOTIONAL**
  - **Emotional Benefits**
    - How does using the brand make the customer feel?
  - **Personality**
    - How would our customers describe us as a person/ animate object
  - **What does it say about the user**
    - How would others view the users of the brand?
2.3 The Use of Public Relations and Building Relationships to Counteract Negative Publicity

On public relations activity and the payment of honoraria, the Code of Practice states:

“Companies are responsible for information about their products which is issued by their public relations agencies.”

Code of Practice, Clause 20.5

“The payment of reasonable honoraria and reimbursement of out of pocket expenses, including travel, for speakers, is permissible.”

Code of Practice, Clause 19.1

It is clear from the documents that public relations activity forms a key and integral element of marketing activity within the pharmaceutical industry. It emerges as a popular method of communication to both patients and the general public (see Section 2.1) and to members of the health professions. PR activity appears to be particularly important and relevant for countering times of negative publicity, particularly when the safety of products is called into question.

The pharmaceutical industry conduct “extensive media monitoring” to identify coverage of their brands and there are various examples within the documents of negative publicity concerning the safety of certain brands, for example “[Publication] calls for brand X ban”. Strategies to deal with such publicity are devised, including proactive discussion and press releases: “discussion regarding proactive response”, “developing proactive releases and rationale”, and responding to unplanned coverage through planning exercises: “setting the Record Straight plan”, “developing reactive statements based on Company X messages” and utilising media contacts to monitor coverage: “initiating an early warning system for the Lancet via media contacts”.

Building long-term, sustainable relationships with various stakeholders, including journalists, key opinion leaders (KOL) and well respected medics and academics emerges as pivotal in dealing with such negative publicity and when conducting PR activities generally. These relationships are developed to influence media coverage:

“To build relationships with national journalists.”

“To build advocacy with consumer press to secure a greater share of voice.”

Specifically, these relationships are leveraged to have an impact on the coverage relating to certain brands:

“Development of a group of KOLs who will be advocates for Brand X on varying levels through proactive and reactive media opportunities.”

“The media spokespeople will be advocates and prescribers of Brand X who will be involved in issues management and with whom all brand X data is shared.”

In our view all this is far from the “accurate, balanced, fair, objective and unambiguous” communication required by clause 7.2.
Another interesting finding to emerge from the documents is the payment of considerable “honorarium” for such stakeholders to attend meetings organised by the pharmaceutical companies. One document states “In terms of honorarium, I can confirm that we will pay you a total of £10,000 for four meetings plus travel expenses”.

In a similar vein, relationships were also used in order to “maximise sales of brand X in 2004”. For example, one company sought to identify “the most critical people to influence” such as “policy making customers” in order to “persuade these customers to endorse brand X over other . . . brands”. As emerged from Section 2.2, explicit attempts are made to understand the “emotive drivers of these policy making customers”.

“It has been identified that a better understanding of the rational and emotional drivers of these customers, their attitudes and priorities would enable Company X to develop a better approach and communication tools tailored to their specific needs.”

Similar examples were found within a hospital context:

“Drive hospital endorsement and usage of brand X.”

“The development of key advocates and speakers for brand X in order that this hospital support can be taken out to primary care.”

In our view this is again a long way from objective and balanced treatment of important issues such as safety required by the code. It is also extremely debatable that a fee of £10,000 can be described as a “reasonable honorarium”.

2.4 Disguised Marketing

The Code of Practice states that:

“Certain types, styles and methods of promotion, even where they might be acceptable for the promotion of products other than medicines, are unacceptable. These include: “Teaser” advertising whereby promotional material is intended to “tease” the recipient by eliciting interest in something which will be following or will be available at a later date without providing any actual information about it.”

Code of Practice, Clause 9.1, 9.2

“Promotional material and activities must not be disguised.”

Code of Practice, Clause 10.1

An important, and worrying, theme to emerge from the documents is the desire of the pharmaceutical industry to strategically “create the need” among health professionals for new brands before their launch, while not being explicit about the nature of their communication.

One company, for example, devised a six-staged mail-out over a two year period to health professionals for the launch of a new brand. The first two stages of the mail-out were solely designed to communicate that “patients are being targeted with [treatment] but not hitting required targets” and that “there is a need for a more effective [treatment]”. The aim is to “establish current underachievement” and as a “call for new treatments”. At no point in these two stages is the new brand mentioned or is product branding used, nor is the ultimate aim of the campaign—to “create the need” for the new brand—revealed. In short, the promotional aim is being disguised.

Only after five months is the brand finally introduced in a further mail-out. At this point the purpose is to “establish brand X brand values at launch—efficacy, freedom” and to “reinforce brand X efficacy and safety”. Added to this is the need to “encompass a certain degree of education feel” in the mail-out, while the brand image is designed to achieve “freedom and peace of mind for all (controlled power)”.

**Figure 6: New brand mail-out strategy**

**Proposed Timings**

<table>
<thead>
<tr>
<th>Date</th>
<th>Type</th>
<th>Look</th>
<th>Message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>Targeted</td>
<td>50% CV Brand 50% PFL</td>
<td>Patients are being treated with [treatment] but not hitting required targets</td>
</tr>
<tr>
<td>Month 2</td>
<td>Targeted</td>
<td>50% CV Brand 50% PFL</td>
<td>New study shows that in UK patients still not hitting target. There is a need for a more effective [treatment] to help get patients to target.</td>
</tr>
<tr>
<td>Month 5</td>
<td>Blanket</td>
<td>25% CV Brand 75% Brand X</td>
<td>Brand X is the most effective [treatment] for lowering [condition] to target. It has a safety profile to all other treatments</td>
</tr>
<tr>
<td>Months 5-14</td>
<td>Rep activated</td>
<td>100% Brand X</td>
<td>Brand X is the most effective [treatment] for lowering [condition] to target. It has a safety profile to all other treatments</td>
</tr>
<tr>
<td>Date</td>
<td>Type</td>
<td>Look</td>
<td>Message</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Month 15</td>
<td>Targeted</td>
<td>100% Brand X</td>
<td>Brand X is a safe [treatment]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient volumes in the UK</td>
</tr>
<tr>
<td>Onwards</td>
<td>Targeted &amp; Rep activated</td>
<td>100% Brand X</td>
<td>Supporting campaign refinement and resulting data</td>
</tr>
</tbody>
</table>

**Rational for Timings**

<table>
<thead>
<tr>
<th>Date</th>
<th>Rationale</th>
<th>Evidence Item</th>
<th>Access Item (Management Toolkit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>To establish current underachievement of treatment goals in condition</td>
<td>Copy of</td>
<td>To be advised</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[clinical paper]</td>
<td></td>
</tr>
<tr>
<td>Month 2</td>
<td>To reinforce UK Study findings that calls for new treatments to address non titration of patients to guideline targets PFL published November 2002</td>
<td>Copy of article</td>
<td>To be advised</td>
</tr>
<tr>
<td>Month 5</td>
<td>To establish Brand X Brand values at launch</td>
<td>[clinical] Trial</td>
<td>To be advised</td>
</tr>
<tr>
<td></td>
<td>— Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>— Freedom</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brand X Launch March 2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 5-14</td>
<td>To reinforce Brand X efficacy and safety message</td>
<td>[clinical paper]</td>
<td>To be advised</td>
</tr>
<tr>
<td></td>
<td>(Pooled data 24-26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 15</td>
<td>To reinforce Brand X is a safe [treatment] that is being prescribed widely</td>
<td>[Trial] Publication</td>
<td>To be advised</td>
</tr>
</tbody>
</table>

3. **Summary**

Prescription-only medicines are promoted using a combination of advertising, public relations, promotional and scientific meetings, branding and the construction of long-term and mutually beneficial relationships with key stakeholders. This activity is guided by detailed market research along with careful segmentation and targeting.

This analysis shows that, on occasions, this marketing transgresses the Association of the British Pharmaceutical Industry (ABPI) Code of Practice, 2003. Specifically, despite clear rules to the contrary, it is apparent that:

— The general public and patients are seen as key targets for marketing communication campaigns on prescription-only medicines, and clever use is made of such phenomena as channel and source effects and emotional drivers to maximise audience susceptibility. These campaigns are tied in to the performance of specific brands.

— Campaigns targeting health professionals use emotional drivers, irrational constructs and branding strategies that are very far removed from the codes requirement for communications to be “accurate, balanced, fair, objective and unambiguous”.

— Public relations and paid “key opinion leaders” are used to counter bad publicity, especially about product safety. Again the treatment of these issues is frequently neither objective nor balanced.

— Brand marketing is disguised and the need for new brands is artificially created prior to launch.

These findings are especially disappointing as the Code emphasises the need for companies to carry out their marketing “in a responsible, ethical and professional manner” that follows “both the spirit and letter” of the Code.

At the same time, it is apparent that the code has to tackle some complex and ambiguous concepts. Words like “objective” and “balanced” sit uncomfortably with marketing efforts that are by definition partial and techniques like branding which play on patently subjective feelings and emotions.

This suggests a need, not just for a fundamental reappraisal of current pharmaceutical marketing, but of the code itself.

*Gerard Hastings, Elinor Devlin and Susan Anderson*
APPENDIX 34

Memorandum by the Association of the British Pharmaceutical Industry in response to the Institute for Social Marketing’s Analysis of Pharmaceutical Industry’s Marketing Documents (PI 126)

1. Thank you for sending us a copy of the Institute for Social Marketing’s Analysis of Pharmaceutical Industry Marketing Documents. The report is based on promotional and “product support” materials provided by five member companies of the Association of the British Pharmaceutical Industry to the Health Select Committee and raises many general points relating to the conduct of the industry.

2. Having received this report on Monday 14 March we understand that we and the companies concerned have only a matter of days to respond to its contents. It contains a number of serious allegations, many of which are based on a poor understanding of the ABPI Code of Practice for the Pharmaceutical Industry. In particular the report does not distinguish between internal strategy/market analysis (which is not covered by the Code) and external marketing actions (which are).

3. The ABPI has not seen the documents submitted by the companies but it appears that much of the criticism in the Analysis refers to internal company documents not for use with either health professionals or the general public.

4. The focus of the Code is on external activities of the industry and their appropriateness for professional and public audiences. To take an example prominent in the report: the use, in an internal market analysis, of language about “targeting” patient segments that could benefit from a medicine is not tantamount to directly advertising a prescription-only medicine to the patients themselves, the latter being both against the Code and against the law.

Our other main points in response to the Analysis are as follows:

5. We find minimal reference in the Analysis citing any example of specific individual external activities contravening the Code. We have, nevertheless, asked the PMCPA to comment on the Analysis and its comments are attached. The ABPI invites the Select Committee to provide details of any specific complaints regarding external company activities or published material to the Prescription Medicines Code of Practice Authority (PMCPA) which will take up such matters immediately.

6. A number of the products under review in this Analysis have already been the subject of cases considered under the Code of Practice and action taken where breaches have been ruled. The Analysis does not appear to have taken that into account.

7. The Analysis gives the impression that all activities that increase the usage of medicines via the application of established marketing techniques are in breach of the Code and not in the public interest. This is quite wrong. The industry is fully entitled to promote medicines to health professionals (and to provide non-promotional information to the public about medicines so promoted) provided that the requirements of the Code are met.

8. Moreover, marketing techniques that recognise that decisions are made not by computers but by human beings with needs and emotions are also being adopted by Government on health matters. The Government’s White Paper on Public Health issued in November 2004 states (Page 20): “A wide range of lifestyle choices are marketed to people but health itself has not been marketed. Promoting health on the principles that commercial markets use—making it something people aspire to and making healthy choices enjoyable and convenient—will create a stronger demand for health . . .”

9. The fact that targeted messages encourage patients to ask health professionals for advice about a disease and could lead to successful treatment of that disease should be welcomed rather than criticised. Government, through the MHRA, has endorsed the use of such disease awareness campaigns. That is quite different from advertising prescription-only medicines to the public, which the Code prohibits and which is not the subject of any of the criticisms made in the Analysis.

10. The use of public relations is questioned in the Analysis. This is a perfectly legitimate activity within the confines of the Code. Pharmaceutical companies are entitled to inform the media, particularly when this may involve issues relating to product safety. The support of third party medical/scientific experts in this work is also quite valid.

11. The ABPI remains of the view that the Code works well, as set out in the evidence submitted to the Health Select Committee by the ABPI and by the PMCPA. The publication of detailed reports of the outcomes of completed cases shows that the system is fair and transparent.

12. We recognise, however, that there is always room for improvement and have outlined to you in our evidence that the Code and its operation is currently the subject of public consultation and review. We will of course ensure that any legitimate issues emerging from this Analysis that are currently not covered by the Code are included in this review.

13. In the interest of fairness and balance I would hope that you will reflect the above in any publication of the Institute for Social Marketing’s Analysis and accompany it with equal prominence and publication of both this commentary and any being provided by the five cited pharmaceutical companies.
APPENDIX 35

Memorandum by the Prescription Medicines Code of Practice Authority (PI 128)

RESPONSE TO THE ANALYSIS OF THE PHARMACEUTICAL INDUSTRY’S MARKETING DOCUMENTS

The Analysis of the Pharmaceutical Industry’s Marketing Documents provided to the House of Commons Health Select Committee refers to examples which the authors consider contravene the Association of the British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry.

The Prescription Medicines Code of Practice Authority (PMCPA) has not seen the materials submitted by the five companies, much of which was internal documentation not for use with either health professionals or the public. The Code applies to the promotion of medicines for prescribing to health professionals and to appropriate administrative staff and to information made available to the public about medicines so promoted (Clause 1.1). Internal documentation is not usually covered by the Code. It appears that much of the material criticised is internal documentation.

The PMCPA does not know whether the materials requested have already been the subject of complaints under the Code. It appears from the limited details in the Analysis that some of the criticisms may relate to matters previously the subject of complaints under the Code. Most of the products listed have been the subject of complaints over the last couple of years, with some ruled to be in breach of the Code. In every case where a breach is ruled the practice in question has to cease forthwith and a detailed report is published.

The Analysis draws unsubstantiated conclusions from activities and misunderstands the requirements of the Code in that it gives the impression that every activity that increases sales of a specific medicine is a breach of the Code. This is simply not so.

When considering whether or not there has been a breach of the Code the most important considerations are the content of the material actually used with the health professional or member of the public and its effect. As in the interpretation of UK law, the intention of the material/activity is not necessarily relevant although it might be taken into account when trying to decide whether high standards have been maintained (Clause 9.1) or whether there is a reduction in confidence in the industry (Clause 2) or when determining the sanctions to be applied if a breach of the Code is ruled.

It appears from the Analysis that there have been many misunderstandings about what is permitted by the Code and what is not. Detailed comments appear below.

A. GENERAL PUBLIC

Medicines can be named in information made available to the public provided such material complies with Clause 20 of the Code including the prohibition on advertising prescription only medicines and certain other medicines to the public.

1. It is not a breach of the Code to target members of the public (even those that are likely to respond to the message) nor is it a breach of the Code to segment the population. The important point is whether the materials used with the public are in accordance with Clause 20 of the Code.

2. It is not a breach of the Code for a company to carry out its activities in such a way that the public is more receptive to the message, for example by working with patient organisations to produce materials or leaving leaflets in pharmacies and/or surgeries. The content of the material is the important factor, including the requirement to clearly declare sponsorship on materials relating to medicines and their uses (Clause 9.10).

3. Companies may make reference to direct to consumer advertising as some medicines which are promoted to health professionals for prescribing can also be legally advertised to the public for purchase (over-the-counter medicines). Public relations activities to the public are covered by Clause 20. Placing articles in the lay press, TV documentaries, soap operas etc is not necessarily in breach of the Code. This would depend on whether the material provided by the company to the press, TV company etc complied with the Code.

4. It is not necessarily a breach of the Code to run advertising campaigns in the national press; this would depend on the content. A legitimate disease awareness campaign might be referred to by a company as advertising even though it does not mention directly or indirectly any medicine at all.

5. Aiming a campaign at those most likely to take action does not in itself suggest that the campaign is primarily concerned with those who are most likely to benefit the company.

6. A legitimate disease awareness campaign that was in accordance with the Code (which would mean it was also in accordance with the Medicines and Healthcare products Regulatory Agency guidance) would be acceptable even though it resulted in increased prescription of the company’s product.
7. If material for the public complies with Clauses 20.1 and 20.2 of the Code, including the need for it to be factual, balanced information that is not going to raise unfounded hopes of successful treatment or be misleading with respect to the safety of the medicine and for it not to encourage members of the public to ask their doctors to prescribe a specific medicine, then the use of “emotional” messages is not in conflict with the requirements of Clause 20 of the Code.

B. HEALTH PROFESSIONALS

The Analysis does not mention the requirements of Clauses 7.4 and 7.5 that all information claims or comparisons must be capable of substantiation and that such substantiation must be provided without delay following a request from a health professional or appropriate administrative staff. Nor does it mention that the promotion of a medicine prior to the grant of the marketing authorisation is prohibited by Clause 3.

1. If promotion to health professionals and appropriate administrative staff complies with the Code then the use of “emotional” messages is not a breach of the Code.

2. Companies can provide certain information prior to the grant of the marketing authorisation provided the information is not promotional for that medicine.

3. A message to health professionals, appropriate administrative staff or patients that a medicine is “safe” would be a breach of the Code (Clauses 7.9 and 20.2). Information about side effects that reflects available evidence and is capable of substantiation can be provided.

4. Companies can prepare responses to media enquiries. Such responses must comply with the Code.

5. Companies have been ruled in breach of Clause 9.3 for using health professionals to advertise medicines. Companies can use key opinion leaders to present at meetings etc. The involvement of the pharmaceutical company should be made clear and messages from key opinion leaders employed by companies are subject to the Code. Honoraria payments for health professionals should be in line with BMA suggested rates or similar.

CONCLUSION

The only bodies that can decide whether material or activities are in breach of the Code are the Code of Practice Panel and the Code of Practice Appeal Board. Bearing in mind the above comments if details of the specific criticisms were provided to the PMCPA, then the matters could be dealt with as complaints under the Code.

The Code is reviewed approximately every two to three years. The ABPI is currently undertaking a review of the Code and its operation including consultation with stakeholders and others.

APPENDIX 36

Memorandum by Lilly (PI 129)

RESPONSE TO THE MEMORANDUM BY THE UNIVERSITY OF STIRLING INSTITUTE FOR SOCIAL MARKETING ENTITLED “DEALING IN DRUGS: AN ANALYSIS OF THE PHARMACEUTICAL INDUSTRY’S MARKETING DOCUMENTS”

INTRODUCTION

Lilly inputted its views on the House of Commons Health Select Committee inquiry into the influence of the pharmaceutical industry through the Association of the British Pharmaceutical Industry (ABPI). We received a request from the Health Select Committee (“the Committee”) on the afternoon of Friday 10 December 2004, to which Lilly responded on Wednesday 22 December 2004. The Committee requested that we provided all marketing documentation related to two specific healthcare professional programmes associated with two disease areas in which Lilly has medicines. The Committee obtained information from five pharmaceutical companies in total, which was analysed by the University of Stirling Institute for Social Marketing (ISM), formerly the Centre for Social Marketing at Strathclyde University. A memorandum was made available to Lilly on Thursday 24 March 2005 (the “Stirling memorandum”).

While the Stirling memorandum was anonymised as to which companies’ materials are discussed, Lilly was invited by the Committee to respond to the issues raised. We are grateful to the Committee for providing us with this opportunity to put our views on the record.
ETHICS

Lilly’s business is focused on the discovery and development of ethical branded medicines to enable people to live longer, fuller lives. Lilly takes its business ethics and adherence to the ABPI Code of Practice very seriously. We think it is gratuitous that the University of Stirling ISM has chosen to entitle their memorandum “Dealing In Drugs”. In our view, this title misrepresents the type of company and industry we are, and what we are about—“Dealing In Drugs” has connotations of the recreational use of controlled substances, which is very definitely not the subject of the Committee’s inquiry or their report.

Given that the Stirling ISM was following the same process that the Committee asked them to adopt during their earlier obesity inquiry,112 we note that on that occasion the title of the memorandum was balanced and objective, namely “Preliminary Analysis of Food Industry Advertising Documents”.

DISCLOSURE

Paragraph two of the introduction to the memorandum notes that each company was instructed to provide “all promotional and product support material for specific brands or programmes”. As set out in Table 1 of the Stirling memorandum, Lilly was asked for all documents in relation to two specific healthcare professional programmes. Within this context, Lilly disclosed the documents that we held in relation to these, one of which has been endorsed as best practice in the Government’s White Paper on public health, “Choosing Health”113 and is being rolled out across Primary Care Trusts.

We were surprised to see that the Stirling memorandum makes reference to “a very limited set of papers” considering that the five companies supplied 49 boxes of documents before Christmas 2004. Given this opinion, and the powers vested in the Committee, one wonders why this was not pursued in the three months after the initial request.

DISEASE AWARENESS

It is not clear on what basis the Stirling ISM has concluded that disease awareness and public health campaigns are in breach of the ABPI Code of Practice.

EMOTION

In relation to Figure 4 in the Stirling memorandum, Lilly is concerned that one diagram from one company is being used to portray “rational” and “emotional” as being of equal importance, and also of being representative of the approach taken to branding by the industry as a whole.

Lilly believes that a section of one sentence in the Stirling memorandum may refer to the information Lilly provided about one of its programmes. We believe that there is no reference to the other programme.

The Stirling memorandum criticises the use of emotive language to describe attributes of medicines, which it says runs counter to the requirement to provide factual, objective information. Examples given include “intimate”, “relaxed” and “freedom”. Lilly believes that this is a reference to our Cialis “36 Hours of Freedom” campaign to healthcare professionals and that the use of such language is entirely appropriate, legal and within the letter and spirit of the ABPI Code of Practice, given that they were used in the context of a Lilly/ICOS medicine licensed for the treatment of erectile dysfunction.

HEALTH SELECT COMMITTEE REPORT ON SEXUAL HEALTH

Erectile dysfunction impacts the physical and emotional aspects of the lives of men and their partners. So while the claims made about the medicine are objective and accurate, they are presented in a context appropriate to the condition. The recently published “Recommended standards for sexual health services”114 highlights the fact that people with sexual dysfunction may wait years before seeking professional help and notes: “It is important to create supportive environments that will enable early self-referral.” Similarly, in relation to sex and relationships education, the Health Select Committee in its own recent report entitled “New developments in sexual health and HIV/AIDS policy”115 stated that: “The biological facts are intended to be supplemented by, and interwoven with, a broader sex and relationships curriculum, which includes the social and emotional aspects of sexual relationships, through a dedicated framework for “Sex and Relationships Education” (SRE), which forms part of the Personal Social and Health Education (PSHE) curriculum.” Lilly’s activities in relation to erectile dysfunction are intended to provide healthcare professionals with an insight into the experience of the condition in order that they can deal with patients in a sensitive and appropriate way.

114 Medical Foundation for AIDS and Sexual Health, endorsed by the Department of Health.
HEALTHCARE PROFESSIONALS OR THE GENERAL PUBLIC

The Stirling memorandum does not make a clear distinction between promotion of medicines to healthcare professionals and to the general public. The Lilly example mentioned above relates to a specific communication directed solely to healthcare professionals.

INITIAL THOUGHTS OR APPROVED MATERIALS

The Stirling memorandum reflects a lack of understanding of the ABPI Code of Practice. Lilly provided a whole range of documents: initial thoughts, work-in-progress, proposals submitted by our agencies, contracts and final, approved materials. The Stirling memorandum does not distinguish between these different types of document. All Lilly programmes are subject to internal review to ensure that they are consistent with Lilly’s business ethics and the ABPI Code of Practice. There have been no complaints to the Pharmaceutical Medicines Code of Practice Authority (PMCPA) about either of the programmes on which the Committee requested information.

It should also be noted that all member companies’ promotional activities are subject to the ABPI Code of Practice, which is policed by the PMCPA and the Code of Practice Appeal Board.

ABPI CODE OF PRACTICE REVIEW

Lilly notes that the Stirling memorandum analysis was conducted around themes taken from the ABPI Code of Practice, although the memorandum reflects a lack of understanding of the Code. It was established in 1958 and is one of the oldest in the medicines sector. It is updated regularly and periodically there are full reviews. The last major review was held in 1993. The principle of self-regulation is enshrined in EU legislation; it is well established in the UK: the Proprietary Association of Great Britain, the Press Complaints Commission and the Advertising Standards Authority regulate companies working in, respectively, over-the-counter-medicines, print and broadcast media.

Self-regulation provides the flexibility to adapt to change and, from time to time, the pharmaceutical industry has a comprehensive review. The healthcare environment has changed significantly since the last major review. The political focus on creating a patient-centred NHS has led to widespread public debate on how the pharmaceutical industry and other stakeholders should communicate to patients.

Under the chairmanship of Lilly’s managing director in the UK, the ABPI embarked upon a major review of the Code of Practice almost a year ago. We anticipate a new Code of Practice with revised governance procedures will be published later this year.

April 2005

APPENDIX 37

Supplementary memorandum by Pfizer Ltd (PI 130)

RESPONSE TO THE INSTITUTE FOR SOCIAL MARKETING’S REPORT
“DEALING IN DRUGS: AN ANALYSIS OF THE PHARMACEUTICAL INDUSTRY’S MARKETING DOCUMENTS”

INTRODUCTION

1. Pfizer is responding to the committee’s request for comments on the Institute for Social Marketing’s report, Dealing in Drugs: An Analysis of the Pharmaceutical Industry’s Marketing Documents.

2. The inclusion of the words in the title of the report “Dealing in Drugs”, is in our view gratuitous, and undermines the serious nature of the research, development and discovery process that produces medicines.

3. Our overall impression of the report is that it is based on a poor understanding of the ABPI Code of Practice for the Pharmaceutical Industry, and fails to recognise the role of pharmaceutical marketing in assisting patients with gaining access to medicines.

4. The report complains that “three of the five companies produced a very limited set of papers”. Pfizer complied with the request for two years’ worth of promotional and product support materials for three of our medicines. The committee’s request arrived by email after 5.00 pm on Friday 10 December with a deadline of Friday 17 December, which is five working days. Pfizer provided 21 boxes of materials and did not receive any further requests for information from the committee or the Institute for Social Marketing.
FINDINGS

5. The report alleges in an aggregated and anonymised format that there were instances where the materials reviewed appear to have contravened the ABPI’s Code of Practice. It is not clear from the document whether the Institute for Social Marketing understood that the Code focuses on the external activities of the industry that are directed towards health professionals and the general public. The Institute for Social Marketing had access to internal company documents that were never intended for use with either health professionals or the general public, and it appears to have included these documents in the report, even though they would not normally be subject to the Code.

TARGETING PATIENTS AND THE GENERAL PUBLIC

6. Marketing activities, such as disease awareness campaigns, inform patients about their diseases and encourage them to speak to their doctor. The report seems to object to the pharmaceutical industry encouraging patients to present to the medical services but Pfizer is proud to have run disease awareness campaigns encouraging patients to seek treatment for life threatening asymptomatic conditions, for example, high cholesterol and blood pressure. In doing so, we believe we are helping the NHS to achieve its objectives as set out in the cardiovascular National Service Framework, and helping GPs to achieve the targets outlined in the GMS contract. These initiatives should be welcomed rather than criticised.

7. Communication with the general public through disease awareness campaigns is regulated by the criminal law and policed by the Medicines and Healthcare products Regulatory Agency (MHRA) as well as by the ABPI. The MHRA issued guidelines on disease awareness campaigns to the pharmaceutical industry in June 2003 that defines ethical and appropriate communication with the general public. For example, the guidelines state that disease awareness campaigns must increase awareness of a disease or diseases and provide health educational information on that disease. The guidelines state that disease awareness campaigns must not encourage patients to request a specific medicine. So far as we could tell, none of the examples of “breaches” quoted in the report breached the Code of Practice, the MHRA guidance or the law.

MARKET RESEARCH

8. Pfizer has been able to identify that one of its documents is referred to in the report in the section entitled “Market Research” where the industry is criticized for “identifying populations who are not currently presenting to the medical services for diagnosis and prescription of medicines. This population dubbed the ‘missing millions’ are estimated to include almost two million people within the UK”. The report fails to recognise that the research that it objects to was undertaken as part of an assessment of the potential to convert a particular medicine from a Prescription-Only Medicine (POM) to a Pharmacy medicine (P) ie to change the regulatory status of the medicine so that it can be advertised directly to patients. It is worthy of note that the Medicines & Healthcare Products Regulatory Authority is generally supportive of companies seeking to convert appropriate POM medicines to P status. Clearly, in this context, the conduct of market research is entirely justified. The wording quoted from the market research document is that of the market research agency, not Pfizer. The market research referred to in the report has not been used for any purpose in relation to the promotion of a prescription medicine or raising awareness of a particular disease and is therefore a legitimate piece of work. We are gravely concerned that this research has been quoted out of context and judged against the standards applicable to the advertising of POMs rather than those applying to pharmacy medicines. This shows a lack of understanding of the Code.

ADVERTISING AND PUBLIC RELATIONS

9. The report criticises pharmaceutical companies’ use of public relations to counteract negative publicity. Pfizer believes that it has a right to defend its medicines and to respond to media coverage, particularly when it is misinformed, and may involve product safety issues. Public relations is a perfectly legitimate activity for pharmaceutical companies and can help to educate and inform health professionals and patients about scientific advances and promote understanding of certain diseases. This activity is also regulated by the Code of Practice and the law.

10. The report seems to object to the advertising of branded Prescription-Only Medicines to health professionals but it is important to recognise that this is expressly permitted by the law and the ABPI Code of Practice.
Summary

11. The report portrays a lack of understanding of the ABPI Code of Practice and the legal framework applying to the pharmaceutical industry. We recognised one example cited in the report and are deeply concerned that it appears to have been taken wholly out of context and criticised for failing to comply with standards that do not apply to it. Similarly, from what we can tell, the examples used to demonstrate non-compliance with the Code appear to have been taken from companies' internal documents that are not subject to the Code. This undermines our confidence in the entire report.

12. The pharmaceutical industry is one of the most extensively regulated industries in the world. Our communications about medicines with doctors and patients are constrained by the criminal law and policed by the MHRA, as well as by the ABPI. Pfizer believes that self-regulation is effective in regulating the pharmaceutical industry’s external communication and marketing activities. The ABPI Code of Practice is currently the subject of public consultation and review.

APPENDIX 38

Letter from AstraZeneca to the Clerk of the Committee (PI 131)

RESPONSE TO THE UNIVERSITY OF STIRLING INSTITUTE OF SOCIAL MARKETING’S REPORT

“AN ANALYSIS OF THE PHARMACEUTICAL INDUSTRY’S MARKETING DOCUMENTS”

Thank you for sending us a copy of The Institute of Social Marketing’s report “An Analysis of the Pharmaceutical Industry’s Marketing Documents” and for the opportunity to respond. We are concerned with the premises upon which the report appears to have been based which leads us to have reservations about its conclusions:

— the report appears to assert that—in principle—the use of commercial marketing techniques in the promotion of prescription pharmaceuticals to the NHS is an inappropriate, undesirable activity and contrary to existing legislation and the ABPI Code of Practice; and

— further, the report does not appear to distinguish in its allegations between internal documents detailing strategy and market analysis, which are not subject to the Code, and external market activities, which must adhere to the Code.

A substantial majority of the material that we submitted to the Health Select Committee was internal documentation of analysis, discussion and planning.

Not only do we operate within the ABPI Code of Practice, but we pride ourselves on our ethical marketing and business practices. We strive to produce appropriate communications and materials all of which go through a rigorous internal approval process. During the two year period for the products considered in the report, activities which resulted in complaints were dealt with under the Code in the appropriate way and actions taken where breaches were ruled (Ref: Code of Practice Review, published by the PMCPA). Whilst the documents provided by us to the Committee must, as agreed, remain confidential, we wish to ensure that the Committee has recourse to the PMCPA. Should they wish to make a specific complaint regarding external activities, we would be pleased to discuss any such example.

We undertake our marketing activities to the highest professional standards. We strongly believe that the marketing and communications regarding our medicines play a crucial role in their appropriate use and the wider provision of healthcare in the UK. We work hard to understand the experiences of patients who may receive our medicines, and the complexities of the diseases from which they suffer. Firstly, this ensures that our communications to healthcare professionals are informed by insight into the patients they will be seeing and treating. Secondly, this supports appropriate communications to healthcare professionals about our medicines and sometimes supports a conscious decision to promote healthcare awareness to patients and patient groups.

The news media play an increasingly influential role in the public awareness of disease, healthcare and medicines. However newspaper articles do not always result in the public being appropriately and accurately informed. AstraZeneca is committed to providing accurate information to meet the needs of healthcare professionals, members of the public and journalists. There must be an accurate understanding of the risks and benefits of medicines. We believe that our activities encourage the appropriate use of medicines and correct misleading information.

Medical treatment decisions are made based on both the rational and emotional motivations of both healthcare professional and patient. It is frequently necessary to take these factors into account in our communications, and in this way to facilitate optimal outcomes for patients.
As an industry, the medicines that we provide are central to the health and wellbeing of UK patients. The reputation and trust of the industry are a vital part of this. As a leading UK pharmaceutical company AstraZeneca takes these issues very seriously. Should the Committee have remaining concerns that are not satisfied by this memorandum, nor by recourse to the PMCPA, we would want to continue this important discussion promptly with the Committee.

We would like to emphasise that a balanced consideration of the marketing of medicines in the UK should be based on a firm knowledge and grasp of the current practice of scientific innovation, medical practice, commercial marketing and ABPI Code of Practice. In our view, the current report represents an overly narrow perspective on these areas.

We hope that these comments are a constructive contribution to an important review by the Health Select Committee.

18 March 2005

APPENDIX 39

Supplementary memorandum by GlaxoSmithKline (PI 132)

COMMENTS IN RESPONSE TO THE INSTITUTE FOR SOCIAL MARKETING ANALYSIS OF MARKETING DOCUMENTS

GlaxoSmithKline (GSK) supports the need for regulation of the advertising and promotion of medicines, and specifically supports self regulation under the PMCPA Code of Practice. Regrettably, the company has, on occasions, been found to be in breach of the Code of Practice. These breaches are taken extremely seriously by the company and are always reviewed to ensure that similar breaches do not recur. If these breaches involve the action of an individual acting contrary to instruction, disciplinary action is always taken.

In respect of the analysis of industry marketing practices undertaken for the Committee by the Institute for Social Marketing, we are unable to respond in great detail given the generality of the analysis and conclusions.

We are disappointed to note, however, that the authors have chosen to entitle their analysis “Dealing in Drugs”. This is somewhat ironic, since they are particularly critical of anything they perceive to be the use of emotive language in industry’s promotional efforts. Our view as to the appropriateness of the title can best be summed up by quoting from the ISM’s authors themselves; that is to say, “words like ‘objective’ and ‘balanced’ sit uncomfortably with . . . techniques . . . which play on patently subjective feelings and emotions”, as this title appears to be intended to do.

The Institute for Social Marketing’s analysis is based on a large amount of information supplied to the Committee by GSK and by other companies. We do not immediately recognise the instances portrayed in the 15-page analysis as representing material supplied by GSK. Our preliminary analysis, however, suggests that some if not all of the analysis is based on a fundamental misapprehension of the nature of the Code and the legal framework that underpins it.

Marketing, and other forms of promotion, exist to increase sales of products beyond the level that would occur if such activity did not take place. Companies would not otherwise engage in this activity. This is entirely legitimate. Neither the Code of Practice, nor the Medicines Act, nor the EU Directive on the Advertising and Promotion of Medicines prohibits this activity; rather they regulate it. However, the Institute for Social Marketing analysis appears to be based in part on an assumption that any activity designed to increase the level of sales of a company’s products is, by definition, in breach of the Code. This assumption is simply incorrect. The ISM analysis also seems rooted in a philosophical standpoint that anything done by a company with the intention of encouraging the use of its medicines and which benefits that company is inherently wrong. We disagree entirely with such a standpoint. ISM’s report is based on muddled thinking and an incorrect appreciation of the regulatory framework, and this therefore calls into question the reliability of the report’s conclusions.

Carried out responsibly, promoting the use of medicines serves not merely the interests of pharmaceutical companies, but is also of benefit to patients and to the UK. Modern medicines can improve the quality and length of life and allow major diseases to be treated without the need for in-patient hospital care. They can allow patients to remain economically active, when they would otherwise be dependent on carers or social services. Medicines are therefore part of the solution, not part of the problem for the NHS. Indeed, the problem in the UK is not the widespread over-use of new medicines, but rather the opposite. Research clearly shows that UK uptake of new medicines is about one quarter of that in the average of comparable countries one year after launch, and remains low thereafter. Put simply, compared to many of their European or American counterparts, UK patients get poorer or later access to life-saving or life-enhancing new drugs.
The Institute for Social Marketing’s report also seems to have assumed that the analyses companies use to inform their marketing campaigns are the same as the execution of those campaigns. Implementation of campaigns is subject to the Code of Practice and the Medicines Act, but the thinking that informs those campaigns, as outlined in some of the documents provided to the Committee, may well not be.

The Institute for Social Marketing’s analysis also appears to find it blameworthy that industry would want to use public relations to counter criticism of medicines in the media—criticism that can often be factually incorrect and therefore unnecessarily distressing to patients who rely on those treatments. It would be astonishing if a company did not seek to defend itself or its products from unwarranted attacks, and we believe such activity to be entirely legitimate.

APPENDIX 40

Letter from the Corporate Affairs Director, Wyeth Pharmaceuticals, to the Clerk of the Committee (PI 133)

Thank you for sending us a copy of The Institute for Social Marketing (ISM) document entitled An Analysis of Pharmaceutical Industry’s Marketing Documents prepared for the House of Commons Select Committee in connection with its investigation into the conduct of the UK pharmaceutical industry. In order to prepare the report we understand that the ISM was furnished with documents supplied by five pharmaceutical companies, including Wyeth, relating to nine pharmaceutical products, including one marketed by Wyeth.

Wyeth is concerned that it has been given only a matter of days to respond to this report. It is not possible in the short time available to provide any substantive comment on the detailed report that has been prepared, in particular because the report provides its findings in an anonymous form.

Wyeth is also concerned that the report as written implicates each of the Companies, and each of the products, listed in the anonymous findings and allegations it makes. We consider this approach to be unfair and potentially misleading. As the ISM had access to a significant volume of material (with adequate opportunity to seek further material from companies if necessary), it would be possible for the ISM to identify whether it found examples of each of the findings and allegations it has made in all of the products reviewed, in only an identified number of them or in only one of the products considered. Had this been done, we consider the report would have been more balanced and it would have helped avoid the impression given that the findings are representative of the practice of each of the companies listed and of the pharmaceutical industry as a whole.

We are particularly concerned that this impression is inaccurate, as to Wyeth. Specifically, Wyeth does not recognise any of the findings as applying to activities associated with the product for which Wyeth supplied material.

8 April 2005

APPENDIX 41

Memorandum by the Chief Executive of the National Pharmaceutical Association (PI 116)

INFLUENCE OF THE PHARMACEUTICAL INDUSTRY

I write following my appearance before the Select Committee on 11 November 2004 to provide additional information on a number of issues raised during the session.

The NPA represents the owners of community pharmacies in the UK. We have in membership the owners of around 11,000 pharmacies—just about all except Boots. In representing the interests of our members we inevitably have extensive contact with pharmaceutical manufacturers and their representatives. We have regular contact with the industry associations (ABPI in the case of prescription medicine manufacturers and PAGB in the case of the manufacturers of non-prescription medicines) to explore areas of mutual interest and to ensure that we keep abreast of developments within each other’s sectors. On a similar basis we have contact with individual manufacturers on an ad hoc basis.

There is considerable interest in community pharmacy at the present time given its changing role. As a means of helping manufacturers understand the changing face of pharmacy so that this can be incorporated into their strategic planning, we have established a corporate members programme—NPA Matrix—through which manufacturers can have a structured dialogue with the NPA’s senior management team. We have six Matrix members, each paying a membership fee of £10,000.

We also look to the industry for sponsorship. This is principally to support training and education materials or resources to improve pharmacy practice provided by the NPA to its members. For example, we have had sponsorship to help cover the costs associated with our medicines counter assistant course, a dispensing technician course, CD-ROMs covering the Drug Tariff and Pharmacy Law and Ethics, and a
guide to implementing standard operating procedures (SOPs) into pharmacies. This sponsorship is a means of keeping costs down for our members. In 2003 we received sponsorship of £54,000. The additional costs associated with the design, printing and distribution of our SOP pack were settled directly by the sponsor with the agencies carrying out the work. We are currently seeking sponsorship of a resource we are producing to help members understand and implement the requirements of the new pharmacy contract, which has just been agreed with the Department of Health.

I should stress that this sponsorship relates to the design, printing or distribution of our materials. However the detail contained in these resources is the sole responsibility of the NPA and materials are normally written and developed in-house. The NPA therefore retains full editorial control over the content. Any sponsorship is recognised through the inclusion of the sponsor’s name and logo within the material.

As one would expect, manufacturers produce their own materials for pharmacists and pharmacy staff. We actively encourage manufacturers to produce objective material, which is truly training or education material rather than company propaganda. To help them achieve this we offer an NPA Training Seal service where the NPA will vet material to ensure they achieve this objective. We charge a fee for this to reflect the time and effort we put into examining their materials. Total revenue from the Training Seal in 2003 was £32,000. A brochure giving further information on the Training Seal is enclosed.

One of the issues raised at the evidence session on 11 November was Patient Information Leaflets (PILs). In dispensing prescriptions, pharmacists face an obligation to provide fully labelled packs and patient information leaflets to patients. Their ability to do this is however frustrated by the fact that they are obliged in many cases to provide the exact quantity written on a prescription. Where a prescription calls for the same quantity as contained in a patient pack, there is no problem; a fully labelled pack with a PIL will be provided. In cases, where the quantity is at variance with the patient pack quantity however, the pharmacist must “break bulk” and issue the required quantity from a larger pack. As there will only be one PIL in the pack this means that subsequent supplies will be made without a leaflet. Clearly this places pharmacists in an invidious position. Attempts by the DH and MHRA to solve this conundrum have not been successful. The last proposal was for pharmacists to either photocopy or download PILs from the internet. For a variety of reasons—principally those of safety—the proposals were rejected by all stakeholders as unworkable.

Pharmacists endeavour to issue leaflets whenever they can. However even where leaflets are issued, they are difficult to understand or interpret by many patients. The reason for this is that leaflets are principally legal defence documents rather than an attempt to provide comprehensible information to patients. At the meeting I read out an extract of one such leaflet. The PIL I selected was for Delta Cortril (a brand of prednisolone). A copy of this leaflet is enclosed.

We have not done any work on improving the content of PILs to make them easier for patients to understand. However, the Committee on Safety of Medicines is undertaking work in this area. They have established a working group to look at PILs. A consultation document toward improving the utility of PILs is, we understand, to be published soon.

December 2004

APPENDIX 42

Memorandum by The Association for Human Pharmacology in the Pharmaceutical Industry (PI 107)

1. AHPPI

The Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI) was founded in 1988. We have 152 members—physicians, nurses, clinical scientists, project managers and various types of support staff (who work for organisations, such as pharmaceutical companies and contract research organisations (CRO), involved in the early development of new medicines. Most of the big pharmaceutical companies and CRO in the UK are represented among the membership.

The purpose of the AHPPI is to provide a forum for continuing education in clinical pharmacology—the discipline that underpins early development of new medicines—and in the regulatory aspects of the early development of new medicines. We hold symposia with invited speakers, twice yearly. Membership of the AHPPI is £15 per year and attendance at symposia is free.

We have links with other organisations involved in developing new medicines, such as the ABPI, Institute of Clinical Research, and Contract Clinical Research Association. Also, we share some of our symposia with the Clinical Section of the British Pharmacological Society, an organisation whose members are mostly from university departments of clinical pharmacology. The AHPPI is run by a committee and provides information to members via a website (www.ahppi.org.uk).
2. Phases of Development of a New Medicine

Medicines research is traditionally separated into four phases, although in practice they often overlap. Phases 1 to 3 are done before a licence to market the new medicine is applied for, and phase 4 is done after a licence has been granted. During phases 1 to 3, the material being tested is called an investigational medicinal product (IMP), whereas after licensing it becomes a medicinal product or simply a medicine. Phases 1 to 3 of a successful IMP can take up to 10 years. Few IMP survive all of the phases. The failure rate is highest in phase 1. The phases of development of a “typical” new medicine in humans are shown below.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number and type of subject</th>
<th>Questions asked</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>100–200 healthy subjects</td>
<td>Is the IMP safe in humans?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What does the body do to the IMP? (pharmacokinetics)</td>
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<tr>
<td></td>
<td></td>
<td>What does the IMP do to the body? (pharmacodynamics)</td>
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<tr>
<td></td>
<td></td>
<td>Might the IMP work in patients?</td>
</tr>
<tr>
<td>2.</td>
<td>200–500 patients with the target disease</td>
<td>Is the IMP safe in patients?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does the IMP seem to work in patients? (efficacy)</td>
</tr>
<tr>
<td>3.</td>
<td>1,500–5,000 patients with the target disease</td>
<td>Is the IMP really safe in patients?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does the IMP really work in patients?</td>
</tr>
<tr>
<td>4.</td>
<td>many thousands patients with the target disease</td>
<td>Just how safe is the new medicine? (pharmacovigilance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>How does the new medicine compare with similar medicines?</td>
</tr>
</tbody>
</table>

Trials of IMP in healthy subjects were excluded from the Medicines Act 1968, simply because healthy subjects derive no therapeutic benefit from an IMP. However, all clinical trials, including ones in healthy subjects, have been regulated since the EU Clinical Trials Directive 2001/20/EC was implemented in the UK on 1 May 2004. The main impact of the Directive is on phase 1 trials in healthy subjects.

3. Phase 1 Trials in Healthy Subjects

IMP must not be tested in humans before the necessary pre-clinical studies (the chemistry, pharmacology, toxicology and pharmacy of the IMP) have been completed.

Most IMP can and should be tested first in healthy subjects. But the risk must be minimal. The first trials of an IMP in healthy subjects are usually of single doses of the IMP of increasing size. The next trials are usually trials of repeated doses. The aims of the early trials in healthy subjects are to assess the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of the IMP, and to compare the findings with those in animals. Subsequent trials in healthy subjects may:

- assess the efficacy of an IMP or to define the dose for trials in patients, by measuring biomarkers or using challenge agents against which the IMP is tested;
- compare the bioavailability (how much gets into the bloodstream) or the bioequivalence (if the amount that gets into the bloodstream is not significantly different) of different formulations of an IMP;
- assess the effects of things such as food, gender, age and genetic differences on the activity of an IMP;
- assess the possible interaction of an IMP with marketed medicines; and
- assess the absorption, breakdown and elimination of a radiolabelled IMP.

Some of these trials, such as interaction trials, may be done during any phase of IMP development. Compared with patients, healthy subjects are easier to find, more robust, free of other medicines, more likely to respond uniformly, and better at completing long and complex trials. Trials of IMP in healthy subjects have a good safety record.

4. UK Phase 1 Trials

The AHPPI surveyed 29 UK phase 1 units that did trials of IMP for the pharmaceutical industry during 1999 and 2000. The total number of trials per year was just over 600. 82% were done by CRO, 17% by pharmaceutical companies with their own phase 1 units, and 1% by academic departments that provide a service to the pharmaceutical industry. Ethics committees took an average of 14 (range seven to 28) days from submission of an application to written approval. That response time formed the basis of the target of an average of 14 (maximum 21) days that the MHRA set itself to review an application for a phase 1 trial, after implementation of Directive 2001/20/EC.

Since the AHPPI survey, the academic departments have stopped their service and two of the pharmaceutical companies have closed their phase 1 units. So, probably 90% of commercial phase 1 trials in the UK are now done by CRO. Some of the CRO are based in or are close to NHS hospitals, for safety reasons.
One of the CRO (HMR) surveyed over 300 phase 1 trials that it carried out from 1993 to 2001. About one third of the trials came from UK sponsors, one third from sponsors in other European countries, and one third from countries outside Europe, mainly Japan and the USA. The average income per study in 2002 was £284,000 (range £40,000 to £830,000). If we assume that the data for HMR apply to the 600 phase 1 trials done in the UK each year, the total income is about £170 million per year, two thirds of which are exports. If companies do their phase 1 trials in the UK, they are more likely to do their late phase trials in the UK (“pull-through trials”) as well. Also, phase 1 units use various subcontractors and support services, which need to be taken into account when assessing the overall contribution of phase 1 trials to the UK economy. Although income from phase 1 trials is small in comparison with that from the pharmaceutical industry as a whole, phase 1 trials are a vital part of medicines development.

5. COMPARISON OF EARLY AND LATE PHASE TRIALS

Clinical development of a new medicine can take 10 years and cost up to £500 million, so time is money. At one time, only academic clinical pharmacology units did phase 1 trials in healthy subjects in the UK. In recent years, CRO have taken over that role because they can provide an efficient, effective and high-quality service that enables companies to plan and execute the early clinical development of their IMP to tight timelines. The ABPI estimates that the UK does over half of the commercial phase 1 trials done in Europe.

The pharmaceutical industry would like but rarely gets such a service for phase 2 and 3 trials in the UK, which are usually done in a hospital setting. Recruitment of patients is often slow. Failure to keep to the protocol can render data unusable. Also, failure to comply with good clinical practice may impair the quality of the data, even if usable. Payments demanded by investigators vary widely for the same trial, and can be excessive. Academic institutions add overheads, often high, to investigators’ charges. A strong pound sterling makes matters worse for overseas’ companies. For those reasons, companies are increasingly placing their phase 2 and 3 trials outside the UK, in low cost areas such as Eastern Europe, Russia and India.

6. IMPACT OF DIRECTIVE 2001/20/EC ON UK PHASE 1 TRIALS

Feedback from AHPPI members since implementation of the Directive on 1 May 2004 indicates that the MHRA has been keeping to its target of 14 to 21 days to review applications for phase 1 trials, whereas the time for ethics committees to review applications for phase 1 trials has increased. Also, the MHRA and ethics committees are both proving slow to review and approve substantial protocol amendments, which are often essential to during phase 1 trials. That is causing serious difficulties for many CRO. Also, there is uncertainty about the future of many of the ethics committees that are currently allowed to review phase 1 trials in healthy subjects.

The evidence so far suggests that the Directive has reduced the number of phase 1 trials being done in the UK. Some pharmaceutical companies are choosing to do their phase 1 trials in EU countries that have not yet fully implemented the Directive. Pharmaceutical companies from countries, such as the USA and Japan, that are outside the EU are deterred by the extra bureaucracy involved in doing their trials in the EU, and not just the UK.

We intend to repeat our AHPPI survey of UK phase 1 units one year after implementation of the Directive, to get more objective information about its impact.

7. REFERENCES


APPENDIX 43

Letter from Malcolm Boyce to the Clerk of the Committee (PI 107A)

Here is my company’s publication policy that I first wrote several years ago and recently revised to mention the EU Directive on Good Clinical Practice. It covers in more detail some of the things, including examples of publications, that I mentioned during my evidence on 2 December 2004. I am still battling with several pharmaceutical companies (all from outside the UK) to get their approval to publish trials that my company carried out for them over the past year or two, so I cannot give you more information at the moment. Anyway, I don’t think that specific examples will help the Committee.
Also, here is a list of new molecules that my company tested for pharmaceutical companies, UK and non-UK, during 2003 and 2004. Altogether, we tested 47 new molecules in a total of 77 trials. So, 61% of the trials involved new molecules. We had to give trial subjects some information about the new molecules they received, in a written information leaflet, so what’s in my list is already in the public domain and I am not breaking confidentiality.

We work for most of the big pharma companies and what we do reflects development of new medicines worldwide. Thus, this evidence does not support the view, expressed by one member of the Committee, that new products are mostly line extensions and me-too products. Incidentally, my list shows that we tested several different new molecules for some classes. That’s because several companies are competing to be the first to the market in the same research area. If all the new molecules in the class come good, which is extremely unlikely as the attrition rate is normally high, the second, third, fourth etc to the market might end up being referred to unfairly as me-too products!

New molecules studied by HMR 2003–04

- Adenosine $A_2$ receptor antagonist
- Adenosine $A_3$ receptor agonist
- Adenosine $A_3$ receptor antagonist
- Dopamine $D_2$ agonist with 5-HT1A agonist activity
- 5-HT1A and 5-HT2A receptor antagonist
- SSRI with 5-HT1D and 5-HT2 antagonist activity
- NK1 antagonist (five different new molecules)
- Norepinephrine reuptake inhibitor
- Antimalarial
- Antimicrobial
- Atypical antipsychotic
- Long-acting $\beta_2$ adrenoceptor agonist (two different new molecules)
- Cannabinoid CB1 receptor antagonist
- Sigma site antagonist
- Neuronal calcium antagonist
- Peripheral benzodiazepine receptor antagonist
- Sodium channel blocker
- CCR3 antagonist
- CXCR2 antagonist
- VLA-4 antagonist
- Etotaxon blocker
- Centrally-acting skeletal muscle relaxant
- Corticotrophin releasing factor antagonist
- Gastrin antagonist
- Gonadotrophin releasing hormone antagonist
- MC4R agonist
- PPAR$\gamma$ agonist (two different molecules)
- Phosphodiesterase-4 (PDE-4) inhibitor (oral)
- Inhaled PDE-4 inhibitor
- Monoamine oxidase-B inhibitor
- Xanthine oxidase inhibitor (three different new molecules)
- Serine protease inhibitor
- Inhaled corticosteroid: new excipient for use with inhaled dry powder medicines
- Nasal “soft” corticosteroid
- Microglial inactivator
- Novel plasma protein fraction
- Prostacyclin analogue
- Thrombopoietin analogue
- SPET ligand

Total 39 types of new molecule
47 different new molecules
1. **Purpose and Scope**

Publications include the following: abstracts or papers about specific trials or general aspects of drug development at external meetings or in a scientific, medical or other journal; theses (eg MD, PhD); dissertations (eg BSc, MSc); course work (eg CIPD, TVU) for academic or professional qualifications. HMR encourages its staff to produce publications.

This policy describes our philosophy about publications and how we review them before releasing them into the public domain. The purpose of the review process is to:
- prevent release of confidential information about trial subjects;
- prevent release of the sponsor’s confidential information;
- prevent release of confidential information about HMR or its staff;
- improve the quality of the publication; and
- recognise, either by authorship or acknowledgement, the contribution of staff of HMR or the sponsor or others to the publication.

2. **Responsibilities**

Writers and co-writers of any of the above documents must follow this policy. The Staff Training Manager (or delegate) reviews course work of ward staff. Line managers review course work of other staff. The Medical or Managing Director reviews manuscripts, theses or dissertations, negotiates with sponsors who restrict unreasonably publication of trial-related data, and deals with requests for information from the media. The Medical and Managing Directors decide on authorship of papers. The Managing Director has overall responsibility.

3. **Methods**

3.1 *Our philosophy about publishing trial-related data*

The ICH Guideline for Good Clinical Practice (GCP), section 6.15, requires the trial protocol to include a statement on publication policy, if not covered in a separate agreement. Article 4 of the EU GCP Directive also requires the trial protocol to include a statement on publication policy.

Our policy is that if the data merit, either the trial sponsor or we may prepare a draft manuscript, for review and editing by both parties, before a final version is submitted for publication. Authorship should recognise those responsible for designing the trial, analysing or interpreting the data, and writing the paper, in accordance with established principles (Davidoff *et al* 2001). Unfortunately, not everyone involved with generating trial-related data can be a named author, but whenever possible the contribution of individuals should be acknowledged in the publication.

The templates for our protocols and agreements contain statements about our publication policy. Most sponsors have a similar policy. However, some sponsors insist that the trial data are exclusively theirs, and forbid publication. That policy is contrary to ours. But more importantly it is contrary to the Declaration of Helsinki (Edinburgh, 2000) and to the policy of the editors of 13 of the world’s most influential medical journals (Davidoff *et al* 2001). They have agreed that they “will not review or publish articles based on trials that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication”. We should follow the spirit of our quality policy (CP002) and not agree to a sponsor’s protocol or contract that forbids publication, except for patent-sensitive reasons. Once patents are in place, publication should be permitted.

3.2 *Manuscripts, theses or dissertations based on trial-related data and written by HMR staff*

Manuscripts prepared by HMR that contain trial-related data for publication in a scientific, medical or other journal must be well researched, accurate, and well written, and the interpretation of the data must be balanced. The writer and reviewer(s) prepare as many drafts as are necessary to give a final, polished version. The sponsor should be given reasonable time to comment on the draft manuscript(s). Both parties must agree to the final version. Theses or dissertations that are prepared by HMR staff for higher degrees must meet the same criteria, but the role of the supervisor or reviewer is advisory only. Individual trial subjects must not be identifiable in any publication, unless their specific consent has been obtained. Also, information provided by the sponsor that we have agreed to keep confidential must not be included.
3.3 Manuscripts based on trial-related data and written by the sponsor or co-investigator

Sponsors (eg Sardina et al 1995) or co-investigators (eg Watts et al 1997; Bryan et al 2000) with whom we share trials may write the manuscript for publication in a journal. Most sponsors or co-investigators allow us adequate time to comment, and include HMR staff among the authors. But not all sponsors or co-investigators are as well behaved. Some give us very little time to review and comment on their manuscript (eg Harada et al 2002). Some submit manuscripts for publication without giving us any opportunity to comment (Curtin et al 2000; Moore et al 2001). Sponsors sometimes publish papers, based on trials that we have done for them, without respecting our contribution and without ever informing us; we may discover their existence while searching the literature (eg Thompson et al 1999; Shangold et al 2000). Occasionally, investigators publish articles based on our trials, using data from the investigator’s brochure (eg Hornung et al 2002).

We should not allow sponsors or co-investigators to influence adversely our philosophy about publication. We should always involve them in publication of trial-related data. Furthermore, if we are given the opportunity to review and comment on manuscripts written by sponsors or co-investigators, we should try as best we can to apply the same standards of quality that we apply to manuscripts that we write ourselves.

3.4 Course work written by HMR staff

Course work is unlikely to be read by people outside of HMR other than the candidate’s tutor. Nevertheless, course work may contain trial-related data or information that is the property of HMR or confidential information about HMR staff. Therefore, course work should be vetted in a similar way to a thesis or dissertation. Some course work, eg for TVU, should be vetted to check that it is the candidate’s own work.

3.5 Signing off publications

The author(s) of a publication, and the relevant person(s) identified in section 2, must complete and sign FM840 before releasing the document. Authors of manuscripts for publication in a journal may have to sign a statement that the work is theirs and that they concede ownership to the publisher of the journal.

3.6 Dealing with the media

Requests for information about HMR, from journalists who work for newspapers, magazines, radio or TV, must be passed to the Medical or Managing Director. Sometimes journalists participate in our trials, to gather information for publication. Their requests for information should also be referred to the Medical or Managing Director.

4. Associated Records

Approval of a publication
External meeting or course

FM840
FM812

5. Internal and External References

Note that HMR authors are in bold font.


ICH Guideline for Good Clinical Practice, section 6.1

Data Protection Act, 1998
Declaration of Helsinki, Edinburgh, 2000
Quality policy CP002
Data protection policy for HMR staff CP014
Trial protocol HMRserver1
Trial information and consent form HMRserver1
Trial agreement HMRserver1
Thames Valley University (TVU)
Certificate in Practical Pharmacology Modules 1 and 2, and Course Handbook
MSc in Drug Development, Queen Mary College & Barts Medical College Course Handbook

6. SUPPLEMENTARY INFORMATION
— Staff intending to write a document for release into the public domain should first seek agreement of the appropriate supervisor (see section 2).
— If the publication is not trial-related, the writer should add a statement that his/her views are not necessarily those of HMR, and mark the document “confidential”.
— Writers must comply with the Data Protection Act (1998) and the Data Protection Policy for HMR staff (CP014).

APPENDIX 44

Memorandum by Pfizer (PI 28)

EXECUTIVE SUMMARY

Pfizer

Pfizer Inc is a research-based global pharmaceutical company that discovers, develops, manufactures and markets leading prescription medicines for humans and animals, and many of the world’s best-known consumer products. In the UK, Pfizer Ltd is the largest single supplier of prescription medicines to the NHS.

Medicines Innovation

The key to Pfizer’s continued investment in the UK is the strength of the UK and European science base. High quality science is essential to the innovation that leads to the invention and delivery of new medicines to patients, and the improvement of the health and wealth of the nation. Pfizer actively supports the science base and since 1998 has invested more than £1 billion in the UK, including over £450 million on research
buildings and pilot plant facilities. Pfizer spends £10 million on research and development in the UK every week, nearly £1,000 a minute. If the UK is to continue to attract inward investment from global pharmaceutical companies, then it needs to remain committed to investing in the science base.

**Conduct of medical research**

The implementation of the Clinical Trials Directive ensures that all clinical trials covered by the directive conducted in the UK, whether public or private, will be conducted to uniformly high standards. Pfizer partners and collaborates with the NHS in the support of both commercial and non-commercial research, which benefits many NHS research units. Pfizer’s support helps to make up the shortfall of public sector funding within the UK. As the UK is one of the most expensive places to conduct research, this seriously reduces its competitiveness when competing for the placing of research by global companies. Further government action is required to drive down the cost of clinical research to maintain the attractiveness of the UK as a location to conduct research.

**Provision of medicines information and promotion**

A medicine’s marketing authorisation includes an obligation for the pharmaceutical company to provide information on request to healthcare professionals. To comply with the Code of Practice, companies are obliged to have a “scientific service responsible for information”. This obligation continues beyond the date of loss of data and patent exclusivity, which means that information may be requested and supplied on a generic medicine not produced by the pharmaceutical company, which invented the original product. The cost of running such a department to meet this obligation involves considerable expense. Generic manufacturers are under no obligation to provide this service and therefore do not have to bear the costs of providing it. The overall cost of Pfizer’s medical information provision is in excess of £1 million per annum.

**Professional and Patient Education**

Pfizer’s principal objective when providing professional and patient education is to achieve the best outcome for patients through appropriate use of its medicines. Pfizer provides both professional and patient education programmes in line with the legislation and the ABPI Code of Practice. Pfizer can only engage in patient education through information contained in patient information leaflets and disease awareness campaigns, for example, the “Cholesterol” campaign, designed to educate patients about cholesterol and coronary heart disease. Disease awareness programmes can only communicate information about the disease, available treatment options and advice to patients to consult their healthcare professional. Pfizer supports the industry’s call for legislative change to allow pharmaceutical companies to communicate scientifically reliable information directly to patients. Pfizer shares the view of Government and regulators that greater access to scientifically accurate, non-promotional information about medicines will greatly improve patient concordance and health outcomes.

**Regulatory review of medicines safety and efficacy**

Pfizer operates within the UK and EU legislative frameworks to bring innovative new medicines that will deliver health benefits to patients. Pfizer shares a common objective with government and patients in ensuring that the MHRA’s assessment process is transparent, robust and based on a high level of scientific evidence. This process must be efficient in order to maximise the improvements in quality of life, or the life saving potential, of a new medicine. Pfizer recommends that the MHRA continues to build close working relationships with the other international regulatory institutions and the pharmaceutical industry. This approach will benefit patients by increasing the efficiency with which medicines are made available to a large international community, utilising data gathered from a heterogeneous patient population.

Pfizer suggests that transparency for licensing decisions made by the MHRA is in the interests of patients, regulators and industry. Current levels of interaction are not sufficient and it could be argued that further openness in the MHRA’s decision-making process is needed. Industry could also play a more proactive role in providing non-commercially sensitive data. Pfizer welcomes all opportunities to work closely with the MHRA to protect public health.

**Product evaluation, including assessments of value for money**

Pfizer recognises that it has a responsibility to develop medicines that are clinically effective and represent an efficient use of NHS resources. Many innovative new medicines deliver significant and obvious improvements in patient outcomes at the point of approval. However, it must be recognised that some produce incremental improvements in patient care that are only demonstrated after several years use by the NHS.
Pfizer recognises that it needs to collaborate with Health Technology Assessment (HTA) organisations effectively and early in the medicine’s development process to agree which data are required to conduct value for money assessments. HTA organisations, when planning to introduce additional data requirements for medicines approval, must recognise that pharmaceutical research and development programmes are planned in advance and can take up to 10 years. There should therefore be a gradual phasing in of planned changes to ongoing research and development programmes. HTA organisations should establish a formal process for ongoing dialogue with companies from the second phase of clinical trials of a medicine in human beings onwards. This would promote better understanding of the medicines and its potential impact on the condition as well as its value to the NHS. These organisations should work more closely with the appropriate regulatory authorities to reduce duplication of effort and to accept regulatory evidence.

Pfizer is keen to see the end of post-code prescribing and believes that patients should have access to the same high quality of care, irrespective of where they live.

1. Introduction

1.1 Pfizer Inc is the world’s largest research-based global pharmaceutical company. The company discovers, develops, manufactures and markets many leading prescription medicines for humans and animals as well as many of the best-known consumer medicines.

1.2 Pfizer’s medicines help millions of people in the UK manage conditions or alleviate symptoms in areas such as cardiovascular disease, diabetes, respiratory disease, oncology, central nervous system disorders, chronic pain, mental health, ophthalmology, urology, sexual dysfunction and endocrinology. Every month over 2 million people in the UK take a Pfizer medicine. Pfizer is dedicated to producing medicines that improve patient care, add value to healthcare and represent good value for money to the NHS.

1.3 Pfizer Ltd is the largest single supplier of prescription medicines to the NHS and also provides a wide range of over-the-counter medicines. The company is also a leading pharmaceutical partner of the NHS in areas such as smoking cessation and chronic disease management, and operates under the principle that the pharmaceutical industry has the potential to do more good for more people than any other sector through the discovery, development and distribution of innovative medicines.

1.4 Pfizer is one of the largest inward investors into the UK and has around 6,985 employees throughout the country. Of these approximately 3,600 work for Pfizer’s European Headquarters for Research and Development based at Sandwich in Kent. A further 700 employees work in the new award winning UK Business Headquarters at Walton Oaks in Surrey. There are four regional offices in Birmingham, Edinburgh, Manchester and Watford and a field force based throughout the UK.

1.5 Throughout the course of Pfizer’s presence in the UK, it has supported and worked in partnership with government; the NHS; the Royal Colleges and other healthcare professional and trade bodies; educational and research institutions; NGOs; parliamentarians; patient groups; and the local communities where it is based. The company has provided assistance and resources to support a diverse range of projects and programmes, and has always endeavoured to be in open and reciprocal partnerships, governed by mutually agreed and transparent guidelines.

2. Medicines Innovation

2.1 Pfizer Global Research and Development (PGRD), the company’s research and development division, is the largest private biomedical research operation in the world, and employs 15,000 scientists worldwide. In 2003, Pfizer spent more than $7 billion globally on research and development (R&D), more than any other private organisation.

2.2 Although Pfizer’s investment is an important contributor to the company’s success in the UK, the key to continued investment here is the strength of the British and European science base. As a research-based organisation, Pfizer recruits talented, innovative scientists from around the world who want to apply their knowledge and energies to discover and develop new medicines for conditions such as HIV/AIDS, neuropathic pain, chronic obstructive pulmonary disease and asthma. The company’s state-of-the-art laboratories and access to the latest technologies give bio-medical research scientists the tools to make a difference to the health of patients worldwide, and the working environment provides a broad range of opportunities for them to grow and develop their careers.

2.3 High quality science is essential to the innovation that leads to the invention and delivery of new medicines to patients, and the improvement of the health and wealth of the nation. Pfizer actively supports the science base, and since 1998 has invested more than £1 billion in the UK, including over £450 million on new research buildings and pilot plant facilities at the Sandwich Laboratories. Pfizer spends £10 million on research and development in the UK every week, nearly £1,000 per minute. In addition, to ensure the
continuing strength of research in the UK more than £5 million was spent funding science education in the
last year alone. Projects ranged from raising the standard of science teaching in primary schools, through
to financial grants for young scientists and funds for research projects.

2.4 This massive investment in the UK has returned a significant dividend in terms of innovative new
medicines for patients. Over the last 20 years the Sandwich laboratories have discovered and developed
many novel medicines such as:

- Amlodipine (Istint®), calcium antagonist for the treatment of high blood pressure and disease
  caused by the inadequate supply of blood to the heart.
- Fluconazole (Diflucan®) and voriconazole (Vfend®), therapies for the treatment of life
  threatening systemic fungal diseases.
- Sildenafil (Viagra®), the world’s first oral therapy for the treatment of erectile dysfunction.
- Doxazosin (Cardura®), to treat high blood pressure and benign swelling of the prostate gland.

2.5 This success in producing innovative medicines continues today. For example the Sandwich
laboratories have recently unveiled a significant new approach to the treatment of HIV with a new class of
medicines, known as CCR5 antagonists. For the first time, this treatment will enable doctors to prevent the
access of virus into human cells, thereby reducing the threat of viral resistance, an enormous problem in
treating this disease.

2.6 In summary, Pfizer has invested and continues to invest large sums in the UK to fund its own research
and to support the science base. The innovations resulting from this investment have lead to world-class
medicines for the treatment of many cardiovascular and infectious diseases.

2.7 Pfizer welcomes the work begun by Government in partnership with the industry through the
Pharmaceutical Industry Competitiveness Task Force to support and develop the UK science base, and is
working in partnership with the Government to deliver the ten-year strategic plan for the future funding of
the science base in order to put the value of excellence in science and innovation onto the balance sheet of
UK plc.

2.8 However, the past successes and current excellence of the science base give no room for complacency
if the UK is to remain competitive for the future. Medicines discovery and development is becoming
increasingly complex and challenging and the war for talent in a competitive global environment, coupled
with ever-tightening and increasing regulation, all pose threats to Britain’s past excellent record in this area.

3. CONDUCT OF MEDICAL RESEARCH

3.1 The primary aim of medical research is to develop safe, effective and innovative medicines for the
benefit of patients by treating and preventing disease. Studies are conducted in a safe and ethical manner to
the highest standards. All data are presented to the regulatory authorities for their independent assessment
and consideration as to whether a marketing authorisation can be provided. All safety data generated from
studies and normal clinical use are regularly submitted to the regulatory authorities.

3.2 Post-licensing studies are conducted to identify further indications, investigate, develop and validate
clinical assessments and demonstrate the health economic value of our medicines.

3.3 The outcome of important studies improves medical practice and delivers better patient outcomes.
The pharmaceutical industry generates the majority of the corpus of research that serves to make evidence
based medicine possible. In the UK alone with regard to funding of healthcare related research and
development by resource in the year 2000, the pharmaceutical industry funded 65% of research.116

3.4 The implementation of the European Clinical Trials Directive now ensures that all clinical trials
covered by the directive conducted in the UK, whether public or private, will be conducted to uniformly
high standards.

3.5 Pfizer partners and collaborates with the NHS in the support of both commercial and non-
commercial research to the benefit of many research units within the NHS and can now do so without
becoming the sponsor of the research. The company’s support also helps to make up the shortfall of public
sector funding in the UK.

3.6 However, the UK is still one of the most expensive places to undertake research, which seriously
reduces its competitiveness with regard to the placing of research in a global company. FastTrack for 2002,
an international annual assessment of cost comparisons of clinical trials, showed that the UK was the second
most expensive country to undertake research. Further government action is required to drive down the cost
of clinical research if further research is not to be placed abroad in more competitive countries where cost
is lower, speed is faster and quality at least equivalent.

3.7 Pfizer supports the recommendations of the American Pharmaceutical Group in respect of the
development of a publicly available registry of late-stage clinical trials in order that patients should have the
benefit of more information about their medicines.

4. Provision of Medicines Information and Promotion

4.1 Information about medicines, and the way in which pharmaceutical companies promote them, is regulated by both statutory controls, and market constraints. In addition, a voluntary Code of Practice exists to ensure that medicines are promoted in an ethical way in the United Kingdom.

4.2 The Marketing Authorisation of a medicine includes an obligation for the pharmaceutical company to provide information on request to healthcare professionals (HCPs). The Code of Practice (The Code) of the Association of the British Pharmaceutical Industry (ABPI) states that:

“Upon reasonable request, a company must promptly provide members of the health professions and appropriate administrative staff with accurate and relevant information about the medicines which the company markets.” (Clause 7.1 of the Code).

4.3 To achieve this, companies are obliged to have a “scientific service responsible for information” (Clause 13 of the Code).

4.4 This obligation continues beyond the date of loss of data and patent exclusivity. This means that information may be requested by healthcare professionals on off-patent Pfizer medicines now being produced by generic manufacturers. These “generic companies” are under no similar obligation, and therefore do not have to bear the costs or providing this service.

4.5 The employment, training, and equipment of a department to meet this obligation involves considerable expense. Over a financial year, the Medical Information Department of Pfizer Ltd receives over 26,000 requests for information directly from Health Care Professionals and administrative staff, and 12,000 indirectly through Sales Representatives. This equates to about 150 requests per day. The responses to these requests can range from a simple telephone call or a written answer, to the provision of detailed data either in written form or even as a presentation from a suitably qualified member of Pfizer’s Medical Department. The overall cost of Pfizer’s medical information provision is in excess of £1 million per annum.

4.6 As approximately 97% of prescriptions are supplied by the NHS, it is clearly appropriate that statutory controls exist to ensure that the promotion of medicines is conducted in an acceptable way. These controls include The Medicines Act (1968), the Medicines Advertising Regulations (1994) and amendments and the Control of Misleading Advertisements (1988) and amendments. The Code of Practice of the ABPI was introduced in 1958 and now virtually all the pharmaceutical companies in the UK accept its jurisdiction. The Code is regularly revised in consultation with the British Medical Association, the Royal Pharmaceutical Society of Great Britain and the Medicines and Healthcare products Regulatory Agency (MHRA) of the Department of Health. “The Code reflects and extends well beyond the legal requirements controlling the advertising of medicines” (The Code, 2003, Introduction, p 4).

4.7 The Code covers all aspects of the promotion of medicines, including advertisements, Representatives’ activities, meetings, the provision of education and hospitality and the provision of medical information, as discussed above.

4.8 The Code accepts complaints from competitor companies, healthcare professionals and members of the public. The Director of the Prescription Medicines Code of Practice Authority (PMCPA) is also obliged to scrutinise advertisements in the medical press, which provides another check on the quality of this medium of promotion. Most significantly, the outcomes of the Code’s proceedings are made public and are available to the statutory body. Moreover, the MHRA undertakes its own surveillance of pharmaceutical companies’ advertisements. This surveillance is becoming increasingly active.

4.9 A fundamental review of the Code is imminent in the face of an ongoing review of the European Code of Practice for the Promotion of Medicines, which is administered by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The preliminary draft of this EFPIA Code closely mirrors the UK Code. This is in keeping with our understanding that the regulations and the Code governing medicines promotion in the UK are widely considered to be as stringent as those of any other country in the world.

4.10 Since 1994, the Association of Information Officers in the Pharmaceutical Industry (AIOPI) has convened a working party to create an industry standard for medical information functions. The purpose of this initiative was to provide a reference against which medical information departments could monitor and improve their performance in line with customer requirements.

4.11 The working party consists of representatives of medical information departments from a range of pharmaceutical companies, both small and large, and from hospital-based information pharmacists (the UK Medicines Information Pharmacists Group, UK-MIPG). Endorsements for successive revisions of the guidelines are sought from the AIOPI committee, UK-MIPG membership, and the ABPI. All pharmaceutical company representatives have to achieve standards in qualifications set by the PMCPA within two years of joining the industry.
5. Professional and Patient Education

5.1 Professional and patient education is tightly regulated by UK and European law, and is supported by a voluntary, enforceable and transparent ABPI Code of Practice. The principal objective of Pfizer’s effort to provide professional and patient education is to achieve the best outcome for patients from the most appropriate use of its medicines.

5.2 Pfizer provides professional education in regulated medical education programmes and partnership activities with healthcare professionals; their professional bodies and trade associations; educational institutions; medical societies and publishers; the government and the NHS. New partnerships initiated in the past 12 months include an initiative with Brighton and Sussex Medical School, where there is to be a Pfizer staff member on the Clinical Research Unit management team to give expert input. Another example is a partnership with the Royal Colleges of Physicians and General Practitioners, working with their education unit at the University of Bath, in support of their existing Medical Education efforts for specialists in training and General Practitioners.

5.3 The promotion of prescription-only-medicines to the public is not permitted. Pfizer can only engage in patient education about prescription-only-medicines through information contained in medicines packaging. Communication with the public is therefore limited to information about disease awareness and must not be considered to be an inducement to request a specific medicine. Pfizer has launched several educational disease awareness campaigns in a variety of disease areas. There can now be little doubt that such campaigns are contributing hugely to the nation’s understandings of health and disease. They can provide valuable support to the successful attainment of targets set out in National Service Frameworks and the General Medical Services contract. The “Cholesterol” campaign, designed to educate patients about cholesterol and coronary heart disease, is ongoing and is an excellent example of such an initiative. These programmes can only communicate information about the disease, available treatment options and advice to patients to consult their healthcare professional. They cannot in any way be brand-specific or speak only about a medicinal intervention. These public health campaigns are carried out a significant cost to Pfizer.

5.4 Pfizer’s relationships and partnerships with patient groups, voluntary sector and other stakeholders are governed by its published guidelines. Many stakeholders are of great importance in ensuring the delivery of good quality cost-effective healthcare, including healthcare providers, patient groups and political organisations.

5.5 The establishment of collaborative working relationships with shared objectives between Pfizer and patient groups can result in real benefits for those affected by the disease or condition who are represented by the patient group, especially where there are shared objectives, common goals, and mutual benefits.

5.6 Support for patient groups can be provided in different ways, for example, financial sponsorship; donations; project funding or core funding. It can also be delivered through other benefits in kind, for example, resources to support internal and external communication; education and external policy initiatives.

5.7 It is important that such partnerships and collaborations are based on the understanding that all activities should be conducted within a clearly understood and mutually accepted set of key operating principles, in order to avoid both the reality and the perception of improper or undue influence.

5.8 The principles of Pfizer’s guidelines state that there should be transparency at all times in any activities between Pfizer and the patient group. Confidential information about members of the patient group, individuals associated with it, or other confidential information should remain the property of the patient group and should not be made available to Pfizer. The independence of internal policy making, political judgement and other activities of the patient group are assured at all times. Copies of our operating principles are attached.

5.9 Pfizer has been working closely with patient groups and think tanks to understand and address growing concerns for patient safety because of threats to the integrity of the European pharmaceutical supply chain. Constructive relationships have been built with groups such as Depression Alliance and the Patients Association to better understand patients’ concerns.

5.10 As a member of the ABPI, the company supports the Association’s Informed Patient Taskforce’s objectives and the industry’s call for legislative change to allow pharmaceutical companies to communicate scientifically reliable information more directly to the ultimate consumers of its medicines. In common with the Government and the regulators, Pfizer believes that a greater access to scientifically accurate non-promotional information about medicines will greatly improve patient concordance and health outcomes.

6. Regulatory Review of Medicines Safety and Efficacy

6.1 In common with other research-based companies that invent new medicines, Pfizer operates within a legislative framework that is enforced by UK and EU regulatory authorities. This legislation is frequently updated and revised to reflect new medical outcomes and scientific advances. Medicines are either approved through the Mutual Recognition Procedure (MRP) or the Centralised Procedure (CAP).
6.2 The MHRA evaluate the safety, efficacy and quality of each medicine and will only approve it for use in the UK if satisfied that the benefits of a medicine outweigh any risks associated with it. Pfizer submits a comprehensive dossier containing all research and development data when applying for a licence for a new medicine. This comprises on average around 60,000 pages. Pfizer’s responsibility does not end at that point, as there is a legal requirement to inform the MHRA of any information that may affect the risk-benefit profile of the medicine. This is something the company takes very seriously and to which it commits a significant proportion of resource involving a team of around 50 people within the UK who co-ordinate globally with colleagues in similar functions.

6.3 As is routine amongst companies that invent new medicines, Pfizer complies with the normal standards of Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). The MHRA’s inspection enforcement group can inspect for these practices. The MHRA has also recently introduced Pharmacovigilance inspections.

6.4 Pfizer shares a common objective with government and patients in ensuring that the MHRA’s assessment process is transparent, robust and based on a high level of scientific evidence. Pfizer’s purpose is to invent innovative new medicines that will deliver much needed health benefits to patients. It is important that this process is as efficient as possible in order to maximise the improvements in quality of life, or the life saving potential, of a new medicine.

6.5 There is a need for the existing ongoing dialogue between the MHRA and Pfizer throughout the development of a new medicine. This is essential in order to ensure that the requirements of the regulators are fully met to address areas within new indications that have not been previously investigated and generally to ensure that the proposed pre-clinical or clinical trial programme is appropriate. Advice sought can be diverse, including ascertaining the most appropriate regulatory procedure to use for registration purposes in Europe, defining the criteria for a new indication, the scope and design of the clinical trials, and the recommended risk management programme. Advice can also be sought on how best to design the trial so that the data required by the regulatory authorities can be obtained. Both a Clinical Trial Application (CTA) approval from the MHRA, and independent local and national ethics committee approvals are needed to conduct a clinical trial.

6.6 Pfizer cooperates closely with regulators and other stakeholders (eg patient groups and consumers associations) during the drafting of new guidelines. These provide guidance on the implementation of European law. Pfizer plays a critical role in highlighting the practical implications of these proposals, ensuring that they are actually able to deliver the benefits sought. This can be achieved through a consultation process or through the setting up of advisory committees on which there is industry representation. Successful examples in which MHRA has engendered a particularly productive engagement with all stakeholders including Pfizer are: the pan European review of medicines’ legislation; the labelling best practice guidance issued by the MHRA devised to reduce medication errors; and the Committee on the Safety in Medicine’s review of Patient Information Leaflets, currently in progress, to improve the quality of patient leaflets supplied with medicines.

6.7 The applicant is not present, even as an observer, at the review of a new medicine by the independent Committee on Safety of Medicines. It is therefore imperative that the applicant continues to have an opportunity to explain the data, provide clarification and answer questions in the lead up to this meeting. The MHRA seeks independent scientific advice through their advisory committees, including the CSM. Declaration of interests by Committee members ensures that scientific opinion is independent and unbiased.

6.8 In common with other pharmaceutical companies, Pfizer pays fees to the MHRA for the assessment of the marketing authorisation application and subsequent variations. Fee details and levels are published and revised by the MHRA on a yearly basis.

6.9 Pfizer informs the MHRA of the evolving safety and adverse event profile of all medicines. Pfizer and the MHRA update the product information and labelling to reflect such changes so that healthcare professionals and patients have access to the latest information.

6.10 At the time of licensing there will be extensive clinical data on the use of the medicine. However Pfizer has pharmacovigilance/risk management systems in place to monitor and assess the use of the medicine by patients in the post-marketing phase. The Pharmacovigilance team reviews Adverse Drug Reaction (ADR) reports, expediting their reporting to the MHRA where appropriate, and summarising all the data received in a regular Periodic Safety Update Report (PSUR). The MHRA periodically conducts pharmacovigilance inspections of ADR reporting systems and have enforcement powers including company closure if serious non-compliance is found. The requirement for Pharmacovigilance is heavily embodied in legislation and there are severe penalties for non-compliance, both for the company and the individuals held accountable. Pfizer works closely with the MHRA to ensure full compliance with pharmacovigilance obligations.

6.11 Newly approved medicines are subject to intensive monitoring by the MHRA as part of the CSM Yellow Card/Black Triangle (adverse event reporting) scheme. This scheme allows rapid monitoring of new safety signals as medicines become available on prescription. The MHRA publish all significant conclusions drawn from this safety surveillance system in “Current problems in Pharmacovigilance”. Pfizer considers this scheme to be of tremendous value for patients, doctors and the research based industry and shares the MHRA’s aspiration that the current review will only introduce changes that enhance its integrity and effectiveness.
6.12 Good communication channels between the MHRA and pharmaceutical companies are also essential when the MHRA requires information at very short notice, for example, paediatric data summaries.

6.13 The benefit-risk assessment for each medicine is a continuous process based on quality, safety and efficacy. It is important to have dialogue with the MHRA, or indeed other regulatory agencies, prior to, during and post approval. This ensures rapid delivery of a rigorously evaluated medicine to the patient, accompanied by the appropriate advice on how it should be used. Pfizer supports any initiative that enhances the quality of that communication.

6.14 Pfizer suggests that transparency for licensing decisions made by the MHRA is in the interests of patients, regulators and industry. Current levels of interaction are not sufficient and it could be argued that further openness in the decision-making process by the MHRA is needed. Industry could also play a more proactive role in providing non-commercially sensitive data to patients.

6.15 The MHRA, along with the pharmaceutical industry, aspires to have an assessment process that is transparent, robust and based on a high standard of scientific evidence. It is recommended that the MHRA continues to build close working relationships with the other international regulatory institutions and the pharmaceutical industry. This approach will benefit patients by increasing the efficiency with which medicines are made available to a large international community, utilising data gathered from a heterogeneous patient population.

6.16 Pfizer welcomes all opportunities to work closely with the MHRA to protect public health.

7. **Product Evaluation, Including Assessments of Value for Money**

7.1 Pfizer recognises that it has a responsibility to develop medicines that are clinically effective and represent an efficient use of NHS resources.

7.2 Faster patient access to clinically effective and cost-effective new medicines is an important means of improving health outcomes in the UK. Pfizer fully supports the National Institute for Clinical Excellence’s (NICE) objective of faster and consistent access to innovative, new technologies across England and Wales.

7.3 “Innovative new medicines” should not be restricted only to those that deliver significant and obvious improvements in patient outcomes at the point of approval. It must be recognised that many new medicines produce incremental improvements in patient care, the full impact of which may only be demonstrated after use by the NHS for some years.

7.4 Pfizer has invested heavily in developing capabilities in health technology assessment in order to meet the information needs of NICE, All Wales Medicines Strategy Group, Scottish Medicines Consortium (SMC), and the NHS.

7.5 Health Technology Assessment (HTA) organisations must recognise the significant time and financial investment made by pharmaceutical companies engaged in the research and development (R&D) of new medicines. Pharmaceutical research and development programmes are planned in advance and can take up to 10 years or more.

7.6 The introduction of additional HTA data requirements for product approval should therefore be phased in gradually to enable the required changes to ongoing R&D programmes. In the interim, HTA organisations will need to recognise and accept the difficulties associated with providing some of the data they request.

7.7 Pfizer recognises that it needs to collaborate with HTA organisations effectively and early in the medicines development process to agree what data are required to conduct value for money assessments.

7.8 Pfizer is committed to sharing new product information with the National Horizon Scanning organisations to inform early understanding of the medicine.

7.9 HTA organisations should establish a formal process for ongoing dialogue with companies from the second phase of clinical trials of a medicine in human beings onwards. This would promote better understanding of the medicine and its potential impact on the condition as well as its value to the NHS.

7.10 These actions should inform appropriate topic selection and timing of HTA appraisal. They should also provide for expert information to inform the development of appropriate evidence of the medicine during the third phase of clinical trials in humans, and to reduce uncertainty regarding the outcome of a future HTA appraisal. The model for consultation used in the regulatory process is recommended for this purpose.

7.11 HTA organisations should work more closely with the appropriate regulatory authorities to reduce duplication of effort and to accept regulatory evidence.

7.12 Pfizer actively participates in the development of working processes for HTA organisations via formal consultation processes, in the appraisal process for its medicines and in the monitoring of the uptake of HTA guidance, and is keen to see the end of post-code prescribing. Pfizer believes that patients must have access to the same high quality of care, irrespective of where they live.
7.13 NICE and the SMC have made some progress in addressing postcode prescribing but large variations in use still remain.

7.14 Implementation of HTA guidance is a complex process and places a significant burden of work on health organisations like Primary Care Trusts. Pfizer is committed to developing partnerships with these organisations, professional and patient groups and with HTA groups to support implementation of guidance of mutual interest.

Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPI</td>
<td>Association of the British Pharmaceutical Industry</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AIOPI</td>
<td>Association of Information Officers in the Pharmaceutical Industry</td>
</tr>
<tr>
<td>CAP</td>
<td>Centralised procedure</td>
</tr>
<tr>
<td>Code of Practice</td>
<td>The ABPI Code</td>
</tr>
<tr>
<td>CSM</td>
<td>Committee on Safety of Medicine</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trial Application</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practice</td>
</tr>
<tr>
<td>HCP</td>
<td>Healthcare professionals</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MRP</td>
<td>Mutual Recognition Procedure</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>PGRD</td>
<td>Pfizer Global Research and Development</td>
</tr>
<tr>
<td>PMCPA</td>
<td>Prescription Medicines Code of Practice Authority</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>RMS</td>
<td>Reference Member State</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>UK MIPG</td>
<td>UK Medicines Information Pharmacists Group</td>
</tr>
</tbody>
</table>

Annex (PI 28A)

PFIZER OPERATING PRINCIPLES FOR WORKING IN PARTNERSHIP WITH PATIENT SUPPORT GROUPS

Pfizer is a global research-based healthcare company. Our medicines span a wide array of therapy areas, and all of them are designed with the goal of improving the quality of people’s lives.

Many stakeholders are of great importance in ensuring the delivery of good quality cost-effective healthcare, including healthcare providers, patient groups and political organisations. We believe that Pfizer has an active and strong role to play in the provision of healthcare, and as such in the need to build close working relationships with all of our partners in healthcare.

The establishment of collaborative working relationships between Pfizer and patient support groups (PSGs) can result in real benefits for those affected by the disease or condition who are represented by the PSG, especially where there are shared objectives, common goals, and mutual benefits.

Support for PSGs can be provided through financial sponsorship and/or donations to fund projects and/or core funding, or through other benefits in kind, such as resources to support internal and external communication, education and external policy initiatives.

It is important that such partnerships and/or collaborations are based on the understanding that all activities should be conducted within a clearly understood and mutually accepted set of key operating principles, in order to avoid both the reality and/or the perception of improper or undue influence.

The purpose of this document is to outline our own definition of these key principles, as guided by Pfizer values, mission and culture.

**Principles:**

— There should be transparency at all times in any activities between Pfizer and the PSG.

— Confidential information about members of the PSG, individuals associated with it, or other confidential information remains the property of the PSG and shall not be made available to Pfizer.

— Parameters and timeframes should be understood and agreed from the outset.

— Joint agreements or projects undertaken between Pfizer and the PSG should be based on equal partnership with mutual respect and trust.
— The PSG may offer information across a range of products, but Pfizer must not demand the endorsement of a single pharmaceutical product be it prescription-only or OTC.
— No undue influence should be exerted on the agenda, priorities or operations of the PSG.
— The independence of the internal policy making, political judgement and activities of the PSG should be assured at all times.
— Association with Pfizer should in no way compromise, or be seen to compromise, the independence of the PSG.
— Pfizer will at no time use the name or logo of the PSG, or make any claim of association with the PSG, without its prior written agreement, nor use any unauthorised quote from a member of the PSG.
— The PSG should be consulted on and retain ultimate editorial control over all materials produced in their name and the use of their logo.
— Wherever necessary, Pfizer and PSG should provide each other with copies of reports, accounts and other appropriate information relating directly to the partnership or collaboration, excluding any confidential information.
— Pfizer will always try to comply with applicable rules and regulations governing their attendance at, and participation in, PSG meetings.
— Pfizer will ensure that it respects the independence of any of its employees actively engaged in PSG work.

APPENDIX 45

Memorandum by the British Association of Pharmaceutical Wholesalers (PI 24)

PHARMACEUTICAL WHOLESALING—THE INDUSTRY’S ROLE

1. Full-line pharmaceutical wholesalers are an essential link in the medicines supply chain. They act as a one stop shop for almost all pharmaceutical products and services, playing a key role in the cost effective and safe distribution of a diverse and comprehensive range of healthcare products.

2. They deliver to the front line of health services—pharmacists, doctors, hospitals, sometimes even to individual patients across the whole country. In some countries, elements of full-line pharmaceutical wholesaling are viewed as a public service and receive state subsidies, although in the UK this is not the case. Wholesalers buy most of the medicines they supply direct from manufacturers to meet the demands of the customer—the NHS. In essence, the industry carries all the risk and investment involved in distribution of medicines with no specific investment or subsidy from, or cost to, the NHS.

As an industry, pharmaceutical wholesale:
— Employs almost 9,000 staff.
— Makes more than 235,000 deliveries per week.
— Carries and supplies around 20,000 essential drugs, medicines and services.
— Delivers over 85% by value of the medicines dispensed in pharmacies, as well as around half of the medicines used in secondary care.
— Picks and delivers more than two billion items per year, with a combined value of over €15 billion.
— Achieves service levels touching 99%.
— Operates over 50 depots nationwide.
— Provides 50% of the computer equipment used by pharmacies.
— Provides a round the clock, on demand service to pharmacies and hospitals, 365 days a year.
— Offers very short lead times on orders and deliveries—typically less than half a day.

PHARMACEUTICAL WHOLESALING—A COMPETITIVE INDUSTRY UNDER PRESSURE

3. Typically, wholesalers run at net margins of less than 2%. Some wholesalers take advantage of the fact that there are bigger margins to be made on certain products and concentrate wholly on them—these are known as short-liners. However, the British Association of Pharmaceutical Wholesalers represents only full-
line wholesalers, who offer the entire range of licensed medicines needed by patients, not merely the most
profitable ones. As an industry, wholesaling is under continuous pressure to meet the needs of its customers
in what is currently a highly uncertain market. The prices of both generic and patented drugs are currently
under negotiation, whilst the role of our principal customers is also likely to change significantly once the
pharmacy contract is agreed. The danger of these pressures to our customers (ultimately the NHS) is that
full line wholesalers could eventually be required to reduce their ranges, making the least profitable
drugs difficult to source for the pharmacists, hospitals and doctors.

**Pharmaceutical Wholesaling—Securing Value from the Supply Chain**

4. Pharmaceutical wholesaling is a lean industry, operating at low profit levels in a highly competitive
market. And, like any part of an efficient supply chain, an onus exists on wholesalers to offer ever more
competitive prices for products. One way pharmaceutical wholesalers can meet this demand for good value
is by buying products sourced from markets with lower prices. This practice is sometimes known as parallel
importing and, whilst this is a perfectly legitimate and legal activity, practiced in markets across the world,
it is understandably a source of irritation to some domestic manufacturers, many of whom would like to see
an end brought to the practice. Medicines made and sold by UK manufacturers and identical in make-up
to those sold direct to the UK, can be re-imported from foreign markets, repackaged in English and sold
safely here, all at a lower cost than the same medicine sold directly to wholesalers from the manufacturer.
The savings made are passed on to pharmacists, allowing them to subsidise some of their loss-making
activities and also benefit the Department of Health’s coffers by means of a greater clawback (the process
of recovering discounts offered by wholesalers to pharmacists).

5. Similarly, in common with wholesalers in other markets, the margins made on lines will differ.
Typically, a wholesaler will discount many hundreds of the lines offered in order to attract custom. Many
products are also offered at prices that derive no profit when other costs (e.g. delivery) are taken into account.
At the other end of the scale, and to offset these no-profit lines, higher margins are set on other products,
typically generic medicines. Operating in such a competitive market, with overall margins of just 2%
wholesalers rely upon these higher margin lines to remain profitable. Without them, it is uncertain whether
wholesalers could continue to provide their efficient, effective service.

6. On the supply side, pharmaceutical companies are always attempting to maximise the prices they
receive for their products and typically offer branded ethicals to all wholesalers at the same price. However,
in a model of supply used by one manufacturer, wholesalers are used as an agency and are paid a fee for
distributing its products. However, it is only because wholesalers have the necessary delivery infrastructure
already in place that they can afford to cede to this manufacturer’s demands. If other manufacturers were
to follow suit, this valuable medicines supply infrastructure would become unsustainable and the twice daily
deliveries which the industry’s customers currently enjoy would almost certainly disappear. This, of course,
would seriously damage the ability of pharmacies, hospitals and dispensing doctors to meet the needs of
patients. In contrast to the service wholesalers offer—twice a day deliveries with half-day lead times—
manufacturers can typically only offer weekly deliveries with three day lead times.

**Pharmaceutical Wholesaling—A Proven Performer in the Private Sector**

7. Pharmaceutical wholesaling is subject to a variety of very strict regulations to maintain the safety and
efficacy of drugs. Some products are subject to specific temperature controls, whilst others are controlled
under the Misuse of Drugs Act and require secure storage and are subject to burdensome administrative
procedures. (Indeed, the manner in which the wholesale industry manages controlled drugs was praised in
the most recent report of the Shipman Inquiry.) The Department of Health has recognised that these drugs
incur greater costs of storage and distribution and because of the importance of observing the appropriate
regulations, these products are generally not discounted and are known as ZDs or zero discount products).
However, market demands are already putting pressure on wholesalers to begin to discount these medicines
in order to undercut competitors.

8. Pharmaceutical wholesalers have long provided a valuable role in the supply chain for medicines. In
many countries, wholesaling is a public service obligation which receives government subsidy, such is its
importance in delivering medicines to patients in a timely, safe and efficient manner. The industry’s twice
daily deliveries across the UK, its contribution to the success of pharmacy in extending and deepening
professional competencies and its potential for meeting the demands of pharmacists in light of the new
pharmacy contract all mean that the pharmaceutical wholesaling business can continue to play an essential
part of the UK’s health services. However, like its regulatory and economic environment, its role remains
uncertain. The industry cannot sustain continued pressure on its profitability without cutting its cloth
accordingly. In reality, this could mean the reduction of its delivery capabilities to front line NHS services
or a scaling back of its contribution to pharmaceutical services at a critical time for the profession.
In August the British Association of Pharmaceutical Wholesalers (BAPW) submitted written evidence to the Health Select Committee’s inquiry into “The Influence of the Pharmaceutical Industry”.

Further to that evidence, the BAPW wanted to highlight a practice the branded pharmaceutical industry is increasingly adopting, which is to limit supplies of vital medicines to pharmaceutical wholesalers, which we believe is ultimately to the detriment of patients.

Under this new practice, branded pharmaceutical companies are arbitrarily setting quotas on the amount of medicines they will sell to wholesalers, purportedly in order to “better manage medicine stocks” for themselves. This is done without consultation or discussion with wholesalers, who, as a result, have no opportunity to influence the level at which their quotas are set. Indeed, some of those companies imposing quotas make no attempt to explain the criteria by which levels are set.

Clearly in the classical manufacturer-wholesaler-retailer-patient model, where most manufacturers are anxious to meet wholesale demand to reach customers as soon as possible, this is an unusual development. And the BAPW believes that they may have worrying consequences for patients.

Under usual circumstances, our members would order from manufacturers the amount of stock they needed to meet patient demands and deliver it quickly and safely up to four times a day to hospitals and pharmacists, as it was required. However, under the new quota systems, some manufacturers have begun to set a limit on the amount they will supply to wholesalers.

But as in any market, demand for medicines peaks and troughs. And when demand is high, some wholesalers have exceeded the limits set on them by manufacturers who have then refused to supply any more. Rather gravely, this means that with increasing regularity, some of our members have been unable to supply local doctors and pharmacists with the amount of medicines they need to treat their patients. (The BAPW would be happy to provide more details of where this has happened and with which manufacturers.)

We believe that the only way demand can accurately be measured, and the supply chain to patients be made to work properly, is for wholesalers, retailers and manufacturers to follow the signals of the market. For generic medicines, wholesalers could source products from alternative suppliers to meet demand but in the case of proprietary medicines, manufacturers know that, because of patent protection, they have a monopoly over supply—if they do not supply their medicine, they know no one else can. And to the safe and quick delivery of medicines to patients, this could represent a serious impediment.

In most, if not all of these cases of supply failing to meet demand, retailers will have been able to source medicines from other wholesalers, but this may not always be the case. If demand for a product were to peak—for instance because of a high winter demand for a product—doctors and pharmacists have little or no assurance that wholesalers would be able to meet it because quotas limit the amount of stock they are able to hold and supply. The BAPW therefore believes that the quota system has the potential to seriously disrupt the supply chain, slowing down access to vital medicines, and endangering patients’ lives.

Manufacturers may defend their actions by saying that they have provided enough stock to satisfy demand, but patient requirements and expectation in Penzance are not satisfied by the stock only being available in Newcastle, or Manchester, for example, where a pharmacist or doctor may have no relationship with the wholesaler stocking it.

Whilst pharmaceutical wholesalers are firmly committed to leading improvements in the supply chain (for example, wholesalers provide the computer systems to 50% of the UK’s pharmacies), we believe that in this case the adage “if it ain’t broke, don’t fix it” firmly applies. At the very least the pharmaceutical industry should be able to make the case that this change has made the supply chain more efficient and has real benefits for those who need the medicines they supply—patients. We believe that on this occasion it has not done so.

Letter from the Chairman, Medicines and Healthcare Products Regulatory Agency to the Clerk of the Committee (PI 124A)

In your letter of 21 December you asked for additional information in advance of my appearance before the Health Select Committee. I am pleased to be able to answer your questions and supply the documents requested.

I should preface my answer to your first question regarding the assessment of data submitted by the applicant and the reliance on summaries of data by explaining that European law does not require that actual raw data is submitted as part of the application. It requires, instead, that marketing authorisation holders must arrange for clinical trials documents (including case report forms) to be kept by the owners of the data. Clinical trials carried out and results obtained from the raw data for each study are written into a final clinical study report signed by the investigators and submitted as part of the application.
Article 8 of Directive 2001/83/EC sets out the procedure for obtaining a marketing authorisation for a medicinal product. Annex I of the Directive, requires that applications for a new drug must be accompanied by the following particulars and documents in respect of clinical documentation: These data are presented as a series of modules including a Clinical Overview (a critical analysis of the clinical data included in the clinical summary and all the clinical documentation), a Clinical Summary (a detailed summary of the all the clinical information) and the Clinical Study Reports. In this module, all reports of individual clinical studies must be provided. The textual part of each study report can be 50-60 pages or more and can be supplemented by several volumes of appendices and supplementary tabulations and listings of data. In a new drug application, the number of volumes of clinical documentation could be in the hundreds.

If considered necessary, companies are required to make all raw data and documents available to relevant authorities upon request. During the conduct of clinical trials, inspectors from MHRA will often go to companies and clinical trial sites to audit them to ensure complete and accurate documentation of data and records.

With this in mind the number of cases where there has been significant partial reanalysis of raw data is very low indeed compared to numbers of products licensed. This has happened in the cases of the revocation of the Marketing Authorisations for Evening Primrose Oil and in the case of the Review of SSRIs.

Turning to your second point regarding the licensing process and the extent to which the Agency’s assessors might be informed of all of the trials undertaken on a product, applicants are not allowed to be selective in the data which they submit. The applicant is obliged by Directive 2001/83/EC to supply all relevant information for evaluation of the product, whether favourable or unfavourable and especially if there are incomplete or abandoned trials which may not have been published. It is a criminal offence not to comply with these requirements of the Directive.

I am enclosing the Assessment Reports presented to CSM and the Medicines Commission (the other main medicines advisory body) on human albumin, evening primrose oil and sertraline. These Assessment Reports are sent in confidence as we have not redacted them to remove personal or commercially confidential information in view of the time available, or to seek permission for such information to be released into the public domain. However, should these documents be published as part of the final evidence of the Inquiry I would be grateful for the early opportunity to ensure that personal or commercially confidential information is removed and/or relevant permissions sought. You will note of course, that the history of these products goes back to the late 1980s in some cases.

You have asked about the relationship between the MHRA and NICE. Since the establishment of the MHRA (in April 2003), there has been one meeting at CEO level (with other senior management) where a range of general issues of mutual interest were discussed (June 2004). Agenda items included a general update on events in each organisation and a more targeted examination of ways of involving each Agency in the other’s business where appropriate, through the discussion of a series of possible future interactions. The next meeting at this level is in March 2005. More specific operational level meetings have also taken place. For example, the MHRA and NICE have worked closely together on an ad hoc basis where it is necessary to ensure a joined up approach—most recently in the MHRA’s review of the safety of SSRIs and the NICE clinical guidelines on the treatment of depression, where NICE were observers on the CSM Expert Group. The MHRA also sits on a number of NICE working level committees.

You have asked which of the recommendations from the National Audit Office inquiry into the MHRA have been implemented. A table showing the main recommendations and the extent to which they have been implemented is attached (at annex A). While very few of the recommendations have been completed in their entirety (partly because of their very nature), they have been influential in setting the direction of the new Agency and, overall, there has been a great deal of progress. You will, of course, be aware that the NAO Report was only published in January 2003 and the PAC Report in June 2003.

Turning to your final point about benzodiazepines, it is not possible to determine how many deaths have been caused by benzodiazepines using data from the Yellow Card Scheme. It is important to note that not all reported adverse reactions were caused by the drug. Health professionals are asked to report “suspected” adverse reactions regardless of doubts they may have as to whether the drug caused the suspected reaction. Also, there is an unknown degree of underreporting associated with the Scheme which varies depending on a number of factors, including how long the drug has been on the market and any media attention surrounding the drug. The number of reports of suspected adverse reactions should be seen in the context of the millions of prescriptions for benzodiazepines over the last 40 years.

The table below shows the number of reports of suspected adverse reactions received for benzodiazepines since the beginning of the Yellow Card Scheme, and how many of those had a fatal outcome. A number of the substances named are no longer licensed in the UK and these are marked with an asterisk.
TABLE SHOWING THE NUMBER OF REPORTS OF SUSPECTED ADVERSE REACTIONS TO BENZODIAZEPINES SINCE 1964, AND THE NUMBER OF REPORTS WITH A FATAL OUTCOME

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Year of first reported reaction</th>
<th>Total number of reports</th>
<th>Total number of reports with fatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>1983</td>
<td>118</td>
<td>3</td>
</tr>
<tr>
<td>*Bromazepam</td>
<td>1982</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>1964</td>
<td>302</td>
<td>13</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1974</td>
<td>141</td>
<td>4</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>1973</td>
<td>128</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1964</td>
<td>921</td>
<td>58</td>
</tr>
<tr>
<td>*Flunitrazepam</td>
<td>1982</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>1974</td>
<td>141</td>
<td>2</td>
</tr>
<tr>
<td>*Ketazolam</td>
<td>1980</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1973</td>
<td>450</td>
<td>19</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>1981</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>1965</td>
<td>477</td>
<td>26</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>1966</td>
<td>79</td>
<td>2</td>
</tr>
<tr>
<td>*Prazepam</td>
<td>1982</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Temazepam</td>
<td>1977</td>
<td>404</td>
<td>29</td>
</tr>
<tr>
<td>*Triazolam</td>
<td>1978</td>
<td>409</td>
<td>7</td>
</tr>
</tbody>
</table>

Data lock point 22 December 2004
*There are currently no licensed products for these drug substances.

11 January 2005

Annex C

LIST OF RECOMMENDATIONS FROM NAO REPORT “SAFETY, QUALITY AND EFFICACY: REGULATING MEDICINES IN THE UK” (JANUARY 2003)

The Agency should:
(a) identify resources and work with others to fully implement and deliver its excellence in pharmacovigilance strategy, which is designed to make safety monitoring less reactive

(b) ensure transparency in the arrangements for preventing conflicts of interest in the Medicines Act bodies that advise Ministers

(c) continue to work to identify what improvements to medicines labelling and information leaflets can be made in the UK within existing legislation, building new guidelines for industry and involving the public

The Department and the Agency should:
(a) ensure transparency in the arrangements for preventing conflicts of interest in the Medicines Act bodies that advise Ministers

The MHRA Pharmacovigilance Strategy has been accepted as the basis for the development of a collaborative European Risk Management Strategy capable of achieving high standards of protection of public health in relation to all medicines regardless of route of authorisation. UK is playing a leading role in co-ordinating the roll-out of the strategy designed to make best use of the Community resource for pharmacovigilance.

A revised policy on interests has been developed which will apply to the chairmen and members of the restructured advisory bodies when they are appointed in the autumn 2005. We are currently undertaking a public consultation on our proposed policy (MLX316) but we expect that that in the future the chairmen and members of the new Commission and the committees that advise on homoeopathic products and herbal products will not be permitted to hold current financial interests in the industry producing products on which that committee advises. All other interests, including those of immediate family, will have to be declared and will be published annually.

Following the publication of the NAO Report, the CSM made recommendations on how medicines labeling might be improved within the current regulatory framework. Guidance was published by the MHRA in March 2003. [Best Practice Guidance on the Labeling and Packaging of Medicines (BPGLPM) available at www.mhra.gov.uk]. Improvements to medicines labeling are already becoming apparent in the marketplace as medicines manufacturers embrace the principles of best practice.
Since then, the MHRA and CSM have set up an Expert Working Group, under lay chairmanship, to advise on steps to improve the quality of PILs supplied with medicines. It includes members from a range of backgrounds, including patient groups. The work-plan includes the production of guidance on risk communication and addressing issues of access. The Group has also considered specific patient information leaflets, including the results of a focus group hosted by the MHRA for a particular product.

Importantly, the UK has implemented early changes to UK law on the requirement for user testing of patient information resulting from the review of European law designed to accelerate improvement of the quality of information.

The MHRA is also committed to delivering pilots of patient reporting of suspected adverse drug reactions which also offers the potential for improvements to patient information though a clear understanding of the patient perspective.

(d) build on actions already taken to ensure that the Drug Alert distribution system for recall of defective medicines across the UK reaches all appropriate health professionals, especially in the light of widened prescribing powers

(e) continue to inform the public giving higher profile to the risks of purchasing Prescription-only medicines on the internet and publicise its work in this area, subject to the need to avoid jeopardising the Agency’s covert investigation activities

(f) consider whether its public profile is sufficient to enable it to fulfil effectively that part of its mission involving the provision of information that contributes to the safe and effective use of medicines and consider in what ways this profile can be strengthened

(g) build on its existing regional networks, and work with others, such as hospital and community pharmacists and consultants, to disseminate key information on medicines safety more effectively to health professionals including GPs

The drug alert system involves distribution of alerts by fax to a list of NHS and other contacts that is updated on a regular basis. In order to validate the system contact is made at random with recipients of drug alert letters to confirm receipt and clarity. A formal system of six-monthly checks on all recipients is to be introduced by end 2004-05 as part of the continual review of the quality management system.

Enforcement and Intelligence staff continue to be proactive in communicating the risks of purchasing prescription-only medicines via the Internet and to take part in national and international forums where these issues are discussed. A strategy to inform the public more widely will be further developed with the Director of Communication when he is in post. The forthcoming creation for a separate Group to manage the Enforcement and Intelligence work of the Agency will give this work a higher profile.

The management of the newly created MHRA were aware of the changing context of their work and the need to ensure that public health messages were received by stakeholders. Accordingly, in December 2003, the Agency commissioned a major study of its external profile involving 27 external stakeholder interviews, an online survey of health and social campaigners and an internal consultation programme.

The Review has been a key part of the MHRA’s strategy to increase its profile. The MHRA’s communication aims, as defined in the report are both to ensure that day to day messages get through and are heard by those who need to hear them, and that in the long term, patients and carers become more aware of the risk benefit balance in medicines and devices.

The communications strategy will be spearheaded by a new Director of Communications who takes up post shortly.

Following the Independent Review of Access to the Yellow Card Scheme the MHRA is currently considering how to optimise local networks to enhance communication of drug safety issues—in both directions. The Agency has made strenuous efforts to increase the effectiveness on its communications of drug safety issues, including by using the Public Health Link quickly to convey safety information to all health care professionals and by ensuring patient focussed information is available on the MHRA website and through NHS Direct and NHS Direct online.
The Department and the Agency should:
(h) work with Royal Colleges and other professional organisations to integrate a greater knowledge of medicines regulation and surveillance into health professionals’ training

This recommendation is closely connected to the work of the (yet to be formed) Communications Division and, while there is no formal programme in place, this issue is being actively discussed with the Academy of Royal Colleges. Three issues have been raised with them: how the work of the Agency in regulation of medicines and devices can be better appreciated by undergraduate and postgraduate medical staff; whether the roles and responsibilities of the Agency could be incorporated into the teaching curricula; how the importance of adverse reaction reporting can be reinforced within the medical culture. Agency staff lecture to pharmaceutical physicians at their Diploma course, and are involved in setting questions for examinations and marking them.

The Agency should:
(i) continue its client survey work across all services to industry and publish details of how it has responded to feedback

Client survey work continues to be done mainly by the Trade Associations representing the industry we regulate. The results of this survey work has been disseminated within each trade body but not, for example, published on our website.

The Department and the Agency should:
(j) ensure where necessary that the Department’s and the Agency’s objectives are better integrated

The NAO report drew attention in its paragraph 1.11 to the Department’s NHS Plan set against corresponding Agency work which was underway at the time but not represented in the Agency’s objectives. Paragraph 1.11 highlighted four themes—overlapping those of Figure 5—not represented in Agency objectives. All four of those themes subsequently had objectives published in the current MHRA Business Plan for 2004–05 (referenced as H12; K6, K7, H18, H22 and H24; H10; H20). The first two items in Figure 5 also have objectives for 2004–05 (H3; H18). The Agency continues to be mindful of the Department’s objectives when proposing its own to Ministers.

(k) identify clearly for stakeholders and managers the Agency’s key performance objectives, ensuring that they reflect the full breadth of its functions

The 2004–05 Business Plan, published for all stakeholders and Agency staff to see, contains 46 objectives, 12 of them key targets. With the diversity of work within the Agency, it is not possible for 12 key targets to reflect the full breadth of function. But the 46 objectives reflect most of the breadth.

(l) examine the scope to adopt performance indicators which measure progress towards outcomes, rather than simply outputs

As the NAO report conceded (paragraph 1.13), this is difficult. An output is something produced by the Agency usually completely within its control. The Agency understands an outcome to be something desirable that usually happens in the world outside the Agency, subject to the Agency’s influence but also subject to countervailing influences from other parties, for example other Member States of the EU. It is inappropriate to publish targets for such outcomes, for the Agency could not be fully accountable for their fulfilment.

There were several discussions within the Agency during 2004 which identified desirable outcomes for pieces of the Agency’s work, and studies of the relationships between activities, outputs and outcomes. That has led to clearer thinking about the Agency’s role and its activities in support of its aims, but not yet to any systematic set of performance indicators measuring progress towards outcomes. There are nevertheless some such indicators. Several of the Agency’s targets for 2004–05 have them, though none are quantitative. Key target 3, for example, has an indicator in the development and agreement of a communications strategy, to fulfil the desirable outcome of a better-informed public. The concept of outcomes in now embedded in the Agency’s thinking and discussions on how to extend that concept will continue.
(m) ensure, when setting objectives for the new Agency that, in achieving the dual objectives of protecting the public and providing a service to industry, potential conflicts of interest are minimised and effectively managed.

The Agency should:
(n) review the strategic plan to ensure that the Agency can continue effectively to protect UK public health within the changing European regulatory environment.

This encompasses legislative change, maintaining standards of scientific quality and representing national interests. The changes to the EU regulatory system proposed by the European Commission and the new herbal directive have been negotiated and we are currently transposing the provisions into UK law to come into force end of October 2005. The Agency’s strategic approach is to ensure that it continues to play a leading role in the revised EU regulatory system by ensuring it has access to high quality scientific resources. This ensures that MHRA makes appropriate decisions to protect UK public health. The UK is seen as a leading Member State in the EU medicines regulatory system and our experts make a significant contribution to the EU regulatory system. Industry continues to be attracted to using MHRA rather than some other regulatory authorities where they have a choice because of the high quality of our assessments. The Agency’s overall objective is to ensure that wherever possible UK experts are appointed to EU scientific committees and make a key contribution in support of public health protection.

(o) implement a permanent cost and time recording system to allow continuous review of its costs against income streams.

This has been implemented as part of the Agency’s Information Management Strategy, a major programme to develop new ways of working supported by a new, integrated, IT structure. All members of staff with access to the Sentinel (the MHRA’s new system) participate in the process.

APPENDIX 48

Further letter from the Chairman, Medicines and Healthcare Products Regulatory Agency to the Clerk of the Committee (PI 124B)

Thank you for your letter of 21 February. I am pleased to answer the questions you set in that letter.

Question 1

Please will you send the Committee copies of all papers relating to the EWG report tabled at the meeting of the CSM held on 25 November and full minutes relating to this agenda item.

I am enclosing the papers which relate to the EWG (Annex A) that were tabled at the meeting of 25 November and the minutes of that meeting. Other papers were discussed under this agenda item but were not tabled. We can provide these if required.

All data considered by the EWG was not included in the final report . . . is the MHRA intending to publish or make publicly available all the evidence on which the EWG based its conclusions?

The report of the Expert Working Group contains the evidence which formed the basis for the conclusions of the Group. In the 18 month period of the review the Expert Working Group considered a large number of analyses and assessments of data from different sources. It was not possible to include every piece of data in the final report, which was designed to be a readable and accessible document for both health professionals and patients. Therefore the data provided in the report was that on which the key decisions were based. The MHRA will, subject to any relevant exemptions in the Freedom of Information Act, make available on request the full data and assessments considered by the EWG.
On the subject of efficacy, the EWG’s remit did not extend to re-evaluation of the efficacy of these products, although the risks were considered in the general context of the benefits. The EWG specifically looked at the balance of risks and benefits with increasing dose of SSRIs and the efficacy and safety data reviewed are included in the final report. One patient group where the lack of evidence for efficacy had a fundamental impact on the balance of risks and benefits of the products was in paediatric use. Therefore the efficacy data for children is included in the final report.

**Question 2**

**The Agency communications strategy**

As requested, I am enclosing a copy of the MHRA Communications Review conducted by Stonehenge, the public relations firm appointed after a procurement exercise launched in late 2003.[117] The Report, entitled “A Case for Change” was presented to the Agency in April 2004. The Report also contains the Patient View Report at Annex C. I am also enclosing as requested the extracts from the minutes of the Agency and Executive Boards where this issue was discussed (Annex B). Should the Report be published with the evidence of the Committee, I would be grateful for the time to ensure that anyone named individually in the Report is happy for their name to appear. I have also removed Appendix E as this is a comparative study of the press functions of other Agencies not within the remit of this Inquiry.

Stonehenge’s report was comprehensive and extremely detailed. It provided the basis for the development of short and long term plans for our communications policy. Given the detail the Report contained, and the relatively low base from which the Agency started its work, much progress has been made.

Recruitment of a Director of Communications started almost immediately. However, as with any senior appointment, the process and the notice period which followed the successful appointment, has meant that our new Director of Communications was only able to take up post at the end of January 2005. The new Communications Division, consisting of existing and newly recruited staff under Simon Gregor’s direction will come into being on 1 April 2005. However, an internal working group set up before Mr Gregor’s arrival has progressed a number of issues, including an audit of all internal and external publications, the preparation for the launch of a procurement exercise seeking advice on the “re-branding” of these documents using an agreed Agency format and livery, the recruitment of a media relations team and the development of the Agency website. The results of these activities will be visible within the next few months. For example, the Agency will be taking over responsibility for its own press and media relations in mid March (work previously carried out on our behalf by DH media centre). The new website, with considerable additional functionality, will be launched in the early Autumn of 2005. In the longer term, the Agency is planning to work with key stakeholders in raising a better awareness of risk literacy among patients and healthcare professionals.

**Question 3**

**Increasing the patient voice in regulation**

The MHRA seeks to involve patients as stakeholders in the regulatory environment in a number of ways, including formally, through the Committee on Safety of Medicines and its sub-committees and in less formal ways across the range of its work.

In 2004 you may be aware that the Agency consulted on the reform of the Medicines Act Advisory Bodies. The Agency’s restructuring plans will include greater patient participation in the regulatory process. There will be two lay members on the on the Commission for Human Medicines and the Committees set up under section 4 of the Medicines Act. The Agency is also establishing Expert Advisory Groups to advise the Statutory Committees, and each of these will have two patient members. The lay and patient members will meet independently and regularly as a patient forum. The new committee structure will be in place for the Autumn of 2005.

As you also will be aware, in 2003 Ministers commissioned an independent review of access to the Yellow Card Scheme Scheme, which looked in particular at transparency issues. This publication is also available on the MHRA’s website and gives examples of some important early warnings of new ADRs identified through the yellow card scheme. In May 2004, the Review concluded that there should be greater access to Yellow Card data to ensure the full potential of the data was realised, and proposed a system for facilitating this. Of particular note, is the fact that recommendation in the report on direct patient reporting to the Scheme was accepted immediately and, after piloting several different options, launched a direct patient reporting scheme in January this year.

The MHRA has been proactive in ensuring that leaflets, labels and packaging meet patients’ needs for clear and authoritative information, especially in the recent Review of EU legislation. Labelling of medicines will have to include the name, strength and pharmaceutical form in Braille and changes to the order of the information in the PIL will be required. The Review importantly introduces a requirement for user testing.

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117 Not printed.
which should help to ensure improvements to the PIL to make them more understandable for patients. Guidance on user testing is being developed by the MHRA, supported by advice from a CSM Working Group on Patient Information. The Group is also advising on possible revisions to the European Guideline on Readability. This will all involve patient consultation and be of direct benefit to patients.

In addition, the Agency is seeking to be more transparent in its working ways of working. The Agency now publishes details of all complaints received about medicines advertising and the outcome of its investigations as well as being more open about how such decisions are made. This transparency in decision making has also extended to drug safety issues where the Agency has released previously unpublished data. The MHRA has published summaries of clinical trial data to support key communications on drug safety when it has been in the public interest to do so. Summaries of clinical trial data have been released in respect of SSRIs used in children as well as for anti-psychotics (risperidone) used in the treatment of dementia. A full and open consultation process is also carried out before a decision to re-classify a medicine (from Prescription Only to a Pharmacy or General Sales List medicine). Patient groups and charities are included on this consultation list.

Question 4

Connections with Smithkline Beecham

From 1987 until the end of 1992, my advice was sought at irregular intervals by Beecham Pharmaceuticals, later to become Smith Kline Beecham, on general issues in the field of clinical pharmacology. My advice was not sought on specific drugs and did not involve discussion on Seroxat. From 1992 until 1997, I sat on a formal committee of Smith Kline Beecham which met regularly to discuss broad scientific areas of drug development. Specific products were not discussed. At the meeting of SCOP on 24 February 1998 there was a general discussion of SSRIs which led to a decision to set up a review of the adverse effects of the drug class of SSRIs and I felt it appropriate to chair that meeting. At the meetings on 24 September and 22 October, there was discussion about specific SSRIs, including Seroxat and it was not appropriate to take part in these discussions, in spite of the fact that I had left the Scientific Advisory Committee of Smith Kline Beecham. My actions were taken in consultation with the then Chairman of the Committee on Safety of Medicines and were fully in line with the procedures in place at the time.

Question 5

At Q797, you expressed the view that “when a patient starts to take SSRIs, there is a period of time before the benefit takes place and in that time . . . the patient is at a great risk of suicide.” . . . The Committee has not been able to identify any such interpretation in the EWG final report.

My response to that question was not meant to imply that there was no possibility of an adverse effect of treatment increasing the risk of suicidal behaviour. The EWG considered these issues very carefully and was unable to reach a firm conclusion as to whether the increased risk of suicidal behaviour seen particularly in early treatment was due to the antidepressant treatment, the underlying disease, or part of the early recovery of depressive illness.

Turning to Professor Healy’s analysis of events on withdrawal of paroxetine, the advice of the EWG was sought on the calculations and conclusions drawn by Professor Healy from the tables previously supplied to them. The Group considered this an extremely important issue. Other analyses and data sets considered by the EWG had not indicated an increase in suicidal events on withdrawal of Seroxat in adults, although an increase in suicidal thoughts and self-harm was seen in paediatric clinical trials on withdrawal of Seroxat. The EWG advised that certain limitations of the data, as presented by Professor Healy, had to be taken into account. In particular, the analysis did not take into account differences in the at-risk period and follow up between the populations on Seroxat and placebo. This is important when focussing attention on small periods of time at the end of clinical trials because by this time follow up may differ substantially between groups. In addition the denominator figures used in the calculations pertain to those randomised to start periods of time at the end of clinical trials because by this time follow up may differ strongly between patient groups. In addition the denominator figures used in the calculations pertain to those randomised to start periods of time at the end of clinical trials because by this time follow up may differ strongly between patient groups. In addition the denominator figures used in the calculations pertain to those randomised to start periods of time at the end of clinical trials because by this time follow up may differ strongly between patient groups. In addition the denominator figures used in the calculations pertain to those randomised to start periods of time at the end of clinical trials because by this time follow up may differ strongly between patient groups. 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In addition the denominator figures used in the calculations pertain to those randomised to start periods of time at the end of clinical trials because by this time follow up may differ strongly between patient groups.

The EWG considered that, although inconclusive, the data supported the need for close monitoring of patients during taper and withdrawal of Seroxat, which was a key recommendation of the EWG. In order to fully clarify this issue the EWG advised that a large placebo controlled double-blind randomised trial of withdrawal events would be required.

You have asked for the best estimate of the proportion of SSRIs prescribed for mild and mild-moderate depression. As part of the EWG review of the safety of SSRIs, the MHRA commissioned a study using the General Practice Research Database (GPRD). The aim of the study was to investigate whether there was an association between antidepressants and self harm in patients with first time treated depression. As part of this study two psychiatrists carried out a classification of the depression diagnoses entered by the GPs into mild, moderate and severe depression. It should be noted that patients with severe recurrent depression
are likely to be under-represented in this dataset as it considers first time treated depression and is based in primary care. Furthermore, the classification was carried out without seeing the patients and therefore relies on the way that GPs use the coding system for entering diagnoses into GPRD which is known to be variable.

In this study, approximately 95% of patients with first time treated depression had diagnoses consistent with mild or moderate depression. This proportion was the same across SSRIs, TCAs and other antidepressants with no suggestion that SSRIs were preferentially prescribed in mild depression. This information is available on the website of the British Medical Journal as supplementary material to the published GPRD study (Martinez et al BMJ 2005;330:389).

**Question 6**

At Q798, you were asked if the MHRA/CSM statement, that SSRIs were effective medicines in the treatment of depression, required some qualification, in view of the lack of evidence of efficacy of the products in treating mild depression. Would you address this point . . .? Could you specifically advise the Committee why no restriction on the use of SSRIs was proposed in the Summary of Product Characteristics?

SSRIs are indicated for treatment of depressive illness. It is for the individual practitioner, informed by clinical guidelines, to consider whether the risks and benefits of treatment are appropriate for an individual. The recent NICE guidance on treatment of depression concludes that antidepressants are not recommended for the initial treatment of mild depression, because the risk-benefit ratio is poor. However the guidance states that the use of antidepressants should be considered in patients with mild depression that is persisting after other interventions. The currently licensed indications reflect the patient population studied in clinical trials and allow for the individual prescribing judgement necessary in each case.

**Question 7**

In relation to paroxetine withdrawal reactions, you wrote in your letter of 4 February that, “the MHRA has never indicated that withdrawal was rare . . .” the Committee would wish to know if the statement in your letter applies also to the MCA. Specifically, the Committee invites you to comment on the 1996 paper published by MCA/CSM staff that concluded “overall, symptoms due to stopping an SSRI are rare . . .”.

You ask whether the statement “the MHRA has never indicated that withdrawal was rare” also applies to the MCA in the light of the paper by Price et al published in the British Journal of Clinical Pharmacology in 1986. I can confirm that this is the case. The conclusions of this paper were based purely on spontaneous reporting, a data source which has limitations for the assessment of incidence of an adverse reaction and particularly so for withdrawal reactions. Neither the MCA nor the MHRA considered spontaneous reporting alone a sufficiently robust data set to form regulatory decisions or prescribing advice on the incidence of withdrawal reactions.

You have asked that I comment on your observations relating to the incidence of withdrawal reactions. My comments on each observation are provided below as numbered in your letter.

**Lack of evidence for a taper regimen**

(a) We fully accept that clinical trial data for Seroxat do not provide direct evidence that gradual withdrawal of an SSRI will reduce the incidence of withdrawal symptoms.

(b) The recommendation that the dose should be tapered gradually at the end of treatment is based largely on the knowledge of the pharmacology of these products and detailed descriptions of tapering regimen described in individual case reports from patients and prescribers. In addition, the clinical trial data for venlafaxine and sertraline provide some evidence to suggest that tapering of dose may be beneficial.

**Failure to warn about incidence of withdrawal reactions**

(c) At the time of licensing, data from 222 patients withdrawn abruptly from Seroxat did suggest that some patients experienced events on withdrawal. This information was included in the product information for Seroxat from the time of licensing. The data sheet stated that “As with many psychoactive substances it may be prudent to discontinue therapy gradually because of the possibility of discontinuation symptoms such as disturbed sleep, irritability and dizziness.”

In responding to this point it may be helpful if I provide a brief description of the paper published by Price et al in the British Journal of Clinical Pharmacology in 1996. It was a comparison of spontaneous reporting data for four SSRIs. The paper was not intended to be a review of all available data sources and did not include any clinical trial data. It did not reflect any agreed position of the MCA or CSM and was not a document on which regulatory decisions were based.
The paper by Price et al clearly describes the biases and confounding variables which influence the interpretation of spontaneous reporting data. The authors highlighted data which suggested that paroxetine was associated with a higher frequency of reporting of withdrawal reactions than other SSRIs. Further information on the nature of withdrawal reactions with paroxetine was specifically sought through a retrospective survey of doctors who had reported such reactions through the Yellow Card scheme. In relation to severity, the paper includes the following information “21% of reactions were said to be mild, 58% moderately severe, and 21% severe.”

The review which was considered by SCOP and CSM in 1998 looked at all sources of data for all the SSRIs and related antidepressants, including unpublished clinical trial data. From review of all available data the CSM concluded that “to date, studies had not been carried out of an appropriate design to allow an estimation of frequency of withdrawal reactions”. As a result of this review the CSM advised that product information for all SSRIs and related antidepressants should contain warnings about withdrawal reactions. The CSM further advised that any reference to withdrawal reactions being “rare” should be removed from the product information for SSRIs (it was present in the product information for fluvoxamine and sertraline only). This review did not contradict the data on paroxetine which was available at the time of licensing—the paper included these data and resulted in strengthened warnings in product information on the basis of accumulating post-marketing data.

The estimate of withdrawal reactions added to paroxetine product information in 2003 was based on more recent trials which included a taper phase during which events on withdrawal were systematically recorded. These trials indicated that 25% of patients experienced symptoms on stopping treatment and 15% of those experienced symptoms described as severe. In the same trials, 15% of patients experienced symptoms on stopping placebo and 9% of those experienced symptoms described as severe. The most common events reported in clinical trials as occurring on stopping both paroxetine and placebo were similar and included dizziness, nausea, insomnia, anxiety and headache.

Doubts about evidence for efficacy of paroxetine in relapse prevention

(d) In responding to this point I would like to draw your attention to a systematic review which looked at evidence for efficacy of antidepressants in relapse prevention in 31 randomised trials (including that by Montgomery and Dunbar) and was published in The Lancet in 2003 (Geddes et al, Lancet 2003; 361:653–51). The authors took into account the possibility that withdrawal effects associated with stopping active treatment could inflate the effectiveness of the active treatment in prevention of relapse. However their review did not identify an excess of cases of “relapse” within a month after discontinuation, which argued against this possibility.

The recent NICE guidance on treatment of depression concludes that responders to medication, who have had multiple relapse, should stay on medication to avoid relapse, with appropriate re-evaluation of treatment taking into account their individual risk factors.

Question 8

At Q800, you stated, in relation to paroxetine, that, “There was additional, clear information for the patients”. The first reference to withdrawal symptoms appeared in the patient information leaflet five years after the introduction of Seroxat. The 1996–97 Seroxat patient information leaflet stated that withdrawal symptoms were “unusual”. Please could you clarify and explain the basis on which withdrawal symptoms were described as “unusual”.

There was no requirement for a medicine to have a patient information leaflet when Seroxat was first licensed. At that time the warning about withdrawal reactions was in the information for prescribers.

The first patient information leaflet for Seroxat after patient information leaflets became a requirement stated, “Some people find that if they suddenly stop taking these tablets, they feel dizzy, shaky, sick, anxious, confused or have tingling sensations. They may also have difficulty sleeping and vivid dreams when they do sleep. But these symptoms are unusual and generally disappear after a few days. To avoid these symptoms, your doctor may tell you to take smaller doses or to spread doses further apart before you stop taking the tablets altogether”. This wording was considered generally to reflect the wording in the summary of product characteristics at the time which stated that “Symptoms including dizziness, sensory disturbance (e.g. paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt discontinuation of Seroxat”. They are usually self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore recommended that when antidepressive treatment is no longer required, gradual discontinuation by dose-tapering or alternate day dosing be considered”. The word “unusual” has no specific regulatory meaning.