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The Influence of the Pharmaceutical Industry

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The Health Committee

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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).

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Summary

Medicines contribute enormously to the health of the nation. The discovery, development and effective use of drugs have improved many people's quality of life, reduced the need for surgical intervention and the length of time spent in hospital and saved many lives. Our consumption of drugs is vast and is increasing. About 650 million prescriptions are written each year by GPs alone. Medicines cost the NHS in England over £7 billion every year, 80% of which is spent on branded (patented) products. The industry which has produced these drugs has understandably been described as "world class and a jewel in the crown of the UK economy". It is the third most profitable economic activity after tourism and finance. While the United States is the industry's largest market and is the site of most drug research and development, the UK industry, nevertheless, has a remarkably impressive record. It is a centre of world class science, accounting for 10% of global pharmaceutical R&D expenditure. It has been estimated to fund 65% of all health-related R & D in the UK.

However, there are disadvantages in the increasing use of and reliance on medicines. The inappropriate or excessive use of medicines can cause distress, ill-health, hospitalisation and even death. Adverse drug reactions are responsible for about 5% of all admissions to hospitals in the UK.

The interests of pharmaceutical companies and those of the public, patients and the NHS often overlap but they are not identical. For the industry, medical need must be combined with the likelihood of a reasonable return on investment. An effective regulatory regime to ensure that the industry works in the public interest is essential. Unfortunately, the present regulatory system is failing to provide this. The system is at times frustrating, arguably with excessive attention to unimportant detail, but it is, as we describe below, insufficiently effective.

The Department of Health has for too long optimistically assumed that the interests of health and of the industry are as one. This may reflect the fact that the Department sponsors the industry as well as looking after health. The result is that the industry has been left to its own devices for too long. It may be relevant that this is the first major select committee inquiry into the pharmaceutical industry for almost one hundred years – the last was undertaken by the Select Committee on Patent Medicines which reported in August 1914.

The consequences of lax oversight is that the industry's influence has expanded and a number of practices have developed which act against the public interest. The industry affects every level of healthcare provision, from the drugs that are initially discovered and developed through clinical trials, to the promotion of drugs to the prescriber and the patient groups, to the prescription of medicines and the compilation of clinical guidelines. We heard allegations that clinical trials were not adequately designed – that they could be designed to show the new drug in the best light – and sometimes fail to indicate the true effects of a medicine on health outcomes relevant to the patient. We were informed of several high-profile cases of suppression of trial results. We also heard of selective publication strategies and ghost-writing. The suppression of negative clinical trial findings leads to a body of evidence that does not reflect the true risk:benefit profile of the medicine

in question. Guidance produced by NICE and others relies on the published evidence. If all the evidence is not published, or if negative findings are hidden, accurate guidance cannot be issued and prescribers cannot make truly evidence-based decisions.

Once licensed, medicines are intensely promoted to prescribers. The very high costs of developing a new drug make it vital that a company recoups its costs as quickly as possibly after licensing. Coupled with company-sponsored information from medical journals and supplements, 'medical education' materials, advertisements and sponsorship to attend conferences, workshops and other events, it is little wonder that prescribing practices are affected. GPs are particular targets; they have more prescribing freedom than hospital specialists and their prescribing practices are not limited to hospital formularies. Promotion of medicines to patients and links between drug companies and patient organisations may add to this problem, leading patients to demand new drugs from their doctors. The problem is far less to do with any particular activity; rather the volume may distort prescribing practice. At the heart of the problem may be the trend for the industry to become ever more driven by its marketing force.

The most immediately worrying consequence of the problems described above is the unsafe use of drugs. Over-prescription of the COX-2 inhibitors, Vioxx and Celebrex, has been linked to thousands of deaths and many more cases of heart failure. These case illustrate a series of failures. Manufacturers are known to have suppressed certain trials for these drugs in the US and may have done the same in the UK. In addition, there were inadequacies in the licensing and post-marketing surveillance procedures and excessive promotion of the drugs to doctors.

What has been described as the 'medicalisation' of society – the belief that every problem requires medical treatment – may also be attributed in part to the activities of the pharmaceutical industry. While the pharmaceutical industry cannot be blamed for creating unhealthy reliance on, and over-use of, medicines, it has certainly exacerbated it. There has been a trend towards categorising more and more individuals as 'abnormal' or in need of drug treatment.

The industry is by no means solely to blame for the difficulties we describe. The regulators and prescribers are also open to criticism. The regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), has failed to adequately scrutinise licensing data and its post-marketing surveillance is inadequate. The MHRA Chairman stated that trust was integral to effective regulation, but trust, while convenient, may mean that the regulatory process is not strict enough. The organisation has been too close to the industry, a closeness underpinned by common policy objectives, agreed processes, frequent contact, consultation and interchange of staff. We are concerned that a rather lax regime is exacerbated by the MHRA's need to compete with other European regulators for licence application business.

Inappropriate prescription of medicines by GPs is of particular concern. Some have prescribed SSRIs, for instance, on a grand scale. This is in part due to inadequacies in the education of medical practitioners which has meant that too few non-specialists are able to make objective assessments of the merits of drugs and too many seem not to recognise how little is known about the properties of a drug at the time of licensing, particularly about its adverse consequences. However, many prescribers have behaved responsibly and with

restraint, which makes those who have not, all the more culpable. The constraints in place for hospital doctors do not apply to GPs. Drug companies are criticised for giving hospitality and recruiting 'key opinion leaders', but the prescribers must be equally to blame for accepting the hospitality and some 'key opinion leaders' for lending their names to work they did not produce, often for very considerable sums.

The Government, like the MHRA, has tended to assume that all is for the best. It states that there is no better alternative system. We agree: pharmaceutical companies will inevitably continue to be the dominant influence in deciding what research is undertaken and conducting that research, publishing it and providing information to prescribers. This does not, however, mean that no changes are required.

Our recommendations cover several areas of concern, in particular the licensing process. The key to improvement is greater transparency so that medical practitioners, experts and the public can make an independent assessment of the evidence. We welcome the industry's decision to establish a clinical register but it is important that it should be independent. We make recommendations to this effect.

Greater transparency is also fundamental to the medicines regulatory system. There has to be better public access to materials considered by the MHRA prior to licensing.

The aim of new drugs should be real therapeutic benefit for patients. Clinical trials should focus on using health outcomes that are relevant to patients. To achieve this we recommend better communication between the MHRA and companies early in the early stages of the development of a drug. Improvements in the post-licensing surveillance of medicines are also badly needed. This will require systematic appraisals of medicines.

We recommend that more research be undertaken into the adverse effects of drugs, both during drug development and medicines licensing. The Government should, as a matter of urgency, fund research into the costs of drug-induced illness.

We recommend that the MHRA find ways of ensuring greater restraint in medicines promotion, particularly soon after launch. There should also be strengthened guidelines requiring the declaration of links between pharmaceutical companies and patient groups.

In view of the failings of the MHRA, we recommend a fundamental review of the organisation in order to ensure that safe and effective medicines, with necessary prescribing constraints, are licensed.

It is extraordinary that there are stricter controls on hospital specialists prescribing than on GPs. We recommend tougher restrictions be placed on what non-specialists can prescribe and greater vigilance to guard against excessive or inappropriate prescribing. Nurse and pharmacist prescribing will need to be carefully monitored. Doctors, in particular 'key opinion leaders', should be obliged to declare significant sums or gifts they receive as hospitality. Professional bodies should maintain a register of these declarations.

Government has rightly sought to assist industry, but it needs to do more to help pharmaceutical companies conduct research. They have to cope with confusing ethics approval procedures as well as relatively few adequately trained medical researchers or specialist research facilities. The NHS should build on the success of the National Cancer

Research Network to facilitate research for other treatments.

The Department of Health has not only to promote the interests of the pharmaceutical industry but also the health of the public and the effectiveness of the NHS. There is a dilemma here which cannot be readily glossed over. The Secretary of State for Health cannot serve two masters. The Department seems unable to prioritise the interests of patients and public health over the interests of the pharmaceutical industry. We therefore recommend that sponsorship of the industry[1] pass from the Department of Health to the Department of Trade and Industry.

The UK pharmaceutical industry is in many ways outstanding. We trust that our recommendations will not only protect health but also help the industry. It is not in the long term interests of the industry for prescribers and the public to lose faith in it. We need an industry which is led by the values of its scientists not those of its marketing force. In making our recommendations we were very impressed by the comments of Sir Richard Sykes:

"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."

[1] Now known as "responsibility for representing the interests of the industry"

1 Introduction

"After careful consideration of the evidence laid before them your Committee find:

(1) That there is a large and increasing sale in this country of patent and proprietary remedies and appliances and of medicated wines.

(2) That these remedies are of a widely differing characters, comprising (a) genuine scientific preparations; (b) unobjectionable remedies for simple ailments; and (c) many secret remedies making grossly exaggerated claims of efficacy…

(3) That this last-mentioned class (c) of remedies contains none which spring from therapeutical or medical knowledge, but that they are put upon the market by ignorant persons, and in many cases by cunning swindlers who exploit for their own profit the apparently invincible credulity of the public.

(4) That this constitutes a grave and widespread public evil…"[2]

Select Committee Report on Patent Medicines, 1914

1. The consumption of medicinal drugs[3] is vast and is increasing. Purchase of medicines currently accounts for about 12% of the NHS budget. 650 million prescription items were dispensed in England in 2003, an average of 13.1 prescription items per head of population. This represents a 40% increase over the previous decade. The cost[4] of prescriptions dispensed in England has risen remorselessly with year-on-year increases well above inflation. In 1993 the cost was £3.1 billion. In 2003 it was £ 7.5 billion, an increase of 9.7 per cent or 6.4 per cent in real terms on 2002.[5] In addition, £1.8 billion was spent on over-the-counter medicines.[6]

2. The drugs are produced by a very large and successful industry. It employs 83,000 people directly and many more indirectly, and makes a huge contribution to the balance of trade each year. Overall, the industry represents the country's third most profitable economic activity, after tourism and finance. It is of great importance to the UK economy.

3. Drugs have produced many benefits. They have an important, sometimes vital, role to play both in saving lives and improving the quality of life. No one should take these benefits for granted: at some time or other, most people need drugs and are grateful for them. Our recent report on venous thromboembolism underlines this Committee's recognition of the need for appropriate pharmacological interventions.

4. However, the increasing consumption of drugs has also brought disadvantages. Two stand out. One is a syndrome which has been described as 'medicalisation', that is an

---

[2] Report from the Select Committee on Patent Medicines, Session 1914, HC 414.

[3] The terms 'medicine' and 'drug' are used interchangeably throughout the report.

[4] Net ingredient cost

[5] Prescriptions dispensed in the community. Statistics for 1993-2003: England. http://www.publications.doh.gov.uk/prescriptionstatistics/index.htm

[6] Figures provided by PAGB

unhealthy reliance on, and over-use of, medicines – the view that there is a pill for every ill. There is a strong and growing tendency to believe that life's problems are best dealt with as medical conditions. Diagnostic labels are readily applied and drug intervention follows. People hope for health solutions, and come to rely on the inspiration of 'get well' messages from commercial and professional sources rather than focus on sometimes grim realities. Medicalisation could lead to unsustainable demand on the NHS, a confused vision of how good health is maintained and a failure to ensure preventative public health measures are at the forefront of health policy.

5. The second disadvantage arises from the first. Excessive use of medicines leads to increased exposure to the risk of drug-induced illness and harm. No figures for the economic burden of drug-induced illness yet exist, but it is feared that it could amount to several billions of pounds per year. The adverse drug reactions, which account for some 3% to 5% of all hospital admissions in the UK, cost in the order of £500 million per year. No estimates have yet been made of the presumably greater cost of adverse drug reactions which do not lead to hospital treatment at all, nor of those experienced by perhaps 15% of all hospitalised patients.

6. These problems are not caused by the pharmaceutical industry, but do reflect its influence. People have been taking ineffective and harmful medicines for centuries. However, there is reason to fear that the industry has positively nurtured anxieties about ill-health. The fundamental problem, it is alleged, is that the industry is increasingly dominated by pressure from its investors and the influence of its marketing force and advertising agencies rather than its scientists. The industry is hugely influential, affecting every aspect of the medical world, including prescribers, patients, academics, the media, and even the institutions designed to regulate it. Its influence in Parliament is extensive. The Annex lists the All-Party Groups the pharmaceutical industry supports. It is claimed that pharmaceutical companies encourage us to see ourselves as 'abnormal' and thereby requiring (drug) treatment. They have a powerful incentive to do so. The more people who see themselves as suffering from a medical condition, the larger the market and the greater the profits.

7. The timing of this Inquiry coincided with an investigation by the medicines regulator into the safety of the newer 'SSRI' antidepressant drugs, and we refer to these drugs to illustrate some concerns. Depression can be a severely disabling and life-threatening condition, when urgent treatment is needed, but only about 5% of all prescriptions are written for 'severe' depression, and about two-thirds are for forms of depression classified as 'mild'[7]– i.e. mainly for people who are unhappy and distressed by difficult situations and circumstances. Although it is often suggested that antidepressant drugs will help these people, there is no good evidence that they will. Most people prescribed SSRIs in such circumstances can expect modest benefits, but are exposed to substantial risks of harm.

8. Government has a dilemma: it has to balance the need to promote the competitiveness of this industry with the need to address health concerns and to promote the effectiveness of the NHS. The Department of Health has constantly to balance trade imperatives and

[7] Martinez C, Rietbrock S, Wise L et al. *BMJ* 2005;330:389, doi:10.1136/bmj.330.7488.389. See http://bmj.bmjjournals.com/cgi/content/full/330/7488/389

health priorities. This is a hard task. Sometimes, it means serving two masters at the same time.

9. In view of these concerns, in June 2004 we announced our decision to undertake an inquiry. Our terms of reference were as follows:

The Health Committee is to undertake an inquiry into the influence of the pharmaceutical industry on health policies, health outcomes and future health priorities and needs. The inquiry will focus, in particular, on the impact of the industry on:

- *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, including assessments of value for money*

In doing so, the Committee will examine the influence of the pharmaceutical industry on the NHS; National Institute for Clinical Excellence (NICE); regulatory authorities and advisory and consultative bodies; prescribers, suppliers and providers of medicines; professional, academic and educational institutions; the (professional and lay) press and other media; and patients, consumers, the general public and representative bodies.

10. The pharmaceutical industry includes companies which differ hugely in size, work in many different spheres, and do quite different things. There are giant international companies and medium, small and modest enterprises. The people who work for them may be engaged in research, academic medicine, clinical practice, production and quality control, public relations (PR), administration, law and more. Our main focus was on the companies that lead the industry, and on the driving forces behind them.

11. This was a major inquiry, but we acknowledge that we have not touched on every detail of what is an enormous subject. The written and oral evidence presented, however, allowed us to gain a strategic sense of the influence of the pharmaceutical industry and of the implications of its significance and impact.

12. We have taken oral evidence on nine occasions. We have heard from Ministers and officials from the Department of Health and the Department of Trade and Industry; health professionals and academics; the pharmaceutical industry; journalists; PR companies; patient organisations; medical charities; Phil Woolas MP and Paul Flynn MP[8]; NICE and

[8] Phil Woolas MP appeared as a trustee of the Beat the Benzos campaign. Paul Flynn MP has a long-standing interest in the activities of the pharmaceutical industry and submitted a memorandum detailing particular concerns.

the MHRA. We received well over 100 written memoranda. We would like to thank all who provided us with oral and written evidence.[9]

13. During the inquiry we made several visits. In Australia, in September, we had the opportunity to observe the operation of a different medicines regulatory system than exists in the UK. We were able to explore the benefits of their National Drugs Policy and also heard evidence regarding the regulatory mechanisms in New Zealand.[10] We received invaluable information from many experts. We much appreciated our visits to GlaxoSmithKline (GSK) and AstraZeneca, where we were able to inspect modern manufacturing plants. In December, we went to Brussels and met representatives from the Enterprise Directorate-General (DG), the Directorate sponsoring the pharmaceutical industry, who explained the role of the EU in drug regulation and sponsorship. Unfortunately, no representative from DG Sanco (responsible for health) could be present. We were also fortunate in being able to visit Pfizer at its impressive facilities in Sandwich. Finally, we went to the Use of Medicines Committee at University College Hospital, where we received a very useful briefing on how mechanisms can be put in place to ensure effective prescribing. We much appreciated the time that all the people we met on these visits gave us.

14. We are also very grateful for the expert guidance we received from our specialist advisers. They were: Professor John Abraham, Department of Sociology, University of Sussex; Professor Joe Collier of St George's Medical School; Professor Gerard Hastings, University of Stirling; Charles Medawar, Executive Director of Social Audit Ltd; and Dr Harriet Scorer, an independent consultant to the pharmaceutical industry.

15. The report is organised as follows. The next five chapters provide brief descriptions of the industry and the difficulties it faces, the process of developing and licensing a drug, the arrangements for controlling the industry and the control of access to medicines. Chapter 7 examines what level of influence the industry should have. Chapter 8 looks at the evidence we received about the industry's influence on key groups. Finally, we present our main conclusions and recommendations in Chapter 9.

16. This is the first major study of the pharmaceutical industry by a Select Committee since the Select Committee on Patent Medicines reported on 4th August 1914. We trust that it will not be another century before the next.[11]

2 The UK pharmaceutical industry

17. The pharmaceutical industry is a global enterprise. It is dominated by a few multinationals. The US is the industry's largest and most profitable market, and is the site

[9] Some of the written evidence is published in Volume 2 of the Report. Volume 2 also contains a list of unprinted written evidence which has been reported to the House but, to save printing costs, has not been printed. Copies will be 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.

[10] We received valuable written and oral evidence from Prof Les Toop and Dr Dee Richards from the University of Otago in Christchurch, New Zealand. We are very grateful to them for travelling to Melbourne to meet with us.

[11] Report from the Select Committee on Patent Medicines, Session 1914, HC 414.

of most drug research and development (R&D).[12] As such, its policies have the greatest impact on the industry's operations.

18. Nonetheless, Europe, and the UK in particular, provide a strong market for medicines and have traditionally been important sites for drug-related R&D. Two of the largest pharmaceutical companies, questioned as to the relevance of UK health policies to their global businesses, testified to the importance of the UK as a site for the marketing and development of medicines:

> **Dr John Patterson (AstraZeneca):** 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 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.
>
> **Mr Gray (GSK):** 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 [questions regarding the industry's reputation]. I think, therefore, we would take them extremely seriously.[13]

19. Both those involved in the UK pharmaceutical industry and its critics have given evidence of its strength and success. It is fifth largest in the world by total sales, representing 7% of world sales, after the US, Japan, Germany and France.[14] The UK is the third largest direct exporter of pharmaceuticals; has the third largest world trade surplus; and accounts for 10% of world pharmaceutical R&D expenditure. The pharmaceutical industry is an important employer and contributor to the economy of this country.[15]

20. The UK industry operates within a highly regulated environment. The way in which it undertakes research, produces, licenses and markets its products are all subject to a detailed regulatory system. In this chapter were discuss the industry. We later go on to look at systems for controlling it.

Research and development

21. R&D facilities in the UK are world-class and British-based companies have a long history of success in drug development. The pharmaceutical industry invests some £3.3 billion a year into R&D in the UK. Drug companies based in the UK employ 29,000 individuals in R&D, making it one of the largest employers of science graduates. The industry funds more healthcare-related research in the UK than every other source combined – six times as much as the Department of Health; five times as much as medical charities; eight times as much as the Medical Research Council (MRC) (See Figure 1).

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[12] PI 35

[13] Q719

[14] Information supplied by the House of Commons Library, based on 'UK Trade and Investment'

[15] PI 35

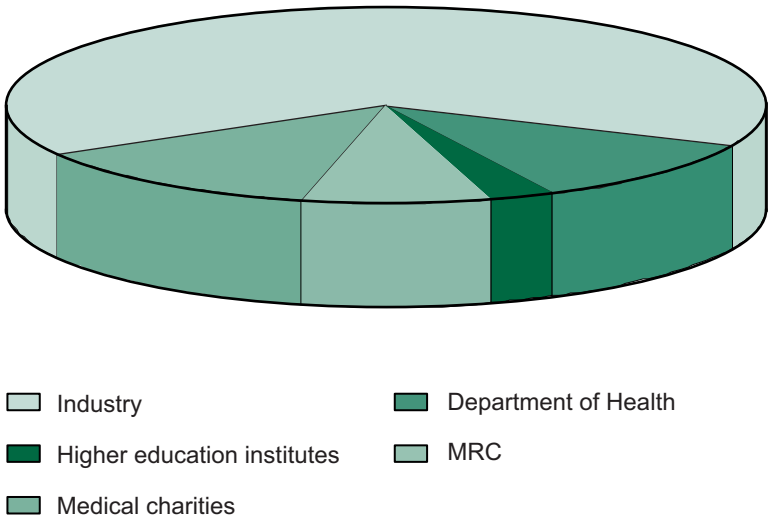

Figure 1. Funding of health-related R&D[16]

22. The pharmaceuticals sector conducts 65% of health-rated R&D, and accounts for around 40% of all industrial R&D expenditure in the UK, spending about £10 million each day. The leading UK companies in R&D are GSK, AstraZeneca, Pfizer, Eli Lilly, Wyeth, Roche, Merck Sharpe & Dohme and Novartis.[17]

23. The combination of a strong history and favourable environment means that the UK pharmaceutical industry 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.[18] This is more than half of the total pharmaceutical R&D investment in Europe as a whole (see Figure 2, below). Twenty-five of the world's leading medicines have their origins in this country, which is more than any country except the US.[19].

[16] Based on 2000 figures. PI 35

[17] PI 22

[18] PI 35

[19] PI 35

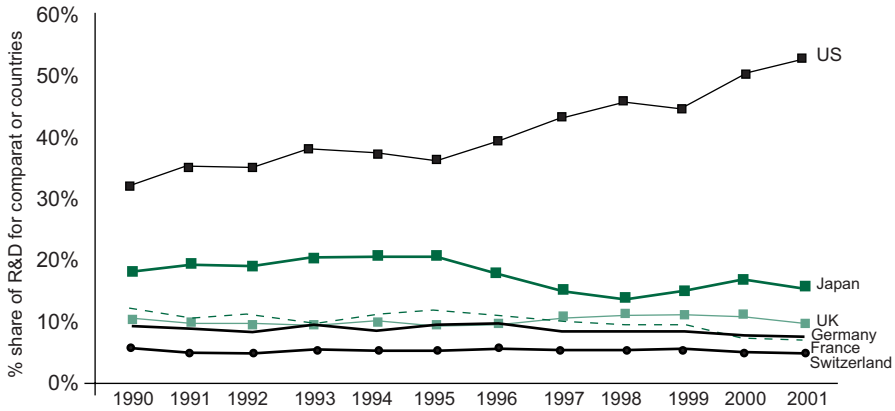

Figure 2. Comparison of share of global pharmaceutical R&D investment[20]

Medicines and health gains

24. The development of effective medicines has contributed significantly to the welfare of patients, over the last 50 years in particular. Examples include the development of vaccines against infectious diseases, the use of H_2-antagonists in the treatment of peptic ulcers and the discovery of AZT for the management of HIV/AIDS. The effective treatment of heart disease with clot-busting medicines and anti-hypertensive drugs has helped reduce related mortality rates by 40% in the last decade alone.[21]

25. According to the Association of the British Pharmaceutical Industry (ABPI), the UK pharmaceutical industry's representative body, improved treatments in 12 areas of serious illness since the 1950s have reduced hospital bed days by a number equivalent to £11 billion NHS savings per year. This is £4 billion more than the total annual spend by the NHS on medicines in England.[22] A successful pharmaceutical industry therefore has unquestionable healthcare as well as economic benefits. Advances in medicines and devices can mean greater convenience in use as well as sometimes significant improvements in treatment.

Generic medicines

26. All the major pharmaceutical companies produce branded products. Another section of the industry has traditionally produced generic medicines, which come to market once the branded drug's patent expires. Generic drugs play a major part in containing NHS drugs expenditure. In 2002, unbranded medicines accounted for 53% of all prescriptions dispensed in England, but 20% of total drug costs. Four years after patent expiry of a branded product, generic drugs will account for about half of the drug's market (UK average) and the average price differential between branded and generic versions of the same drug is approximately 80%.[23]

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[20] PI 35

[21] PI 35

[22] ABPI briefing document, *The Cost of Medicines – Good value for patients*. Available online at http://www.abpi.org.uk/publications

[23] From IMS Health. http://open.imshealth.com/webshop2/IMSinclude/i_article_20040518b.asp

27. In the UK, those prescribing in the community are encouraged to write the generic drug name, whereas in many other countries (and in UK hospitals) there is an automatic generic substitution system in place. Nevertheless, the rate of generic prescribing is still very high compared with other major European pharmaceutical markets, and substantial costs savings are achieved. In 2003, 77.8% of prescriptions were written generically, a record of which the Department is proud.[24] Since 1997, the proportion of prescriptions written and dispensed generically has significantly increased, though cost savings appear to have slowed. [25]

28. Over the past decade, there have been significant changes in the pattern of UK generic manufacturing ownership, leading to increasing domination by large international generic manufacturers. In general, these manufacturers operate independently of, and in competition with, the major brand name companies. However, the £4.4 billion acquisition of two major generic producers by the Swiss firm, Novartis, in February 2005, may presage a major change. Novartis, the world's sixth-largest producer of branded drugs, is now the world's largest manufacturer of generics.

The Pharmaceutical Industry Competitiveness Task Force

29. Despite its continuing success during the 1990s, there were increasing concerns about the competitiveness of the UK pharmaceutical industry that were voiced at a meeting in November 1999 between the Prime Minister and the Chief Executive Officers (CEOs) of AstraZeneca, Glaxo Wellcome and SmithKline Beecham. The CEOs argued that the traditional factors that underpinned the UK's past success in pharmaceuticals were no longer sufficient to guarantee good performance, and that an initiative was required to ensure the UK retained its competitive edge. They expressed particular concern about difficulty in getting their products to the UK market, and intellectual property protection. This led to the establishment of the Pharmaceutical Industry Competitiveness Task Force (PICTF).

30. The overall aim of PICTF was to look at ways of ensuring that the UK remained an attractive location for the pharmaceutical industry, with specific reference to international competitiveness, the free movement of medicines within the EU and European licensing of medicines, the UK as a site for R&D (including partnerships with academia) and the NHS as a location for clinical studies. The group was co-chaired by Lord Hunt, then Parliamentary Under Secretary of State for Health, and Sir Tom McKillop, CEO of AstraZeneca, with equal representation from Government and the industry.

31. PICTF published a report in March 2001 that proposed specific measures and commitments by Government to assist the UK pharmaceutical industry. It also defined 'Competitiveness and Performance Indicators' for the industry, to be recorded and published each year to assess trends over time. These indicators provide the objective data to underpin assessments of how well the UK is performing in the key areas that are crucial

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[24] PI 01

[25] In 1997, 47% of prescriptions were dispensed generically, and accounted for 15% of the England drug bill. In 2002, the 53% of prescriptions prescribed generically accounted for 20% of the bill. Department of Health: Statistics of prescriptions dispensed in the community - England 1992 to 2002, http://www.performance.doh.gov.uk/HPSSS/TBL_B4.HTM

to its competitiveness as a location for pharmaceutical companies.[26] The main indicators of value proposed all related to economic gains rather than health benefits:

- Proportion of world first patents filed for marketed new drugs divided by proportion of world R&D spend;
- UK-based companies' number of 'global top 75' new active substances; and
- Percentage of world pharmaceutical R&D spend.

32. The first set of indicators was published in March 2001 and the most recent set was published in December 2004. They show that the UK currently has:

- A pharmaceutical industry that contributes significantly to the UK economy;
- A comparatively strong scientific research base;
- An impressive record of pharmaceutical innovation;
- A relatively rapid regulatory process for medicines compared to other countries; and
- Relatively slow uptake of medicines by prescribers.[27]

33. Under PICTF, it was agreed that there should be close joint working between Government and the industry on the National Service Frameworks (NSFs) that set standards for the NHS in clinical priority areas. The report also identified the potential for greater use by industry of NHS information, building on existing systems such as the General Practice Research Database (GPRD).

34. The 2001 report resulted in the creation of the Ministerial Industry Strategy Group (MISG), which now meets on an ongoing basis. In addition, the Healthcare Industries Task Force (HITF) was created to examine "issues of mutual interest in the healthcare sector".[28]

35. These measures indicate the importance of the pharmaceutical industry and the Government's desire to respond to its needs. However, questions have been raised about the Government's excessive focus on ensuring the competitiveness of the industry, to the disadvantage of the NHS and patients. These issues are discussed later.

3 Difficulties facing the pharmaceutical industry

36. As PICTF indicated, the UK-based pharmaceutical industry is faced with a number of difficulties in conducting research and operating successfully. The cost of conducting medical research in the UK is second only to the US.[29] Extra security is needed because of

[26] http://www.advisorybodies.doh.gov.uk/pictf/cpi2001.pdf

[27] PICTF Performance Indicators, available at http://www.advisorybodies.doh.gov.uk/pictf/index.htm#pubs

[28] http://www.advisorybodies.doh.gov.uk/hitf/Tor.htm

[29] PI 28

threats from animal rights protesters, for instance. Novartis UK has spent an extra £1 million on security measures at its UK sites in the last two years alone.[30] The cost of research programmes run within NHS hospitals are elevated because of 'overheads', which vary from 30% to 100% extra, depending on the hospital.[31] According to the Department of Health, it has "paid close attention to creating a safe and positive environment for both publicly funded medical research and commercial contract research", and "it is Government policy that Industry must meet the full costs of work that the NHS undertakes for industry under contract".[32]

37. Authorisation to conduct early stage trials in animals has to be obtained from the Animals Procedures Committee of the Home Office and it is more difficult to obtain permission to conduct animal experimentation in the UK than in any other comparator country.[33] This may place an additional constraint on the conduct of research. Cancer Research UK stated:

> 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 comes to market, thus stifling innovation and, more importantly, potential patient benefit.[34]

38. The "fragmented and customer un-friendly nature of academic units and clinical services" was highlighted by the Royal College of General Practitioners (RCGP). The College also mentioned the "multiple layers of Research Ethics approval" that may be required and a "disparate, and sometimes competing, collection of clinical and academic teams" that may need to be brought together to achieve sufficient mass for large-scale research.[35]

39. Many large-scale Phase II and III trials are currently being carried out in Eastern Europe and elsewhere as a result of high costs imposed here.[36] Dr Malcolm Boyce, who runs a London-based Contract Research Organisation (CRO), stressed:

> A strong pound sterling makes matters worse for overseas companies. For those reasons, companies are increasingly placing their Phase II and III trials outside the UK, in low cost areas such as Eastern Europe, Russia and India.[37]

40. There are not enough trained medical researchers in the UK.[38] This means there are too few individuals who can organise clinical trials or take part in a reviewing or implementation capacity. Prof Patrick Vallance, from University College London (UCL), told us:

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[30] PI 29

[31] PI 20

[32] PI 01

[33] PI 51

[34] PI 59

[35] PI 19

[36] PI 19, 107

[37] PI 107

[38] PI 33

> 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.[39]

41. Specialist facilities are also lacking. There are very few centres in which paediatric clinical trials may be effectively conducted, for example. This will become more relevant following the introduction of a new European Regulation on Paediatric Medicines in 2006, which will require more medicines to be licensed for use in children.[40]

42. Witnesses pointed out that the NHS does not have a coherent approach to industry-sponsored clinical trials and lacks the staff and specialist facilities in which to conduct them. This partly explains why a very low percentage of patients are enrolled in clinical trials in the UK; experience shows that recruitment can be increased substantially provided suitable policies and other measures are in place.[41] For example, the National Cancer Research Network (NCRN) provides the NHS with the 'infrastructure' to support cancer clinical trials in England. It was established by the Department of Health in April 2001. Since that date the number of patients taking part in cancer clinical trials in the UK has doubled. All results from NCRN trials are scrutinised by an Independent Data Monitoring Committee, which is the only body to see unblinded data. All results emerging from trials approved by the Clinical Trials Awards and Advisory Committee are published.

43. A flourishing UK pharmaceutical industry is of great importance for healthcare as well as having economic benefits. To achieve this, it is most important for the industry to be able to undertake research effectively. The success of the NCRN shows that it is possible to provide the infrastructure within the NHS that the industry requires. Similar systems need to be put in place throughout the NHS as a matter of urgency. **The industry's ability to compete internationally requires a legislative and organisational framework for research that protects the interests of all stakeholders – patients, researchers and pharmaceutical companies.**

4 From drug development to prescription

44. A medicine progresses 'from bench to bedside' over a period of many years —from initial development in the laboratory, through clinical testing, licensing, promotion to doctor and patient, and final prescription. The rationale for the very existence of major pharmaceutical companies is their ability to bring new and useful drugs to market. According to the ABPI, it takes an average of 12 years and over £500 million investment to bring one new drug to patients.[42] This cost has increased greatly over the years (see Figure 3).

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[39] PI 106

[40] PI 35

[41] PI 106

[42] PI 35

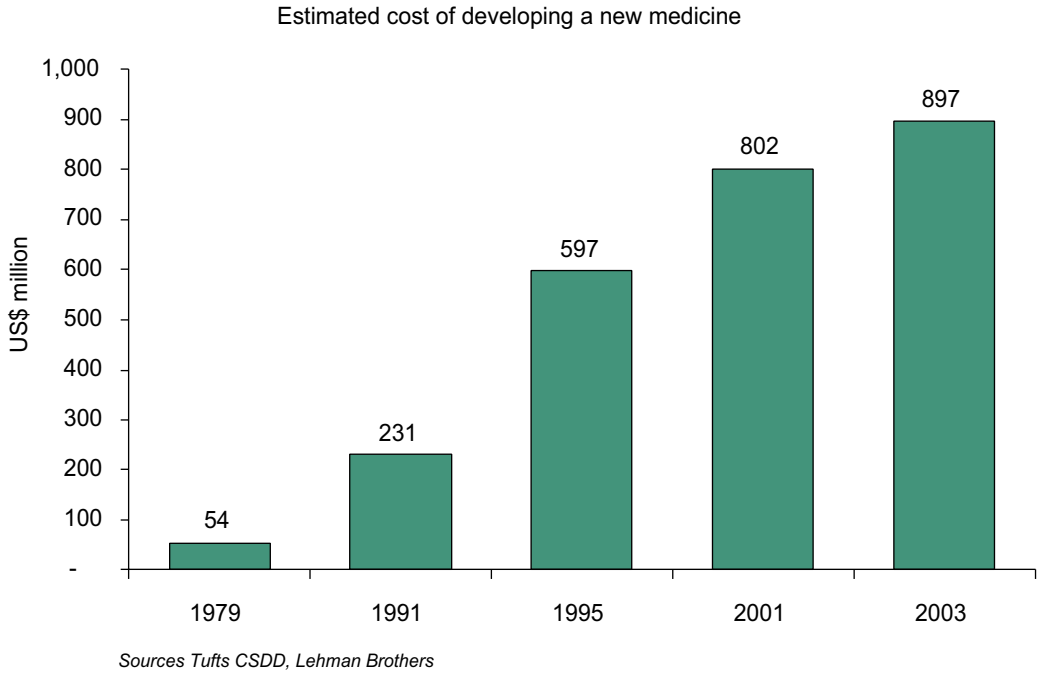

Figure 3. Cost of developing a new medicine

Data supplied by the ABPI.

Drug development and the conduct of medical research

45. A drug innovation is generally defined as the discovery, development and bringing to market of a new molecular entity (NME). Drug discovery involves trying to match understanding of disease with an NME which might promise some therapeutic effect. For example, the search for NMEs may take the form of mimicking and/or building on what is known about the body's natural hormones, the activity of natural products from plants and computer-aided design of molecules. Often the NMEs discovered are original but relatively minor molecular modifications of existing drugs; sometimes, they are radically new creations, such as the first H_2-antagonist (cimetidine) which was a major breakthrough in the treatment and prevention of peptic ulcers. When discovered, the novelty of NMEs can be legally and commercially protected by patents.

46. Following initial drug discovery, NMEs undergo several phases of development involving all levels of research from molecules, cells and tissues, animal models, whole organs and systems to individuals and populations, as shown below:

- Candidate/target selection – selection of a promising compound for development
- Pre-clinical and non-clinical – necessary animal and bench testing before administration to humans plus start of tests which run concurrently with exposure to humans
- Phase I – First Time In Man (FTIM); the first study of a new compound in humans, usually healthy volunteers
- Phase II – Proof of concept (PoC); evidence of efficacy and safety in patients

- Phase III – studies in a large population to generate safety and efficacy data for licence application
- Licence Application (in UK) – filing all data to regulatory bodies (known as Marketing Authorisation Application in Europe, New Drug Application – NDA – in US)
- Phase IV – post-marketing studies.

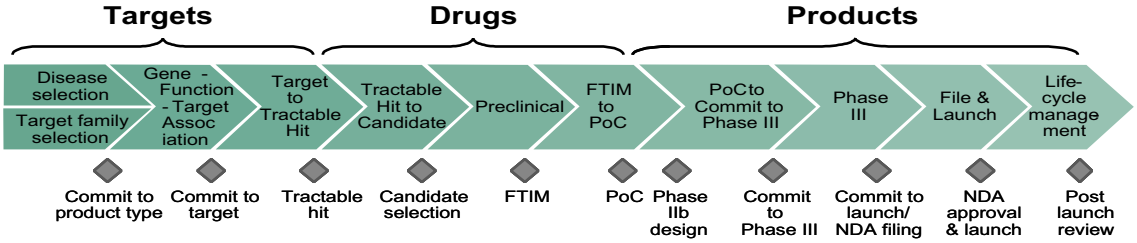

Figure 4. Development of a drug from target identification to post-launch product review[43]

47. Pre-clinical studies are investigations that generally precede product testing in humans. Virtually all pre-clinical and non-clinical testing is conducted by pharmaceutical industry scientists either within the company developing the product or in industry-funded contract research organisations (CROs). This process typically takes about three years. Pre-clinical studies include chemical, pharmacological and toxicological studies in human cells, animal tissues and whole animals. Not all animal testing is completed before human trials begin. For example, long-term animal studies to test for the carcinogenicity of NMEs are generally not completed until after healthy volunteers and/or some patients have been exposed. These long-term tests in mice or rats are particularly important because human trials do not screen for carcinogenicity. This is partly for ethical reasons, but also because the interval between testing for the effects of most carcinogens and the onset of cancer may be many years – far longer than any clinical trial would run. For this reason the long-term carcinogenicity tests in rodents last for about two years in order to approximate the lifespan of the animals, and thus act as a model for cancer induction in humans.

48. A major problem in early stage drug development is uncertainty about the predictive value of results found in cells, tissues or whole animals. Findings in these pre- or non-clinical tests often cannot be extrapolated to human beings and many NMEs which are discovered fail to reach the market because of problems in the development stage. According to Cancer Research UK, failure rates in taking cancer drugs to market are around 95%.[44] There are no UK data, but information from the US Food and Drug Administration (FDA) shows that drug innovation has been declining steadily over the last 10 years (see Figure 5). At the same time, the cost of innovation is high and rising.

[43] PI 51

[44] PI 59

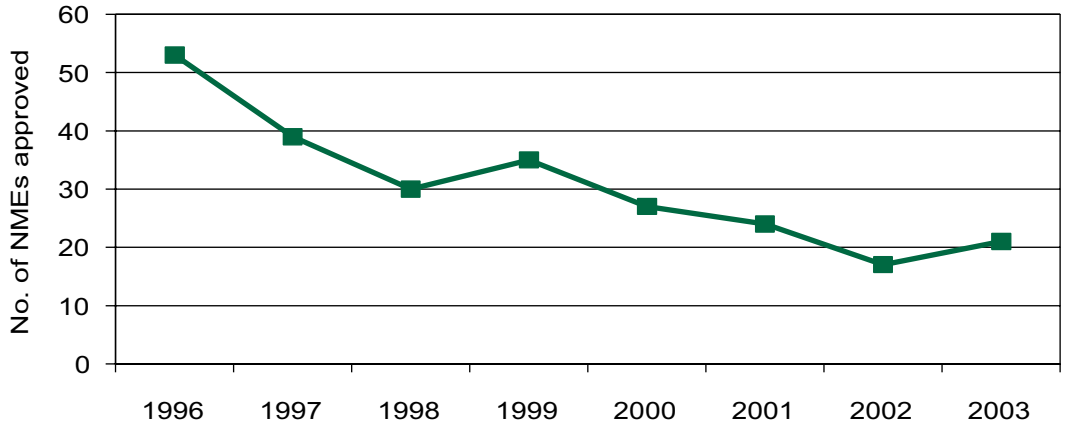

Figure 5: New Molecular Entities approved in the US, 1996–2003

FDA website at www.fda.gov/cder/rdmt/NMEapps93-03.htm

49. On the other hand, it is argued that, as approaches to disease change with results from the Human Genome Project and advances in biotechnology increase, so the drug discovery and hence innovation process will be enhanced. Improvements in the techniques used in drug discovery and increased understanding of disease mechanisms at a molecular level that have taken place over the last decade may also bring about a rise in medicines innovation in the future.[45]

50. The clinical stage of research (that involving humans) is traditionally separated into four phases, although in practice they often overlap. Phases I, II and III are carried out before a licence to market the new medicine is sought, and Phase IV trials are carried out after a licence has been granted. It may take as long as 10 years for a product that is eventually successful to progress from Phases I to III. A significant proportion of compounds fail to progress to the next stage with the highest failure rate being observed in Phase I. It is estimated that of every 100 drugs entering Phase I, 70 will go into Phase II, 33 into Phase III, 25 to regulatory submission and 20 to final approval.[46]

51. Phase I trials involve healthy adults. Until quite recently, this work was only carried out by academic clinical pharmacology units, but in recent years CROs have taken over that role almost entirely because, according to the Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI), they:

> …provide an efficient, effective and high-quality service that enables companies to plan and execute the early clinical development of their drugs to tight timelines.[47]

52. Between 100 and 200 healthy volunteers usually take part in Phase I trials, which are essentially performed to determine whether the product is safe for use in humans and whether it is likely to work in a particular patient group. Phase I trials examine the

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[45] PI 33

[46] ABPI Report of Seminar 2 Nov 2000 *Medicines; Tried and tested - or an unknown risk?* http://www.abpi.org.uk/amric/tried_&_tested.pdf

[47] PI 107

additional effects of the product on the body and look at how the body's reaction to the drug changes its properties. Patient age, gender or external influences such as food or the presence of other medications may alter the action of the drug and it is important to determine this early on.

53. Initially, single doses of the drug, in increasing sizes, are given to participants. Repeated doses are then given and the safety and tolerability are assessed and compared to results from animal studies. This phase also determines the dosage for subsequent trials. If it appears that the product is likely to be effective in the target patient group, it progresses to the next stage of testing.

54. Phase II trials usually take place in a hospital and may be co-ordinated by a dedicated Clinical Trials Unit within that hospital. It is at this stage that the manufacturing company begins to involve limited numbers of the medical profession outside the company (typically in hospitals) in a major way. Notably by this stage the patenting process is generally completed so the manufacturer's crucial intellectual property protection is in place. Phase II trials involve individuals affected by the target condition and are designed to determine its safety and efficacy in the relevant patient group. Between 200 and 500 individuals with the target disease usually take part in this phase of testing. If the product proves acceptably safe and appears to be efficacious in this relatively small group, tests are then undertaken in a larger group in a subsequent trial.

55. Phase III trials involve larger groups of patients (2–3,000 approximately) although cohort size depends on the condition as some rarer diseases may necessarily involve a smaller group of patients. Phase III trials determine safety and efficacy of the product on a larger scale and either compare the product to a drug that is already on the market to treat the target condition or, more usually, a placebo. These trials form the basis of licence applications.

56. Human trials tend to have limited predictive value due to problems of extrapolation to routine clinical practice. Typically, only a small sample of the prospective population to be exposed to the drug can be studied in clinical trials. Furthermore, those patients who will probably be exposed to the drug if it is marketed may be excluded from clinical trials because they have multiple pathologies or take a number of different medicines. These co-morbidities and the presence of other drugs in the body might affect the drug being investigated and not allow accurate comparison with a placebo or comparator drug.

57. Phase IV, post-marketing trials, may be conducted by the industry to assess the safety and efficacy of medicines in the long term and in routine clinical practice. Drug companies are obliged to report all adverse effects to the MHRA. Other groups may also conduct Phase IV testing, but comparative studies of the drug against the market leader or involving combinations of products are more likely to be performed by non-industry groups.

Medicines licensing

58. Drug approval and licensing systems worldwide are based on detailed requirements and elaborate processes, the scope of which is constantly changing. However, the core elements of drug control remain essentially unchanged. The primary focus is on the

evaluation of pre-licensing (non-clinical tests and Phase I–III trials) data generated or commissioned by companies to obtain approval.

59. The executive arm of the UK Licensing Authority is the Medicines and Healthcare products Regulatory Agency (MHRA), which is also responsible for approving clinical trials[48]. The MHRA is assisted by the Committee on the Safety of Medicines (CSM), and the Medicines Commission. These latter two organisations are due to be merged into one over-arching body, the Commission for Human Medicines. Medicines may be licensed for use in the UK either on a national basis (directly through the MHRA), through a centralised approval system of the European Medicines Agency (EMEA) or through a procedure for 'mutual recognition'. Under the centralised scheme, companies apply for a licence directly to the EMEA. The centralised approval system is already compulsory for biotechnology products and has expanded in scope to cover drugs for AIDS, cancer, neurodegenerative diseases and diabetes. Alternatively, a company may designate one EU country to approve a drug licensing application, and then receive marketing authorisation in various EU countries, provided these other countries agree. Under this 'mutual recognition' procedure, all EU countries in which marketing permission is sought receive the full drug licence application, and any objections are considered and resolved through EMEA's oversight body, the Committee on Human Medicinal Products (CHMP). Details for the arrangements for medicines licensing, regulation and post-licensing surveillance are discussed in Part 5.

60. Once licensed, the drug itself is under patent protection for 10 years, although in certain circumstances this may be extended. Once the period of patent protection has expired, the originating company is deemed to have been rewarded for risks of innovation and generic versions of the drug may enter the market. A generic medicine contains the same active ingredients as an original product that has been researched and developed by a pharmaceutical company. Regulatory standards for safety and efficacy are the same for generic medicines as for branded products and marketing authorisation must be obtained from the MHRA before the drug is allowed on to the market. Additional clinical data is not required. The manufacturers of generic medicines need prove only that their products are effectively identical to the original branded product, implying that they have identical effects on patients.

Post-licensing evaluation, including value for money assessments

61. The initial marketing authorisation lasts for five years, at which time the company must apply to the MHRA for a further, essentially permanent, licence if it wishes the product to remain on the market. The legal criteria for re-licensing are the same as those for the original assessment (safety, efficacy and quality) but in reality scrutiny is much less stringent and would rarely involve the CSM. Efficacy is rarely considered. There is no specific policy regarding the continuing evaluation and safety assessment of medicines.

62. The MHRA is also charged with conducting more general post-marketing surveillance. This may involve scrutiny of Phase IV trials, which include patients in a more typical clinical setting, as well as monitoring published medical literature and evaluation of spontaneous reports of suspected adverse drug reactions (ADRs), for instance though the

[48] Q39

Yellow Card Scheme.[49] Controls over drugs on the market extend also to the testing of medicines (for compliance with quality standards), inspection (e.g. of manufacturing facilities, record-keeping, pharmacovigilance inspections, and quality control) and enforcement (including control of promotional activities and other legal requirements).

63. Drug companies may conduct their own Phase IV studies, comparing the efficacy of their drugs to others, but there is no mandatory requirement for the industry to investigate the long-term effects of their medicines in the community. European legislation sets out requirements for proactive management of pharmacovigilance matters, however, and the MHRA is likely to review this at the time of company pharmacovigilance inspections.

64. After licensing, some drugs may be subject to a review by the National Institute for Clinical Excellence (NICE), which will affect the extent to which they are used in the NHS. Uptake of new medicines is therefore controlled not only by licensing through the MHRA but also through NICE guidance on the provision of novel drugs.

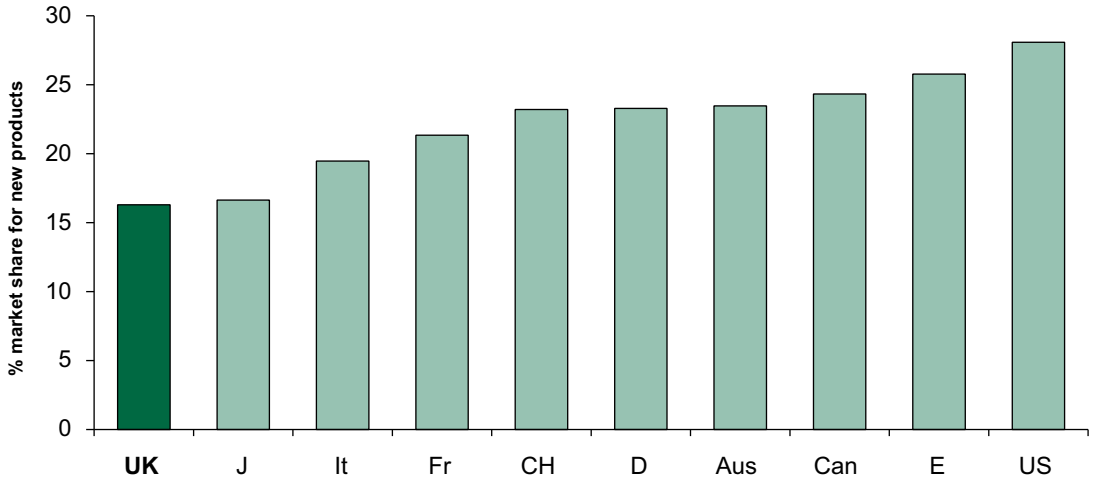

Figure 6. Percentage market share for products launched in the last five years (2003)

UK: United Kingdom; J: Japan; It: Italy; Fr: France: CH: Switzerland; D: Germany; Aus: Australia; Can: Canada; E: Spain; US: United States. *Data supplied by the ABPI*

65. It should be noted that the UK has one of the slowest uptake rates of new drugs in Europe, less than France and Germany. The industry stated that patients suffer as a result of this, for example:

> On average, other major European countries treat more than twice as many [breast cancer] patients with Herceptin per head of population compared with the UK, while Switzerland treats more than three times as many patients.[50]

The provision of medicines information

66. The bulk of the information about medicines which is available to patients and healthcare professionals is provided by the pharmaceutical industry. This information may take several forms: that which must, under law, be given out as part of the licensing

[49] See Paragraph 104

[50] PI 17

process; that which is given in order to educate prescribers or the public; and that which is designed to promote the prescription or use of particular medicines over others. There is a degree of overlap between these groups.

67. Legislation requires that pharmaceutical companies must provide information on their products on request from healthcare professionals. This obligation continues once medicines come off-patent and does not apply to generic companies. Large companies in the UK may each receive 15–30,000 requests for information annually. As an example, Pfizer, the largest supplier of prescription medicines to the NHS, pays over £1 million annually to cover the cost of providing this information service.[51]

Information to prescribers

68. A Summary of Product Characteristics (SPC) is issued to prescribers and other healthcare professionals for every new drug. The detail of content, style, layout and format are closely defined and approval is part of the licensing process.

69. The British National Formulary (BNF), which is published biannually, also provides information to prescribers. The BNF is published jointly by the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain (RPSGB). It provides information on the prescription, dispensing, administration and cost of medicines.

70. A range of alternative sources of independent information is available, including the *Drug and Therapeutics Bulletin* (*DTB*) that is published by Which? and distributed by the Department of Health to all doctors,[52] the Cochrane Collaboration and the James Lind Library. Medical journals provide a variety of specialist and non-specialist data relating to clinical trials or basic scientific studies. Industry produced or sponsored information is also provided to prescribers, in the form of journal supplements, reprints and other literature.

Information to patients

71. Patient Information Leaflets (PILs), which are legally required documents written in accordance with EU regulations and approved by the MHRA, are printed and distributed alongside medicines by pharmaceutical companies to inform patients of how to take their medicine most effectively and to warn them of possible risks and side-effects. Like the SPC, they are approved as part of the licensing process; however, the regulations are not so prescriptive for PILs, allowing limited variation in their content and appearance. The PIL must correspond to the SPC. In response to long-standing criticisms, the MHRA set up a Patient Information Working Group in 2003, to review the design, content and utility of PILs. The work of this group is continuing.[53]

72. In addition to the PIL, patients (and carers) may receive industry-produced pamphlets or written instructions through their doctor or other healthcare professional. Patients can also access large amounts of information and promotional material on the Internet. The

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[51] PI 28

[52] The Department provides a grant to cover this service.

[53] http://medicines.mhra.gov.uk/aboutagency/regframework/csm/piwg/patinfowg.htm

variable quality of this information has caused concern to both the pharmaceutical industry and charities/patient groups.

Professional and patient education

73. Doctors are required to continue their education after they have qualified by taking part in accredited activities. These may take the form of attendance at training days or workshops. Industry funds over half of all postgraduate education and training for doctors in the UK, often meeting the travel and accommodation costs of attendance. The pharmaceutical industry also funds a significant amount of training for nurses. In 2003, for instance, GSK funded 235 nursing diplomas in respiratory disease management and 199 diplomas in diabetes management.[54]

74. Education for patients is provided in a variety of ways, including disease awareness campaigns, which are discussed in detail in Part 8. Such campaigns are designed to increase awareness among the general public of particular conditions that may be under-reported or under-diagnosed and to encourage people to seek treatment. Often, such campaigns are sponsored by a drug company and may bear a company's logo; they may be also endorsed by a charity or patient organisation and/or supported by a celebrity.

75. Guidelines for disease awareness campaigns, developed jointly between the MHRA and the ABPI, were published in April 2003. The guidelines state that educational materials may highlight the availability of treatment but may not focus on, or name, any single intervention.

The promotion of drugs

76. Worldwide, there has been a marked trend to substantially increased expenditure on marketing. In the US, major pharmaceutical companies spend of the order of 24% to 33% of sales on marketing, about twice as much as on R&D.[55] Exact comparisons are complicated because of uncertainties about the dividing line/overlap between marketing and related activities, notably provision of drug information and professional education programmes. We have not been presented with UK figures, but direct promotional expenditure in this country is proportionately lower than in most European countries, reflecting the dominance of the NHS as the major drug purchaser and the terms of the Pharmaceutical Price Regulation Scheme (PPRS, see Paragraph 113)

77. Prescription-only medicines may be promoted only to healthcare professionals, except in very specific cases such as Government-endorsed vaccination programmes. Promotion to prescribers may take many forms:

a) *Drug company representatives.* Approximately. 8,000 drug company representatives operate in the UK and play an important role in information provision and medicines

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[54] PI 51

[55] Health Affairs 2001; 20(5): 136; http://www.eaepc.org/parallel_trade/threats.php?n=2; http://www.abpi.org.uk/statistics/section.asp?sect=3

promotion. Many doctors cite them as one of the main sources of information on the use of new drugs.[56]

b) *Sponsored attendance at industry-organised events or medical conferences.* Travel and accommodation costs are often met by the company. Other forms of hospitality are also provided.

c) *Journal articles and supplements supporting use of the company's drug.* These are distributed free to prescribers and are available at conferences and on the Internet.

d) *Direct advertising.* Advertisements are placed in medical journals and magazines. Direct mailing to healthcare professionals often takes the form of informing prescribers of changes in drug delivery systems or the availability of new drug formulations. Approximately 80% of medicines advertising is aimed at doctors, with an increasing amount targeting nurses with new prescribing powers.[57]

78. Public relations and marketing agencies are often used by the pharmaceutical industry to assist with the promotional activities described above. 'Medical communications' play an important role in the marketing of medicines. The main aim is to improve sales figures and there are dedicated agencies that often form part of enormous, multinational PR and communications companies, such as Ogilvy, Burson-Marsteller, Edelman and Ketchum. Medical communications agencies may be involved in all or some of the following:

a) Pre-marketing of drugs;

b) Identification of disease areas;

c) Disease awareness campaigns;

d) Consumer education and marketing;

e) Publications and papers;

f) Conferences, meetings and hospitality;

g) 'Product lifecycle management';

h) Regulatory and policy issues;

i) Grassroots communications;

j) Key opinion leader development; and

k) The production of 'educational' materials aimed at prescribers.

79. A critical element of the work of medical communications companies is the recruitment and training of key opinion leaders (KOLs), who are usually 'authoritative third parties' such as physicians at the top of their field. These individuals may be paid to speak and write on behalf of the sponsoring pharmaceutical company. They attend medical

[56] PI 35

[57] Q784

conferences, for example, and may present research papers, take part in panel debates or field questions in oral sessions. The 'development' of KOLs, we were told, is a well-worked process involving all types of doctors (hospital consultants, clinical academics and GPs).

80. A major part of the work of medical communications agencies involves liaison with the lay media and a significant proportion of their activities may be directed towards building relationships with journalists.

81. In addition to building relationships between KOLs and journalists, medical communications agencies commonly have links with patient organisations. Such groups provide information to their members and the general public and often campaign for increased access to a particular medicine or procedure. Many are powerful lobbying groups, working both through the lay media and in specialist settings. As such, their interests may coincide to some degree with those of the pharmaceutical industry, and the communications company may be used as a mediator in the relationship between the two.

82. PR companies and communications agencies have expanded their work in recent years. They are increasingly involved with research and the design of clinical trials. A well-documented trend is for large medical communications groups to buy into the infrastructure of drug testing by taking over CROs that conduct clinical trials and generate evidence for licensing approval.

83. Increasingly creative methods are used in the promotion of drugs by Industry. Which? cited a financial donation made by the manufacturers of Cipralex (escitalopram, an antidepressant manufactured by Eli Lilly) to Depression Alliance when GPs completed and returned a feedback leaflet relating to their drug[58] and a spoof Mr Man book ('Mr Sneeze') that was sponsored by a drug company and carried information about its anti-allergy product.[59]

84. The direct advertising of prescription drugs to patients is prohibited. Direct-to-consumer advertising (DTCA) of prescription-only medicines is permitted only in the US and New Zealand. Moves towards extending DTCA to Europe proposed by the European Commission were quashed by the European Parliament in October 2002 by a majority of 494 to 42. Only over-the-counter (OTC) medicines may be advertised to the UK general public. The Medicines (Advertising) Regulations 1994, amended in 1999, govern the advertising of these medicines. There are specific regulations relating to promotional methods that could lead to the unnecessary or excessive use of medicines.

85. Complaints regarding advertising material are handled by a variety of bodies. The Proprietary Association of Great Britain (for OTC medicines), the Prescription Medicines Code of Practice Authority (PMCPA, for prescription-only drugs) and the Advertising Standards Authority operate as self-regulatory schemes and take responsibility for handling advertising complaints alongside the MHRA. Corrective statements are rarely mandatory, although a recent increase in the number of such statements required by the MHRA has been observed.

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[58] PI 53

[59] Q150

5 Arrangements for controlling the activity of the UK-based pharmaceutical industry

86. A number of processes are in place to control the research, marketing and promotional activities of the UK pharmaceutical industry. These include:

a) International standards of good clinical practice (GCP) in research;

b) Research Ethics Committees;

c) Medicines licensing regulation;

d) Post-marketing safety surveillance and drug evaluation; and

e) Cost assessment.

International standards and 'good clinical practice' guidelines

87. For many years, the pharmaceutical industry has worked to international standards. Ethical guidance was agreed and internationally accepted under the "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects", drafted and adopted by the World Medical Association in 1964 (and amended regularly thereafter). The Declaration covers fundamental principles of clinical research, such as the need for research to be carried out by scientifically qualified individuals and for the importance of the objective to be in proportion to the risk to the participant.

88. Increasingly, the European Medicines Agency (EMEA) works with its counterpart agencies in the US and Japan, through the "International Conference on Harmonisation on technical requirements for registration of pharmaceuticals for human use" (ICH). Standards developed by the ICH, when adopted by the US Food and Drug Administration (FDA), EU and Japanese authority, become internationally binding. The ICH agreed in 1996 to adopt the same standards of GCP in pharmaceutical clinical trials in the EU, the US and Japan. The adopted GCP standards include provision for audit, based on a checklist of approximately 2,000 items with detailed requirements for protecting the safety and well-being of patients or individuals involved in clinical trials, the need for informed patient consent and high data quality.

89. The European Clinical Trials Directive, which came into force in May 2004, established EU-wide standards of GCP for clinical trials under legislation. Under the Directive, the regulation, monitoring, and standards for early stage clinical trials were tightened. One of the main provisions of the Directive to ensure good practice was for Research Ethics Committees (RECs) to be governed by a national body. RECs should generally respond to applications within 60 days. The Directive required Member States to apply the principles of GCP to both commercial and non-commercial clinical trials with medicines.

90. In the UK, the GCP guidelines set out under ICH were incorporated under the Research Governance Framework for Health and Social Care, issued by the Department of

Health in 2001. The Framework guides clinical research carried out within the NHS. Subsequently, the Medicines for Human Use (Clinical Trials) Regulations 2004 adopted the conditions and principles of GCP.

91. In 1985, the WHO issued a 'Revised Drug Strategy' recommending the adoption of national drug policies. The 39th World Health Assembly, held the following year, which adopted this strategy, also called on governments to implement a National Medicinal Drug Policy. The UK has not responded to this recommendation, but we were able to examine such a policy during our visit to Australia last year. The Australian National Medicines Policy has been in place since 1999. Its overall aim is to balance health outcomes with economic objectives. A key mechanism for achieving this is a dedicated committee involving all stakeholders, including patients, which makes recommendations to ensure the "Quality use of medicines".[60]

Research Ethics Committees

92. All R&D in the NHS involving patients has to obtain local REC approval for clinical trials. This may be a complicated and lengthy process, as PICTF pointed out. The establishment of a UK Ethics Committee Authority, provided for under the Medicines for Human Use (Clinical Trials) Regulations 2004, will maintain a single framework for the review of clinical trials and will monitor RECs.

93. NHS RECs are under the control of Health Authorities and work according to guidance from the Department of Health. Multi-centre RECs can give a single opinion on clinical trials that will be carried out in more than one area. The recently established Central Office for Research Ethics Committees (COREC) works on behalf of the Department of Health to co-ordinate the development of operational systems for local and multi-centre RECs in England. The establishment of COREC aimed to provide operational support and standardise systems, and to maintain an overview of the operation of the research ethics system in England.

94. Although COREC was praised by the Department of Health,[61] others have suggested that the large number of regulations that have resulted from the creation of COREC have neither simplified the procedures for researchers seeking ethics approval nor increased protection for the patients for whom the system was originally established.[62]

Licensing: the MHRA

95. Drug manufacturers are required to submit evidence of the utility of their products to the regulator under the Medicines Act 1968, which became operational in 1971. The Act set up a system of licensing based on evidence of drug safety, efficacy and quality; it applied to the manufacture, sale, supply and promotion of all medicines in the UK.

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[60] Quality use of medicines requires that drugs be used: judiciously, with non-medicinal approaches considered alongside pharmacological intervention; appropriately, taking into account condition, drug type, dosage, length of treatment and cost; safely, to ensure drugs are not over- or under-used; and efficaciously, to achieve changes in actual health outcomes. To achieve quality use of medicines, "people must be provided with the most appropriate treatment, and have the knowledge and skills to use medicines to their best effect". (Australian Government, Dept of Health and Ageing, National Medicines Policy 2000)

[61] PI 01

[62] PI 104

96. The Act designated the Secretary of State for Health in England (and equivalents in Scotland, Wales and Northern Ireland) the Licensing Authority for human medicines in the UK. Executive responsibility for drug control passed from the Department of Health's Medicines Division to a new executive agency, the Medicines Control Agency (MCA), in 1989. The Act included stringent requirements for secrecy.[63] In 2003, the MCA was re-established as the MHRA and became responsible for the regulation of medical devices, as well as ensuring the safe and effective licensing of human and veterinary medicines, operating under a framework of UK and EU legislation.

97. The MHRA is assisted by the Committee on the Safety of Medicines (CSM), which advises on the efficacy and safety of medicines in order to ensure that appropriate public health standards are met and maintained. The CSM may review licence applications and produces an independent assessment. Depending on whether or not it finds the medicine to be of acceptable quality, safety and efficacy and to give overall benefit to patients, the CSM, working through the MHRA, will either recommend that a licence be granted, accept the application subject to modifications or reject the application with reasons. Ultimately, however, it is for the Licensing Authority (Ministers of Health) to grant the licence. The Medicines Commission provides advice to the Licensing Authority on policy issues relating to drug regulation and is the appellate body for medicines where a decision has been made not to grant or to withdraw a licence. Following public consultation in 2004, the MHRA is now reviewing the role and structure of these advisory bodies. It has proposed, in place of the Medicines Commission and the CSM, the setting up of an overarching Commission on Human Medicines.

98. The medicines operation of the MHRA has three main divisions, which concentrate on pre-licensing, post-licensing and inspection and enforcement issues. It has a budget of some £65 million and employs around 750 staff.[64] The MHRA is unusual in being one of few European agencies where the operation of the medicines regulatory system is funded entirely by fees derived from services to industry (drug regulatory agencies in other countries are more often only partly funded by licence fees). The MHRA's activities are 60% funded through licensing fees paid by those seeking marketing approvals and 40% through an annual service fee, also paid by the industry. Most of the income generated from the service fee is allocated to post-marketing surveillance and inspection, as opposed to pre-marketing scrutiny of drug licence applications.

99. In return for the licensing and service fees paid by the industry, companies expect an efficient and rapid service. The need for a swift response to marketing applications is heightened by the presence of alternative European regulatory agencies to whom industry may turn.[65]

100. The speed at which the UK regulatory authority has historically processed licence applications has been one of the fastest in the world, which means that its services are much in demand from EU applications. Recently, the regulatory agency has accelerated its

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[63] Section 118 in particular was a bar to disclosure. It was repealed in January 2005, the date of implementation of the Freedom of Information Act.

[64] HC Deb, 10 Nov 2004: Column 259WH

[65] Several PICTF indicators signal the importance of drug licensing business for the UK – e.g. "In the mutual recognition procedure, the number of times the MCA is chosen as the Reference Member State (RMS)"; and "In the centralised procedure, the number of times the MCA is nominated by industry as the rapporteur"

reviews of their data for new products. In 2003, time from application to the granting of a licence of a new chemical entity, if no further information was needed, was approximately 70 working days, whereas a response may now usually be expected in approximately 30 working days. Licensing times can take rather longer for generic products.[66]

101. The MHRA relies on company data, presented as a series of detailed assessment reports, in its decision whether or not to licence a drug. Raw data is very rarely analysed.[67]

102. Recently, there have been significant changes in drug control, largely because of the increased influence of European legislation. However, safety, quality and efficacy, and the overall balance of benefit to risk, remain the sole criteria for drug approval. Manufacturers are not required to undertake comparative drug testing, nor to demonstrate medical need for products, and regulators may not take price or value into consideration.

Post-licensing surveillance

103. The Post-Licensing Division of the MHRA is in charge of continuing surveillance of safety, whereby reports of adverse drug reactions (ADRs) are monitored and recorded after a licence has been issued and the medicine is on the market. Drug companies are required to report all suspected ADRs, and doctors and other health professionals are encouraged to do so, by sending in Yellow Card reports.

104. The Yellow Card ADR reporting system provides the mainstay of the pharmacovigilance system, with particular attention focused on newer drugs, identified by an inverted black triangle. Adverse reactions are reported voluntarily by doctors, nurses, dentists, coroners, radiographers, optometrists, health visitors, midwives and pharmacists to the CSM using a yellow card. The MHRA/CSM acknowledge considerable under-reporting of suspected ADRs. The purpose of the Yellow Card/Black Triangle system is not to estimate the incidence of ADRs, but to provide signals of possible problems in need of further investigation.[68] The Scheme did not, however, provide an effective signal of problems with Vioxx, with an essentially steady number of reports of heart attacks from 1999 to 2004 (with figures of six reports in 1999; nine in 2000; seven in 2001; five in 2002; seven in 2003; and four in 2004 up until the drug's withdrawal in September). These figures remained constant despite a year-on-year increase in prescriptions for the drug, with figures rising from 162,600 in 1999 to 2,128,600 in 2003.[69] Electronic yellow cards may now be used, a process which is encouraged by the MHRA. The black triangle symbol is removed after a period of time (usually two years) and then reporting is only of serious or previously unrecognised unwanted effects.

105. The Yellow Card Scheme was first formally reviewed, and a report published, in May 2004.[70] One of the recommendations was that patients be able to report their own adverse drug reactions. A pilot scheme is currently underway to assess this process.

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[66] Q729

[67] PI 77

[68] Q802, 854

[69] HC Deb, 21 Feb 2005, Col 183W

[70] See Department of Health announcement 17 January 2005: http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases

106. If drug safety problems are suspected, typically some warning will be added to the SPC but, occasionally, medicines may be taken off the market altogether. Twenty-four prescription drugs were withdrawn due to safety concerns in the UK between 1971 and 1992 inclusive (1.1 per year) and 19 were withdrawn between 1993 and 2004 (1.6 per year). No public inquiry has taken place into the withdrawal of any of these drugs, to determine mistakes that may have been made in the original licensing process and subsequent monitoring.

Orphan drugs

107. In order to increase rates of research into areas of serious disease that affect relatively few people (and therefore might be expected to have low market value) the US Orphan Drugs Act was passed in 1983 in the US and its principles were adopted in the European Orphan Drugs Act in 2000. Incentives to develop orphan drugs include intellectual property protection and 11-year market exclusivity.

108. A number of criticisms have been levelled against the current system for encouraging the development of orphan drugs. The lack of competition drives up orphan drug prices and this may have important economic implications for PCTs and other healthcare providers. An example of this is nitric oxide, which was available for years and, unlicensed, cost very little (it cost approximately £2,000 to supply a neo-natal unit with nitric oxide for one year[71]). Two clinical trials proved the benefit of inhaled nitric oxide and it was approved and received a patent in the US and EU on this basis.[72] Since licensing, nitric oxide now costs many times more (it was estimated that supply of nitric oxide for the same neo-natal unit would now cost over £63,000 per year).

109. Some drugs marketed as Orphan Drugs may have required little research input. The quality of clinical trials of Orphan Drugs has been questioned. In addition, innovation in a particular area may be reduced once a single product is available, due to market exclusivity.

The National Institute for Clinical Excellence

110. The uptake of novel drugs, an issue of great importance to the industry, is partially determined by NICE. The Institute issues guidance about the use of both old and new medicines and procedures. Guidance is of four main forms:

a) 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);

b) Clinical guidelines: recommendations on the appropriate treatment and care of patients with specific diseases and conditions, such as diabetes and schizophrenia;

c) Cancer service guidance: recommendations on arrangements for the organisation and delivery of services for people with cancer; and

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[71] Subhedar NV et al, *The Lancet* 2002; 359:1781

[72] Nitric oxide was patented as an orphan drug in 1999

d) 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.

111. NICE currently publishes around 25 technology appraisals, 12 clinical guidelines and 60 pieces of interventional procedures guidance each year. Of the 25 technology appraisals, not all are for new drugs; they can also be reviews of non-drug treatments, re-reviews or reviews of medicines licensed several years ago. This means that a minority of new drugs approved by the MHRA are subsequently subject to NICE scrutiny. The Department of Health asks the Institute to look at particular drugs and devices only where the availability of the drug or device varies across England and Wales or where there is confusion or uncertainty over its value.

112. The pharmaceutical industry has some say in the selection of topics for appraisal. Drug companies provide information to the National Horizon Scanning Centre on the development of new pharmaceutical products and their licensing position and have one seat on the Advisory Committee on Topic Selection (ACTS), which assesses proposals for work topics for NICE against published criteria. The Joint Planning Group, which considers ACTS' proposals and advises Ministers, who take final decisions on NICE's work programme, does not include the pharmaceutical industry in its membership. NICE's approach to engaging with the pharmaceutical industry in the development of its technology appraisals and clinical guidelines is as follows:

a) NICE drafts a written consultation on the scope for a technology appraisal or a clinical guideline.

b) 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.

c) 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.

d) 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.

e) 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.

The Pharmaceutical Price Regulation Scheme

113. The Pharmaceutical Price Regulation Scheme (PPRS) is a mechanism for determining the profit made by drug companies through the sales of their medicines to the NHS.[73] Details of the Scheme, which has been running since 1956 (when it was known as the Voluntary Price Regulation Scheme) are negotiated periodically by the Department of Health and the ABPI. The present Scheme came into force on 1 January 2005 and, unless either side withdraws beforehand, will continue until at least 2010. The overall objectives of the PPRS are to:

- Secure the provision of safe and effective medicines for the NHS at reasonable prices;
- Promote a strong and profitable industry capable of such sustained research and development expenditure as should lead to the future availability of new and improved medicines; and
- Encourage the efficient and competitive development and supply of medicines to pharmaceutical markets in this and other countries.

114. The PPRS, which applies only to companies supplying licensed brand name products to the NHS, indirectly controls drug prices. Although it nominally applies to all such drug suppliers, only those companies with sales each year to the NHS of more than £25 million become involved in detailed negotiations. Sales by the 44 companies currently involved at this level account for 94% of the total amount the NHS spends on purchasing brand name products.

115. Through the Scheme, each year individual companies are set a level of return on capital (ROC; the amount of money they can earn through sales to the NHS). Once this profit target has been agreed, it is for the company to adjust the prices of its portfolio to reach that target. Companies are required to reimburse the NHS when their returns are above target, and may increase their prices when returns are below target.

116. Target ROCs are set in advance, so the profit actually achieved may differ from that predicted. To take this into account, margins of tolerance (MOTs) are built into the PPRS such that reimbursement is not required until returns are over 140% of the ROC target, and price rises not permitted until returns are less than 40% of the ROC target. Increasing the prices of established drugs is not encouraged, so companies generally aim to reach their ROC targets by charging high prices for their drugs at the time of launch or by broadening their sales base.

117. In order to set the ROC target, each year the company submits details of its business in an annual financial return (AFR). One section of the AFR seeks information on the company's fixed assets (which includes the historic cost of the company's UK sites, land, buildings, plant and machinery). The profit the company is allowed is then calculated as 21% of the fixed asset figure, which, with the MOT, may rise to 29.4% of the fixed assets.

118. Also included in the determination of the final ROC are allowances for the company's spend on R&D, marketing and the provision of information. For R&D, the allowance is

[73] See http://www.dh.gov.uk/PolicyAndGuidance/MedicinesPharmacyAndIndustry/PharmaceuticalPriceRegulationScheme

equivalent to up to 28% of the company's sales to the NHS, and in this figure provision is made for each new drug introduced. For drug promotion, the figure is 4% of sales, and to this is added further allowances depending on the number of drugs available. For providing information, the allowance is again equivalent to 4% of sales to the NHS.

119. By determining company profit margins allowed against the sale of medicines to the NHS, and by incorporating into these margins allowances for R&D, innovation, drug promotion and the provision of information, the PPRS provides a key mechanism by which the Department can act as the UK-based industry's sponsor.

120. The price of generic medicines is not controlled by the PPRS but, since August 2000, the main generics used in the community have been subject to a statutory maximum price scheme. This cap on prices was introduced following 'turbulence' and alleged price-fixing in the generics market that led to substantial prices increases in 1999/2000.

Drug and Therapeutics Committees

121. Local NHS measures may also be in place to control the activities of the pharmaceutical industry. Drug and Therapeutics Committees (also known as Use of Medicines Committees), which operate in local hospital Trusts, address prescribing and medicines use across the Trust, including affiliated primary care trusts (PCTs). Their guidance may be stricter than that of NICE. [See boxed text in Part 6 for an example of a Drug and Therapeutics Committee.]

122. There are also Area Prescribing Committees, which operate across health authorities and aim to ensure appropriate medicines use across the primary and secondary care boundary. In addition, there are prescribing advisers, usually pharmacists, who are employed by Strategic Health Authorities and PCTs, and work to encourage rational and cost-effective prescribing in primary care. According to the Department of Health, over 1,200 prescribing advisers are now in place in England and Wales.[74] This works out at an average of fewer than four per PCT.

Professional bodies

123. The core guidance booklet published by the General Medical Council (GMC), *Good Medical Practice*, warns doctors against "involvement in any relationships with pharmaceutical or other companies which could raise, or be seen to raise, a conflict of interests".[75] The GMC states that this is intended to cover matters such as accepting any kind of substantial hospitality or gifts from pharmaceutical companies. According to *Good Medical Practice*, doctors must be honest 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. No mention is made of guidelines for medically qualified doctors working within the industry but the GMC is reported to be working with Faculty of Pharmaceutical Medicine to set standards for

[74] PI 01

[75] The third edition of *Good Medical Practice* was published in May 2001 and is available at: http://www.gmc-uk.org/standards/good.htm

doctors working for pharmaceutical companies.[76] The World Medical Association also issued guidelines in October 2004 on the relationship between doctors and commercial enterprises, with particular reference to the disclosure of interests in the context of research, conference attendance, gifts and affiliations.[77]

124. Other professional bodies, such as the Royal College of Nursing (RCN), Royal College of General Practitioners (RCGP) and National Pharmaceutical Association (NPA), may have individual policies in place regarding funding received from the pharmaceutical industry. For example, the RCGP, which received 3% of its annual income from the industry in the 2003–2004 financial year, stated:

> The College has strict guidelines on accepting money from any sponsor, in order to ensure that the sponsor has no direct influence on the educational content of an event or conference.[78]

125. Although the GMC pointed out that, "complaints about doctors asking for or accepting inappropriate fees or hospitality" from pharmaceutical companies are unusual, we have not heard of any standard policies in place among professional organisations governing the interaction between industry and their members. There is no centrally held register of personal or financial interests in the pharmaceutical industry. The RCN, which receives approximately 30% of its annual sponsorship income from the pharmaceutical industry[79], stated that individual contact between nurses and drug company representatives does not involve the College:

> Nurses can get offered the opportunity to negotiate payment of expenses for further training directly with company representatives without reference, support or the knowledge of the RCN. In these situations the RCN is not in any way involved, and does not attempt to regulate.[80]

The industry's codes of practice

126. The industry has its own arrangements for regulating the sales and marketing activities of its companies. This is largely achieved through the Code of Practice of the ABPI.[81] The Medicines Act and related EU legislation requires Ministers to exercise oversight of these activities. All aspects of the promotion of medicines, including advertisements, representatives' activities, meetings, the provision of education and hospitality and the provision of medical information by the industry are subject to self-regulation through the Code. The ABPI states that the industry "works well within self-regulation".[82]

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[76] PI 120

[77] Further details can be found at http://www.wma.net

[78] PI 19

[79] PI 42a

[80] PI 42

[81] The ABPI Code of Practice is administered through the Prescription Medicines Code of Practice Authority.

[82] PI 35

127. The Code, first established in 1958 and since revised several times, was drawn up in consultation with the BMA, the Royal Pharmaceutical Society of Great Britain (RPSGB) and the medicines regulator. Compliance with the Code is a requirement for membership of the ABPI. A review of the Code, which began public consultation on December 17th 2004, is currently underway and is expected to conclude in November 2005.

128. The Proprietary Association of Great Britain (PAGB, the trade association representing the manufacturers of OTC medicines) covers promotion of OTC medicines. A condition of membership of the PAGB is the pre-vetting of all material directed to consumers.[83]

129. The Prescription Medicines Code of Practice Authority (PMCPA) was established by the ABPI to administer the Code for the pharmaceutical industry at arm's length from the ABPI itself. The Code covers the promotion of prescription-only medicines to health professionals and other staff, and communication with the general public.[84] There is no requirement for pre-vetting promotional material under the ABPI Code. The PMCPA is responsible for providing advice, guidance and training on the Code of Practice and it also handles complaints regarding advertising materials.

130. Complaints submitted under the ABPI Code come from three main sources: health professionals (30% in 2003); companies (46%) and those nominally made by the Director of the PMCPA (17%). In total, 131 complaints were received in 2003. Of the 122 cases actually considered (some related to matters not subject to the Code with no *prima facie* case and others were withdrawn), 97 (80%) were found in breach of the Code and 20% were not. Allegations may be appealed; 31% of appeals succeeded in 2003.[85] Details are published in the PMCPA's quarterly reviews and are expected to be made available on the Internet.

131. In each case in which a breach is ruled to have occurred, the chief executive of the company concerned must give an undertaking that the practice in question will cease forthwith, and ensure "all possible steps have been taken to avoid a similar breach in the future". This means materials have to be recalled immediately and destroyed. The major sanction is "the publication of comprehensive reports on all completed cases in the Code of Practice Review", which may be picked up by the medical and pharmaceutical press and occasionally the national press.[86]

132. Additional sanctions of the Appeal Board include a requirement to recover items distributed in connection with the promotion of a medicine and for the company to undergo an audit of its procedures in relation to the Code of Practice (two such audits occurred in 2003). In addition, the ABPI Board of Management may make a public reprimand, demand an audit, publish a corrective statement or suspend or expel the offender from the ABPI. However:

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[83] PI 94

[84] PI 14

[85] PI 14

[86] PI 57

> 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.[87]

133. Gifts and hospitality are also covered by the ABPI Code of Practice:

> 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… Hospitality can only be provided for persons who qualify as proper delegates in their own right.[88]

134. Promotional reminder gifts (pens, pads etc) carrying a product name are permitted, up to the value of £6 and providing they are relevant to professional practice. The ABPI's Code of Practice states that hospitality may be offered only at a level that the recipient would be expected to pay him or herself.[89]

6 Control of access to medicines

135. Doctors are the principal gatekeepers of access to prescribed medicines but nurses and pharmacists have been given an increasingly important role. Greater prescribing powers has meant that these groups are now particularly involved in the management of minor ailments and chronic conditions.

136. The NHS is the pharmaceutical industry's primary client in this country. In 2002-3, the NHS spent £7.5 billion on drugs in England.[90] Most of this is spent on branded medicines, which account for around 80% of the NHS drugs bill.

137. The issuing of a prescription is the most common intervention of the health service, after the consultation itself.[91] 650 million prescription items were dispensed in 2003 in England alone.[92] The BNF gives information to healthcare professionals about medicines that may be prescribed on the NHS.

Drug classification

138. Medicines are divided into three categories: those that are obtainable only through the issue of a prescription, which have the status of prescription-only medicines (POMs), those available over the counter from a pharmacist, which have pharmacy (P) status, and

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[87] PI 57

[88] PI 57

[89] PI 14

[90] Prescriptions dispensed in the community. Statistics for 1993-2003: England. http://www.publications.doh.gov.uk/prescriptionstatistics/index.htm

[91] PI 19

[92] See Footnote 90

medicines available in outlets other than pharmacies, such as supermarkets (including many painkillers or anti-indigestion tablets), which have General Sales List (GSL) status. Medicines with both P and GSL status are also known as OTC drugs.

139. At the time of licensing, the great majority of drugs are POMs. Reclassification may take place after a medicine has been available on prescription for some time, when the regulator deems that the drug is safe enough for OTC availability. OTC drugs are often supplied in lower doses than the same medicine that is available on prescription. In 2004, following on from PICTF recommendations, the Government increased the number of drugs to be reclassified annually from five to ten.

140. Applications by pharmaceutical companies to reclassify drugs are evaluated by the MHRA, and the CSM advises as necessary. Public consultation follows, via the MHRA website. Evaluation of responses received, again by the MHRA, is conducted before approval is granted, which occurs provided no additional safety issues are raised. Other companies with similar drugs are prevented from carrying out 'switches' on the basis of the same data for 12 months. Agreement between stakeholders, such as the RPSGB and NPA, on the drug protocol is not mandatory before reclassification may take place. The MHRA is not required to take into account the clinical effectiveness of a product by itself in a public sales setting.

141. Broad controls on who may prescribe what are determined by the regulator. Below we look at doctor, nurse and pharmacist prescribing powers.

Prescribing

Doctors

142. Basic training in drug prescribing is included in medical teaching. Thereafter, prescribers are kept up-to-date about drug selection and prescribing developments mainly through the BNF, which they receive regularly; the work of the National Prescribing Centre, which publishes information and organises events; the *Drug and Therapeutics Bulletin* (*DTB*), which provides independent reviews of medical treatments; the work of NICE and through occasional circulars from the Chief Medical Officer and the MHRA/CSM. Doctors also receive extensive and targeted information from the pharmaceutical industry, in the form of various publications, promotional literature and sponsored events. The Department of Health spends around £4.5 million each year on providing independent medicines information to prescribers.[93] In contrast, the ABPI told us that around 14% of the industry's expenditure is on promotion and marketing.[94] Spend on information from the Department therefore represents about 0.3% of the approximately £1.65 billion a year that the pharmaceutical industry spends on marketing and promotional efforts.

143. Most prescriptions are issued by GPs. Between April 2002 and April 2003, 650 million prescriptions were dispensed to general practice patients in England. This represents an

[93] Public Expenditure Questionnaire 2004

[94] Q740

increase of 5.3% compared to the previous year.[95] Prescribing by doctors is subject to varying types of guidance and control. In some hospitals, Drug and Therapeutics Committees (or similar) demand high standards of benefit versus risk before allowing drugs on to the Hospital Formulary. They may be more stringent than NICE guidelines. In other hospitals, if clinical pharmacologists, specialist pharmacists or physicians with a special interest are not available, controls may be weaker. There are also Area Prescribing Committees, described by the Department as addressing prescribing and medicines use across primary and secondary care and comprising "a multi-disciplinary team, with contributions from PCTs and local NHS Trusts".[96] These Committees vary widely across the country. Remarkably, GPs, who issue the majority of prescriptions, have greater freedom than specialist hospital doctors in the range of medicines that they prescribe. Most PCTs do not have tightly controlled, evidence-based formulary systems, managed by Drug and Therapeutics Committees (or similar) and enforced by pharmacists.

Nurses

144. There are currently about 25,500 nurse prescribers in the UK.[97] Nurses are able to prescribe once they have successfully completed the extended/supplementary prescribing programme, which includes sections designed to equip nurses with the knowledge to assess evidence that may be provided by drug company representatives.

145. There are three types of independent nurse prescriber. The first is district nurses and health visitors, who may prescribe appliances, dressings and some POMs. Secondly, Extended Formulary Nurse Prescribers may, in addition to prescribing all drugs with P and GSL status, prescribe almost 180 POMs, including some specified controlled drugs. Approximately 2,400 nurses are currently qualified and registered to prescribe from the Extended Formulary and around 1,000 more are in training. This process implies that there will be much greater contact between nurses and the pharmaceutical industry:

> 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.[98]

146. Thirdly, from April 2003, amendments to NHS regulations also allowed the introduction of supplementary prescribing for first level nurses and midwives. Supplementary prescribing is defined as a voluntary partnership between an independent prescriber (a doctor or dentist) and a supplementary prescriber, to implement an agreed patient-specific Clinical Management Plan with the patient's consent.

147. Approximately 1,700 nurses and 100 pharmacists are currently qualified to act as supplementary prescribers. There is no restriction on the conditions that may be treated by supplementary prescribing, but chronic conditions are most likely to be treated in this way. There is no specific formulary for supplementary prescribers.

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[95] PI 19

[96] PI 01

[97] PI 01

[98] PI 42

Pharmacists

148. In 2000, the NHS Plan set an objective of making better use of pharmacists. Changes to pharmacy opening hours and the increasing array of services offered to customers form part of a larger programme that aims to increase the use of pharmacies by the general public.

149. Following negotiations with the NHS Confederation and the Pharmaceutical Services Negotiating Committee, which represents community pharmacy contractors providing NHS services in England and Wales, a new contract for high street pharmacists will be implemented (subject to a ballot by pharmacists) in April 2005. The new contract has been designed to encourage pharmacists to increase the range of services they offer. Such services may include, for example, blood pressure testing or smoking cessation programmes in addition to the supplementary prescribing role described above.

150. Supplementary prescribing for pharmacists was also introduced in 2003. In addition, there is currently a public consultation on options for independent prescribing by pharmacists.[99]

151. According to the PAGB, the British public prefer not to take medicines unless it is absolutely necessary.[100] Half of all symptoms experienced in any two-week period are not treated or are managed with a home remedy. The first port of call for treatment is therefore likely to be a pharmacist rather than a GP.

[99] MHRA consultation letter MLX 321: The proposals to introduce independent prescribing by pharmacists. http://www.mhra.gov.uk/news/mlx321feedback.htm

[100] PI 94

1. Control of medicines use at University College London Hospitals Trust (UCLH)

Drug and Therapeutics Committees are an important source of independent medicines information and prescribing guidance and control. Such Committees include representatives from all groups involved in prescribing, including representatives from local PCTs and at UCLH there is also a lay member.

The Committee evaluates applications submitted by consultants or other prescribers to include new drugs on the local formulary by examining clinical trials and other evidence relating to the medicines. Information on efficacy, safety, cost and ease of use are considered, according to a hierarchy of evidence. A decision is made to accept the application, decline it or request further information. Guidance on dose and duration of treatment is given. This information is invaluable, particularly because doctors are usually unaware that the licensing process does not consider the comparative efficacy of drugs.

At UCLH – where the Drug and Therapeutics Committee is known as the Use of Medicines Committee (UMC) – approximately 50% of applications are accepted. The onus is on the applicant to provide information, although the pharmacist will check that a comprehensive data set has been provided. The Hospital Management Board ratifies decisions.

Advice given by the UMC may be more stringent than NICE guidance. The line taken by UCLH on the prescribing of COX-2 inhibitors, for example, was much more restrictive than that of NICE, and preceded the NICE advice by several months. The Committee produced a leaflet on COX-2 inhibitors, explaining the decision on recommended prescribing limitations. As a result, prescribing levels, particularly in the local PCTs (primary care being a strong driver for the use of COX-2 inhibitors), was lower than the national average.

Unusual prescribing patterns, or sudden changes in prescribing rates of particular medicines, may not be immediately identified and addressed by UMCs, however. It seemed anomalous that the electronic production of prescriptions that is in place in most PCTs is not present in hospitals and that there is no centralised record of drugs prescribed and dispensed in hospitals.

Although all NHS trusts are required to have a Drug and Therapeutics Committee (or equivalent), there is no standard structure, membership, processes, powers or terms of reference. The UCLH UMC counts clinical pharmacologists and specialist pharmacists among its members. However, this is not true for many such committees, particularly in small trusts with limited clinical pharmacology and pharmacy support. Furthermore, many PCTs do not have medicines management committees with the scope and influence of secondary care trusts' Drug and Therapeutics Committees.[101]

[101] See Recommendation in Paragraph 380

7 Inappropriate level of industry influence?

152. In the EU, companies undertaking legitimate business have a right to market their goods and services and, as part of accepted business strategy, will endeavour to influence their market environment to the company's advantage.

153. In each member state there are laws, codes and informal arrangements designed to control company activity and ensure probity. UK-based drug companies and those working on their behalf are subject to general legislation as it relates to, for example, employment, contracts, companies, patents, investment, negligence and human rights. In addition, drug companies are subject to legislation related specifically to medicines and their use, such as the laws that control the manufacture, promotion, sales and supply of medicines, or the conduct of clinical trials. Drug companies are also subject to non-statutory codes of conduct and informal arrangements based on 'good practice'. Non-statutory controls determine, for instance, much of the business associated with the PPRS, ethics committees, the MHRA, and aspects of the industry's own Code of Practice.

154. It is clear that influence is inappropriate if it is gained through company activities that breach statutory or other accepted control arrangements. In this instance, inappropriate activity would include, for instance: publishing misleading advertisements; advertising (or covertly promoting) prescription-only medicines to the public; failing to advise the MHRA of new research findings that might indicate additional risks that accompany the use of their products.

155. Notwithstanding that there are areas of influence covered by controls, other areas of influence exist for which there are no such controls. There is evidence that in certain areas, company influence is excessive and contrary to the public good. A distortion in the balance between industry and public interests can be seen as inappropriate not by breaching any law but because the very excess might be a destabilising influence and put patients at risk. Such behaviour would legitimately raise concerns equivalent to those recognised when companies maintain a monopoly position. Examples where the influence might be excessive, and so inappropriate, are discussed in the next chapter.

156. Deciding precisely when 'non-statutory' excesses are being undertaken and that their effects are counter to those of the public interest is not an easy task. It requires the ability to detect the excess, consider the issues in the widest context, act promptly, make judgements that are impartial, and be in a position to provide (or suggest) workable remedies.

157. The degree of the industry's influence leads to questions of expectations, responsibilities, accountability and the nature of its collaboration with other interests. There is obviously huge scope for productive collaborations between public and private sector, but to what extent is complicity and conflict of interest involved? These are clearly issues for public debate, central to the effectiveness of the NHS, and key factors in shaping health policy and responding to medical needs.

8 Influence of the industry on key groups

158. Throughout this inquiry we received much evidence about the influence of the pharmaceutical industry. We were told that it permeates the health service, regulatory and licensing bodies, research institutions, Government and the public perception of medicines. The extent of this influence was pithily expressed by Dr Richard Horton, editor of *The Lancet*:

> The pharmaceutical industry has been enormously successful at inter-digitating itself in the usual process of healthcare 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.[102]

159. Here, we examine the claims made by witnesses about the industry's influence on the processes, groups and organisations that determine what medicines patients receive and how they are used. We also look at how those bodies which regulate the industry, and other potential countervailing forces, have responded. The key processes, groups and organisations include:

a) Research, particularly research priorities and the conduct of medical research;

b) Prescribers;

c) Patients and patient organisations/medical charities;

d) The drug regulatory system; and

e) Government and associated bodies, including NICE.

Research into pharmaceuticals

Research priorities

160. The pharmaceutical industry determines to a great extent what drug research is carried out. Although expert groups may recommend that research be conducted in certain areas, there is no way of ensuring that companies themselves undertake or fund such research.[103] Approximately 90% of clinical drug trials and 70% of trials reported in major medical journals are conducted or commissioned by the pharmaceutical industry. As it does most of the research, inevitably the industry not only has a major effect on what gets researched, but also how it is researched and how results are interpreted and reported.[104]

161. The ABPI stated that the research conducted by the pharmaceutical industry is well-aligned to the priorities of the NHS. For example, some 43% of new medicines introduced

[102] Q517

[103] PI 27

[104] PI 27

over the past 10 years by the industry support four of the NHS's key health priorities – cancer, coronary heart disease, mental health and illnesses of the elderly.[105] Moreover, the industry explores therapeutic areas that have been overlooked by the medical profession, perhaps due to a feeling that 'lifestyle' problems rather than medical issues are involved. An area such as impotence, for example, was not traditionally investigated or treated to any extent by the medical profession, despite being of great concern to the individuals affected. In large part due to industry promotion and awareness campaigns, the issue is now more likely to be broached by patients with their GPs, and patients are more likely to receive treatment.[106]

162. The Government is fully aware of the pharmaceutical industry's dominance of drug research. An official from the Department of Trade and Industry (appearing alongside officials from the Department of Health) told us:

> 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.[107]

163. The Government stated that it could not support any radically different approach to the present system of medicines development and expressed no concerns about its lack of influence on which drugs are developed by industry and which conditions are prioritised by it:

> 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).[108]

164. Others were critical of the Government's approach. They claimed that industry's commitment to provide its shareholders with a good return on investment inhibited development of new and improved treatments in the areas of greatest medical need.[109] It was argued that drug innovation tended to be targeted at diseases of affluence rather than priority health needs, and was primarily directed towards developing products for established and emerging mass markets. [110] Furthermore, it was claimed that, unsurprisingly, there is little commercial interest in non-drug intervention and few clinical trials are carried out in this area.

165. We received evidence about such problems from many quarters. The RCGP noted that more money is now invested in research into the prevention of disease, such as drugs to reduce cholesterol, 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

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[105] PI 35

[106] PI 106

[107] Q9

[108] PI 01

[109] PI 27

[110] PI 19

towards the rich.[111] Similarly, Cancer Research UK was concerned that "there is little incentive for industry to conduct research aimed at small patient populations", and that there is little industry funding for research to determine the subgroups of patients that benefit from particular therapies.[112]

166. However, no one put forward a satisfactory, radically different system. Some witnesses thought that the NHS itself could undertake research on unprofitable areas to counter this problem. Others doubted this, because the NHS lacked robust mechanisms to identify its research priorities and had neither the infrastructure nor funding to undertake this type of clinical research.[113] On the other hand, there were suggestions for a number of relatively minor but useful changes. The Kings Fund argued that new forms of Public-Private Partnership were required in which the public interest would be given greater weight; it added that the Department of Health should use the same criteria for commissioning research on other treatments as on drugs.[114]

167. The RCGP stressed that the health service should encourage drug companies to align their research strategies with the public health aims of the NHS to a greater extent.[115] Lord Warner, Parliamentary Under Secretary of State, had some sympathy with this proposal:

> … 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.[116]

Innovation and therapeutic advance

168. Over the last decade, there has been a drop in the rate of new molecular entities (NMEs) entering the market.[117] At the same time, there has been a high level of 'me-too' drugs – medicines that perform the same or almost the same therapeutic function as one or more products already available. There are no figures for the UK on rates of 'me-toos' that are approved, but evidence from the US, which is likely to be similar, shows this trend clearly. The FDA categorises the NMEs it reviews and approves for marketing into those that deserve priority review and those which receive a standard review. Priority review indicates that the FDA views the NME as offering a potentially significant therapeutic advance whereas standard review implies that the NME is a 'me-too'. Over the last 10 years or so, the proportion of NMEs offering significant therapeutic advance has varied between 23% and 54% (though other sources suggest that these figures overestimate the extent of useful drug innovation[118]). The predominant trend in the absolute number of drug innovations offering significant therapeutic advance is downward. The graph below shows

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[111] PI 19

[112] PI 59

[113] PI 106, 47

[114] PI 81

[115] PI 19

[116] Q1006

[117] See Paragraph 48

[118] Q261. Dr Richard Nicholson suggested that under 10% of drugs licensed are truly innovative.

the change in the number and percentage of NMEs granted priority review from 1996 to 2003.

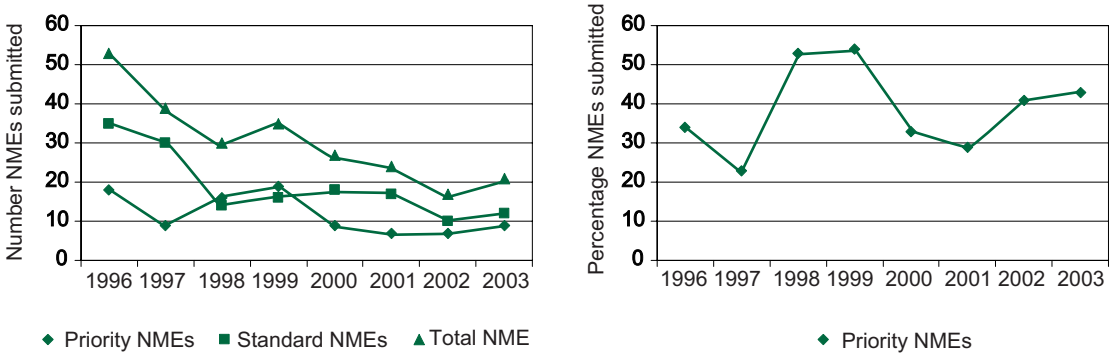

Figure 7
(Source: www.fda.gov/cder/rdmt/NMEapps93-03.htm)

In short, fewer than half of the new drugs approved in the US can be expected to offer significant therapeutic advance and the number of new drugs is falling overall.

169. Several reasons for the high number of 'me-too' drugs and the fall in overall innovation were discussed. One explanation is that investigation into new drug classes or treatments aimed at unexplored illnesses is risky and expensive. AstraZeneca stated:

> 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.[119]

The industry argued that truly innovative medicines are often those which are later shown to have difficult side-effects. Industry representatives felt that this meant that they were, "damned if we do and…damned if we do not".[120]

170. Another theory is that 'me-too' drugs may be more profitable. Prof Patrick Vallance agreed that true innovation is risky, but added that greater commercial benefit may also be associated with the development of 'me-too' drugs.[121]

171. It is also alleged that drug companies have turned to 'me-toos' because they are dominated by their marketing force rather than their research teams.[122] Alternatively, several companies may pursue similar lines of research concurrently, and so often release related drugs within a relatively short space of time.[123]

172. Whatever the reason, it was claimed that the existence of too many similar drugs on the market does not benefit patients. Dr Ike Iheanacho, Editor of the *DTB*, told us:

> 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

[119] PI 33

[120] Q680

[121] PI 106

[122] Q253, Q 471, Q 527

[123] This issue was discussed during our visit to Pfizer in Sandwich.

> actually constitute genuine innovations for patients, you would be surprised, I think, to find that relatively few of them do, and a decreasing number do.[124]

173. Often, however, the first drug in a therapeutic class does not always offer the greatest advance. It may be that the second or third drug of its type to enter the market is more efficacious or has fewer adverse side effects. 'Me-toos' are worthwhile, both because they can produce small therapeutic advantages (e.g. convenience) to patients and prescribers and because unexpected benefits may emerge. For example, Pfizer told us:

> 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.[125]

GSK concurred, stressing the benefits of small ongoing improvements in drug performance and of creating competition between different medicines to drive improvement. Specifically, the company argued:

> 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.[126]

174. Specific examples of occasions when a new medicine was not truly innovative but offered significant advantages to patients or to the organisation and delivery of healthcare over other drugs in its category were provided by the ABPI (see Table 1).

First to Market (condition)	Follower	Class	Benefit of follower
Accolate (asthma)	Singulair	Leukotriene modifier	More convenient dosing (once a day versus twice a day
Beconase (allergy)	Flixonase	Intranasal steroid	Potency; fewer adverse events
Zovirax (cold sores)	Valtrex	Herpes anti-viral	More convenient dosing
Mevacor (high cholesterol)	Lipitor	Cholesterol-lowering	Potency
Tagamet (heartburn)	Zantac	H_2 antagonist	More convenient dosing; fewer drug interactions
Cozaar (high blood pressure)	Diovan	Angiotensin receptor blocker	Potency

Table 1: Benefits of incremental innovation[127]

[124] Q98

[125] PI 28

[126] PI 51

[127] PI 35

175. The existence of a number of similar drugs to treat a given condition brings advantages. One drug might be best suited to one group of patients, another to another. However, there are disadvantages when there are a large number of drugs. It is difficult for non-specialists to stay well-informed about more than two or three drugs in any one therapeutic class. Moreover, comparative studies would be needed to assess the relative efficacy and safety of the available drugs, but these are not usually done.

Conduct of medical research

176. There is widespread agreement that a great deal of first-class research is undertaken by the industry, but witnesses made some criticisms of its conduct. These included:

a) Limited information given to trial participants;

b) Exposure of participants to unacceptable risks;

c) Use of ineffective comparator drugs and their inappropriate dosage;

d) The duplication of research; and

e) Lack of studies of the effects of drugs given in combination.

Much of the criticism was essentially of the lack of transparency and the difficulties for doctors and others in assessing the research which is undertaken.

177. The conduct of trials that do not yield evidence on which decisions can objectively be made was of particular concern. Five out of six systematic reviews published in the last two years have shown that research that is sponsored by a drug manufacturer is more likely to yield a positive result for the company's product than research that is independently sponsored.[128]

178. Patients eligible for clinical trials are required to sign consent forms to confirm that they are aware of the trial's aims and agree to take part. RECs are obliged to ensure that adequate information is provided to patients about the trials in which they participate, such as whether it is a public sector trial, a contract, a licensing study, whether it is being done through the NHS or in a private capacity where the NHS is not involved.[129] Several witnesses argued that, currently, the information patients receive before they enter a trial fails to adequately disclose the risks they might incur and how the data collected from their participation might be used.[130] The consent forms do not inform patients that the raw data may be maintained by the industry, not made available to the general public or even reviewed by the regulatory authorities. Prof David Healy stated:

> The industry takes the data from you, they let you take all the risks, they conceal the 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.[131]

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[128] Lexchin JR. Published online, 23 Oct 2004, www.theannals.com

[129] Qq29-32

[130] PI 104, PI 77, Q195, 503

[131] Q172

179. Furthermore, under ICH, even when conducting clinical trials with new drugs intended for chronic use to treat non-life-threatening conditions, patients (and healthy volunteers) may be exposed to such drugs for six months before long-term animal studies are completed to determine whether the drugs cause cancer. The responses we received from the MHRA and industry did not indicate that patients are made aware of this upon entry into trials nor that the MHRA has given serious consideration to whether this is ethically justified.[132]

180. Clinical trials can provide very important data about drugs but they do not always provide the clear information on drug safety and therapeutic effectiveness that is needed. It is claimed that many clinical trials are designed to fit desired outcomes or, worse, primarily for marketing purposes, rather than the advance of health care or scientific understanding. Dr Richard Nicholson, editor of the *Bulletin of Medical Ethics*, told us:

> 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…and found absolutely no advantage of their drug. They were hoping that by comparing it to naproxen, which had just five per cent of the market, they would be able to show an advantage.[133]

181. In order for a drug to be licensed it has to show that it is more effective than a placebo, usually in two controlled trials. However, according to Prof Healy, companies can run 10 or more trials in carefully selected samples using instruments designed to pick up any effect and, even if the results show that the drug failed to beat placebo in the majority of trials, the drug may still be licensed. The trials producing negative results are commonly identified as failed trials rather than drug failures.[134]

182. Whether the experimental drug is compared to placebo or a comparator drug will affect the outcome. Common flaws in trial design include the use of inappropriate comparator drugs, such as those associated with a higher risk of side-effects than others in the therapeutic group. Selection of dosage may also be used to skew results. Administration of a comparator drug in unduly low doses may result in reduced levels of efficacy. Administration of the comparator drug at relatively high dosages might make the test drug appear safer than it really is. These and other methods of trial design may show the new drug in a misleadingly positive light.[135]

183. Also of concern, because it may lead to an over-estimate of the drug benefit, is reliance on surrogate markers of efficacy or disease (in one case, higher numbers of extra abnormal heartbeats were assumed to correlate with increased risk of death[136]). However, such markers may not be directly relevant to treatment outcomes (in this case, drugs used to reduce the number of heartbeats were actually associated with increased mortality). The

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[132] Q37, 38. This area was also explored during our visit to Pfizer in Sandwich.

[133] Q253

[134] PI 77

[135] PI 65

[136] PI 29

use of combined clinical outcomes can also be problematic, making it difficult to assess which end point has really changed, while the use of inappropriate safety markers makes extrapolation to safety in clinical practice even harder. Cancer Research UK criticised the industry for not investigating the wider effects of drugs and focusing on specific outcomes.[137]

184. Several witnesses were also concerned about the duplication of research.[138] Some organisations make considerable efforts to avoid this problem: the MRC requires groups seeking financial support to identify existing evidence before applying, to show that the new research builds on previous lines of investigation.[139] On the other hand, others either did not attempt to find out about previous research or could not get access to it.[140] Sir Iain Chalmers argued that a systematic review of existing evidence prior to the planning and reporting of new clinical trials should be mandatory.[141] The following example shows what can happen if such a review is not undertaken:

> 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…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.[142]

185. While in Sydney, we heard from the Australian Federation of AIDS Organisations about the reluctance of the pharmaceutical industry to undertake studies of existing drugs given in combination. Other organisations often lack the funding to undertake this work. Cancer Research UK told us:

> 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.[143]

186. The key to solving many of these problems is greater transparency.[144] Prescribers and particularly those involved in compiling formularies need to understand better how medical research is conducted and results are presented. Witnesses suggested that RECs

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[137] PI 59

[138] PI 22, PI 106, Q408, Q508

[139] PI 22

[140] Q408, Q432, Q439

[141] Q408

[142] PI 29

[143] PI 59

[144] Intellectual property protection need not be a barrier to transparency. Sir Richard Sykes commented that "the whole point about intellectual property is to make it available to everybody so that everybody can see what you are doing" (Q416)

might have an important role to play in the design of trials, ensuring the use of clinically relevant end points, the meaningful comparison of drugs and other approaches and the proper disclosure of clinical trial results, taking account of both positive and negative findings.[145] A requirement that the applicant should identify existing research would ensure trials were not duplicated.

187. The major impetus for greater transparency with medicines came from a lawsuit brought in August 2004 by the New York State Attorney General against GSK, alleging the company had concealed negative clinical trial results. As part of the settlement, GSK agreed to set up a public register of all clinical trials on all of its drugs.[146] This breached a long-standing convention, vigorously upheld by the regulators, whereby clinical trial results were regarded as company property and commercially confidential. Other companies soon followed suit, and the industry (through national trade associations) made proposals in January 2005 to establish a clinical trials register before the end of 2005.

188. Information on every trial involving patients will be posted at inception, although the full details of the register are not yet clear. Whether the register will include trials carried out in every country and who will be responsible for maintaining the register have not yet been divulged. Witnesses have stated that the results of trials involving drugs that are approved for marketing by the MHRA will be posted on the register and publicly accessible within one year of launch.[147] However, the period immediately after launch is when doctors prescribing the drug for the first time are most in need of such information. Effective drug use depends on awareness of the strengths and weaknesses of evidence on which the manufacturer relies. We are also concerned that the maintenance of the clinical trials register by the pharmaceutical industry itself will not inspire confidence from either the public or healthcare professionals. We make recommendations regarding the clinical trials register in Chapter 9.

189. **Priorities for research into medicines inevitably reflect the interests of the pharmaceutical companies and are not necessarily well aligned with the medical needs of all patients. The industry will continue to undertake the bulk of research in this area, but there are improvements which could be made. We welcome Lord Warner's recognition of this and look forward to his proposals to align more closely the drug companies' research strategies with the public health aims of the NHS.**

190. **However it occurs, the presence of many 'me-too' drugs on the market creates difficulties for prescribers and the NHS. Although this is a considerable problem, we were given no obvious solution. We expect that there will continue to be a large number of me-too drugs. The National Prescribing Centre and others should particularly consider issuing independent advice in areas where many 'me-toos' exist.**

191. **Much excellent clinical science takes place within the industry and elsewhere, but the current system of clinical testing provides ample opportunities for bias. Too many problems appear to persist unnoticed or unacknowledged by the organisations that are central to the co-ordination, conduct and review of the clinical trials. There is a need for**

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[145] Q186

[146] See http://www.oag.state.ny.us/press/2004/aug/aug26a_04_attach2.pdf

[147] Q769

more transparency and we welcome the contribution that the proposed clinical trials register should make to this approach. The regulators must check that research is designed to provide objective evidence of a drug's efficacy and safety at the time of licensing.

Prescribers

192. Medicines information is provided in a variety of ways, many of which are welcomed by prescribers. Drug companies use representatives, advertising, journal articles and supplements, magazines and other media to communicate the benefits of their products.

193. According to the ABPI, "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." It added:

> 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.[148]

194. On the other hand, some witnesses had serious concerns about how drug companies communicate with doctors. Equally worrying was that some doctors were readily influenced by the promotional activities of the industry.[149] We look below at the use of journals, drug company promotional activities and advertising.

The use of journals

195. Medical journals, which carry articles relating to clinical trials as well as reviews, opinion pieces, case studies and letters, are an important source of information for healthcare professionals. They are also subject to influence by the pharmaceutical industry. It is alleged that too many articles do not present an objective assessment of the merits of a medicine; for instance, we were told that many are the work of ghost-writers and that there is a bias towards submission of articles that show new drugs in a positive light.

Ghost-writing

196. Approximately 75% of clinical trials published in *The Lancet*, the *New England Journal of Medicine* and the *Journal of the American Medical Association* are industry funded. This is only to be expected since drug companies conduct most drug research, but more surprising was the claim by one witness that over 50% of articles appearing in these journals may also be ghost-written.[150] Ghost-writing is the process by which articles are written by professional medical writers but appear under the name of independent physicians or academics, who are paid as if they had written the article. When the ghost-writer helps a busy doctor write up his research this is an acceptable practice. The key question is whether and to what extent these authors designed and conducted the studies, then independently analysed the original data and critically reviewed the article. It is clear

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[148] PI 35

[149] Q117, Q566

[150] PI 77

this is often not the case. This is of much concern, since such articles tend to be targeted at prestigious journals; if published, they are cited more often than articles written by authors not linked to the sponsoring drug company.[151]

197. The practice of ghost-writing articles, mainly in the form of reviews and editorials, on the off-label use of licensed medicines[152] was described by Dr Horton, the editor of *The Lancet* as "standard operating procedure" and he warned of "biased, over-interpreted and misreported research findings." He added:

> A very good example, to be very specific, is this whole story surrounding SSRIs. … 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.[153]

198. Witnesses from both GSK and AstraZeneca strongly denied that ghost-writing was practiced in their respective companies. Dr Stuart Dollow, from GSK, went as far as to state: "The issue of ghost-writing, as alleged, is not something I recognise at all."[154] However, there may be some confusion about what the term 'ghost-writing' actually means. Dr John Patterson, from AstraZeneca, told us:

> 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.[155]

199. Sir Iain Chalmers recommended that the industry adhere to guidelines set out in *Good Publication Practice for Pharmaceutical Companies*[156] that aim to ensure that publications are produced in a responsible and ethical manner. They include the need to publish results of all clinical trials of marketed products, and to report them in a balanced and objective manner. Authors should all have access to the statistical reports and data supporting each publication. These guidelines are clear on the subject of authorship and the role of professional medical writers:

- The named author/contributors must determine the content of the publication and retain responsibility for it;

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[151] PI 77

[152] The use of a medicine to treat a condition other than that for which it was approved

[153] Q533

[154] Q689

[155] Q696

[156] Originally published in *Current Medical Research & Opinion* 2003;19:149-154

- The named author/contributors should be given adequate time to comment on an early draft of the manuscript and approve the final version;
- The medical writer should remain in close and frequent contact with the authors throughout the development of the manuscript; and
- The contribution of the medical writer should be acknowledged.

200. These guidelines leave no room for ghost-writing, in the form of researchers or academics who put their names to articles but have not seen the raw data to which the article refers.[157] Until good publication practice is put in place for all companies, Sir Iain emphasised:

> I think it is a very, very serious situation. In other words, if companies are really genuine about wishing to adopt the sort of publication practices [that do not allow ghost-writing], then they should sign up to that guideline.[158]

201. However, it would be quite wrong to only blame the industry for the excesses of ghost-writing. So-called 'key opinion leaders' agree to lend their name to articles they have not written and may receive a significant fee for doing so. Dr Peter Wilmshurst, a consultant cardiologist told us about the size of fees:

> 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.[159]

Publication bias

202. Several witnesses referred to the fact that studies which reveal a positive result for an experimental treatment are more likely to be published than those showing equivocal or inferior findings.[160] GSK agreed but suggested this might be due to journals' editorial policies:

> 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.[161]

203. On the other hand, allegations that several studies showing negative or equivalent findings for Seroxat (a GSK drug) were suppressed provide an alternative explanation. We were told that publication bias is more likely to arise from drug companies' reluctance to

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[157] The European Medical Writers Association have also recently issued guidelines for medical 'ghost-writers', which are published in *Current Medical Research & Opinion* 2005, 21:317-21

[158] Q423

[159] Q134

[160] PI 05, PI 30, PI 112,

[161] PI 51

submit articles showing their products in a less that favourable light.[162] Studies comparing all clinical trials have shown that, overall, pharmaceutically sponsored trials are less likely to be published than trials commissioned by other organisations.[163] As Cancer Research UK emphasised:

> 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.[164]

204. There is no current obligation on drug companies to publish all trial findings, although individual companies may do so. AstraZeneca's policy, for example, specifically states that selective publication is not acceptable.[165] According to the industry, the proposed clinical trials register[166] will require that the results of all trials on marketed drugs are made available, but only after marketing approval has been given.

205. The number of articles written about specific treatments also contributes to publication bias. Drug company marketing departments often have a target number of publications on their products to achieve each year. Supplements to medical journals, which contain several articles relating to a single drug, procedure or disease area, are an easy way for the company to attain this goal. Often based on a sponsored symposium at a conference, or company-organised 'workshop' that experts are paid to attend, the articles contained in the supplement might be neither written by the experts themselves nor peer-reviewed by the journal editors. The pharmaceutical companies pay a high price to produce supplements bearing a journal's imprint. Once published, the supplements may be reprinted thousands of times, again at the expense of the sponsoring company. The reprints may be distributed to doctors by visiting company representatives and are usually displayed on the company's stands at related conferences. Sale of reprints represents a major source of income for many journals and an important means of marketing for the pharmaceutical industry. The scientific value of these publications can be limited, however:

> 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.[167]

206. In addition, Dr Horton described how journalists working on magazines distributed free (to GPs in particular) may have their travel and hospitality paid in order to attend conferences to report specific research findings. He told us:

> 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…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

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[162] PI 19

[163] Krzyanowska MK, et al. *Journal of the American Medical Association*. 2003;290:495-501. This study showed that late-phase industry sponsored trials were as likely to be published as non-sponsored trials.

[164] PI 59

[165] PI 33b

[166] See Paragraphs 187-188

[167] PI 108

> 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.[168]

207. The "seeding" of this information in literature received by prescribers, and GPs in particular, then "has enormous impact on prescribing habits".[169]

208. These practices, including of ghost-writing and non-publication of negative results, therefore lead to a body of written evidence that may not reflect the true safety and efficacy profile of the drug in question. This may result in potentially dangerous prescribing decisions, as the Royal College of Psychiatrists describes:

> If pharmaceutical companies only publish clinical research that is positive and hold back on publishing clinical research which is negative, then patients may well be given treatments which, unknown to either the patient or the doctor, are likely to do more harm than good.[170]

Drug company promotional activities

209. Research conducted by Which? has shown that GPs may often not have time to keep themselves abreast of drug developments and may therefore place a high value on their relationships with drug company representatives as a source of information and education.[171] AstraZeneca argued:

> Interaction with sales representatives enables healthcare professionals to gain access to the latest information and ensures their continuing professional education…. Representatives educate [healthcare professionals] on the correct use of the Company's medicines through reference to data and licensed indications.[172]

210. According to the ABPI's Code of Practice, visits should not normally exceed three annually but a GP, Dr Des Spence from the group 'No Free Lunch', told us that the cumulative effect was such that drug company representatives' contact with doctors "can almost be on a daily basis".[173] The potential benefits of contact on prescribing habits are not in doubt, however. For example, statistics from IMS Health, an organisation that collects and analyses healthcare data, indicated that the promotion of drugs by representatives increased uptake of NICE guidance:

> 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.[174]

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[168] Q587

[169] Q588

[170] PI 103

[171] PI 53

[172] PI 33

[173] Q93

[174] PI 66

211. The timing of the provision of medicines information and promotion is pertinent. The first few months following drug launch is a crucial period in medicines promotion, during which the industry attempts to establish the market position of a drug; yet this period of explosive marketing occurs at precisely the period in which we know least about the effects of a drug in the community. The MHRA chairman told us that the main lesson learned from investigation into the use of SSRI antidepressants, for example, was that the safety profile of a medicine, when first licensed, "is not very well known".[175]

212. Information is also provided by non-industry sources, such as the National Prescribing Centre, *DTB*, prescribing advisers and committees. Lord Warner described it as "vast".[176] Based on the evidence we have received, however, the volume of such information pales in comparison to the information received, directly and indirectly, from the pharmaceutical industry. According to Dr Andrew Herxheimer:

> The volume [of promotion] 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.[177]

213. Independent information has been described as 'limping along' behind commercially driven information. Not only is it at much lower volumes but it is not so precisely targeted as information from the companies. The imbalance, which is mainly due to the disparity in available funding, is overwhelming.[178] The industry spends £1.65 billion a year on marketing and promotional efforts while the Department of Health spends £4.5 million.[179]

214. In addition to receiving visits from company representatives, doctors are invited to attend sponsored events, meetings, workshops and symposia, which may be little more than "hospitality masquerading as education".[180] In combination with company representative visits, they have a major effect on prescribing practice. When questioned, however, doctors usually deny that drug promotion affects their own prescribing practices (although they do believe that it affects other doctors' prescribing habits).[181]

Promotional campaigns: targeting of healthcare professionals

215. Marketing and promotional activity in the pharmaceutical industry has increased in recent years. Since 1995, research staff numbers have fallen by 2% while marketing staff numbers have increased dramatically.[182] Much competition appears to be based on marketing techniques and PR.

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[175] Q810. See Recommendation at Paragraph 380

[176] Q948

[177] Q200

[178] Q200

[179] Information derived from Q740 and Public Expenditure Questionnaire 2004

[180] PI 05

[181] This evidence was presented to the Committee in Australia, by Dr David Henry of the University of Newcastle, New South Wales.

[182] Staff numbers may have risen by as much as 59%, according to Dr Richard Smith, ex-editor of the BMJ: http://www.websee.org/documentacion/conf_richard_smith.ppt

216. We commissioned an analysis by the Institute of Social Marketing (ISM) at the University of Stirling of samples of company information relating to selected promotional campaigns, some of which may already have been considered by the PMCPA for alleged breaches of the ABPI Code of Practice. The analysis revealed the targeting of specific healthcare professionals, such as GPs and practice nurses[183]. The documents obtained were analysed around key themes taken from the Code:

- Servicing the emotional needs of health professionals and the use of branding;
- Creation of 'need' within the medical profession;
- The use of public relations to counteract negative publicity.

217. The documents were also analysed for evidence of targeting patients and the general public. This is discussed in the next section. The companies, the ABPI and PMCPA were given the opportunity to comment on the analysis. We regret that we had to ask for a speedy response in order to publish this report before the election and are grateful for their swift attention to this matter.[184]

Servicing the emotional needs of health professionals

218. A key theme, consistently emerging from the sample documents examined, was the importance attached to identifying the emotional needs of health professionals and designing marketing activity to satisfy such needs. Brands were deliberately associated with attributes that could not be described as 'objective and unambiguous' as required by the Code of Practice, including, "energetic", "passionate", "desirable", "sexy", "romantic", "intimate" and "relaxed". In subsequent evidence, the PMCPA stated that "emotional messages" may be used as long as the material is "factual [and] balanced".[185]

219. The industry also recognised the pressure GPs are under when prescribing and the difficulties they face on a daily basis, such as the risk associated with prescribing the correct medication, perceived difficulties in patient compliance and the risk of criticism from peers. Such worries and concerns were exploited by the industry to promote use of their brands by conveying "trust", "confidence" and "reassurance". Slogans were chosen to tap into insight of hassle of "how difficult the patients will be to treat", "likelihood of compliance", and the emotional "button" of risk.

Creation of need within the medical profession

220. The documents highlighted the tactics employed by pharmaceutical companies to create a need among the medical profession before the launch of specific brands. For example, one company devised a five-stage mail-out to doctors for the launch of a new brand. The first two stages were used to create a need for new treatments and did not include any information about, or branding of, the new product. The remaining three

[183] PI 125

[184] PI 126, PI 128, PI 129, PI 130, PI 131, PI 132, PI 133

[185] PI 126, PI 128, PI 129, PI 130, PI 131, PI 132, PI 133

stages were used to introduce the new brand and outline its safety and efficacy and the impression that it was being widely prescribed.

The use of PR to counter negative publicity

221. Public relations is particularly important during times of bad publicity, especially when the safety of brands is called into question. Considerable resources are invested into building long-term, sustainable relationships with stakeholders and 'key opinion leaders' and journalists. These relationships are used to promote the use of certain brands and counter concerns relating to safety. Efforts to undermine critical voices in particular were identified, under terms of "issues management". In later evidence, in response to the ISM's memorandum, Pfizer stated that PR is entirely legitimate and can "help to educate and inform". According to the PMCPA, PR activities may include "placing articles in the lay press, TV documentaries, soap operas etc".[186] The following example of a project worksheet shows the marketing campaign process and the targeting of consumers and the press.

[186] PI 126, PI 128, PI 129, PI 130, PI 131, PI 132, PI 133

2. Drug company project worksheet

Objectives

- To build advocacy with consumer press to secure greater share of voice
- To increase understanding of the importance of visiting GPs for [disease marker] checks
- To create a positive press environment for BRAND X in 2005
- To generate awareness of the positive risk: benefit of BRAND X
- To secure publication of three articles within the consumer media by end of March 2005

Description

- Identify target publications within the [publishing house]
- Liaison with publishing house to confirm and arrange logistics
- Liaison with design company to develop press materials including take home booklet
- Liaison with key journalists to confirm attendance
- Liaison with XXX to confirm participation
- Identification and recruitment of a practice nurse and GP to conduct [disease marker] tests and provide medical information
- Ongoing liaison with attendees to secure media coverage

Outputs/Deliverables

- Attendance of eight key journalists at the session
- Three articles in consumer press agreed for publication by March 2005 (availability of case studies will support securing coverage)
- 80% key message delivery within coverage

Outcomes

- Positive press environment for BRAND X
- Increased understanding of the need to approach GPs for information on [disease marker] monitoring
- Increased understanding of the centrality of [disease marker] management in reducing the risk of [condition]
- Strengthened relationships with target journalists to ensure BRAND X possesses a

greater share of voice in the future

Target Audiences

- Consumer journalists
- Consumers

222. While it is clear that the Code of Practice relates only to literature intended for external use, and many of the documents examined were for internal circulation only, the intention of the companies is clear.

Advertising

223. We were told that advertising to prescribers is conducted on a huge scale; it is targeted and orchestrated to increase prescription of particular drugs in particular groups. According to Dr Herxheimer, the influence of the industry:

> …is mediated…by the huge volume of pharmaceutical promotion, direct and indirect …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.[187]

224. The main concerns are not so much to do with the accuracy of individual advertisements but with the scale of medicines advertising, as Dr Herxheimer indicated, and the process and duration of the complaints procedure, which was frequently referred to during the inquiry.

225. Which? cited the following case to illustrate the inadequacy of the current pre-vetting and complaints system for prescription-only medicines advertising:

> 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."
>
> *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 September 9 2002) to sue *DTB* for defamation.
>
> Prompted by *DTB*'s article, the PMCPA began an investigation into the promotion of Yasmin and concluded (on September 18 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

[187] PI 65

> appeal by Schering), in concluding (on 22 November 2002) that the company had breached the PMCPA's Code of Practice on 11 separate counts.
>
> 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.
>
> 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).[188]

226. The MCA did not know that the PMCPA was investigating *DTB's* concerns until alerted by *DTB* itself, indicating a lack of coordination or communication between the two. Following *DTB's* article in August 2002, the MCA undertook a second assessment of Schering's claims for Yasmin, the results of which were released in a letter to *DTB* on 6 December 2002. This time, the MCA found Schering's claims unacceptable and asked the company to withdraw the advertising and to publish a corrective statement in the journals that had carried the original advertisement. The correction appeared in February 2003, which was around 10 months after the launch of Yasmin.

227. The ABPI stated that, "like the House of Commons, the pharmaceutical industry works well within self-regulation,"[189] but the examples cited to us of breaches of advertising regulations, cover-up of negative medicines information and provision of misleading information to prescribers suggest that self-regulation is not working satisfactorily.

228. The delay in investigation and issue of corrective statements, which are not always mandatory, is clearly unacceptable. Where such statements are issued, their effect on the original impact of the campaign is usually limited. Patients may be already taking the new medicine and are therefore unlikely to be switched back to their original treatment. Mr Mike Paling, the director of a large advertising company, stated:

> 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 think if there is a complaint, particularly if it is going to be upheld, it should be adjudicated and sorted out very quickly.[190]

229. Small alterations to advertising slogans may also be requested – from, for example "Protection for hearts" to "Help protect your heart". This case, involving Zocor Heart-Pro, was one on which the MHRA took a "very serious view".[191] We do not consider this a very serious sanction.

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[188] PI 53

[189] PI 35

[190] Q596

[191] See: http://medicines.mhra.gov.uk/ourwork/advertpromed/complaints/zocor_nov04.htm

230. Promotional activity takes place on a huge scale. Nevertheless, it is impossible to solely blame the industry because some doctors do not take enough care when prescribing. Although doctors are taught clinical pharmacology at medical school, the quality of teaching on evaluation of clinical trial data and drug marketing techniques seems to be highly variable and prescribers often lack the time or skills to distinguish between weak and strong clinical studies and to evaluate critically the claims made. The 'How to use a drug' lectures that form part of the Clinical Pharmacology course at UCL Medical School include essential information about the processes needed to evaluate data on new medicines fairly and effectively. Areas covered include the power of the trial and size of treatment effect as well as factors such as conflicts of interest, the use of 'rentaquote' doctors and how new treatments are reported in the lay press.[192] However, it would not be safe to assume that all doctors receive such training.

231. The volume of information received by prescribers and the accuracy (data interpretation, completeness, comparison with existing treatments) of the information provided were questioned by many witnesses.[193]. However, some doctors' failure to recognise that promotional techniques used by the pharmaceutical industry have any effect on their decision-making suggests a dangerous complacency that needs to be addressed. The enormous variation in prescribing of some medicines illustrates this point.

232. **The aggressive promotion of medicines shortly after launch, the sheer volume of information that is received in its many forms by prescribers and the "promotional hospitality masquerading as education", in the absence of effective countervailing forces, all contribute to the inappropriate prescription of medicines.**

233. **Ghost-writing, in conjunction with suppression of negative trial results, is harmful. If prescribers do not have access to fair and accurate accounts of clinical trials they cannot be expected to make informed prescribing decisions. Guidelines on the subject of authorship and the role of professional medical writers (quoted in Paragraph 199) must be followed.**

234. **At the same time, the blame for inadequate or misinformed prescribing decisions does not only lie with the pharmaceutical industry, but with doctors and other prescribers who do not keep abreast of medicines information and are sometimes too willing to accept hospitality from the industry and act uncritically on the information supplied by the drug companies.**

[192] Information supplied by UCL to the Committee.

[193] Q101, Q137, Q200, PI 27

3. Over-promotion and over-prescription of benzodiazepines: legacy of a bad campaign

Although much has changed in drug regulation and prescribing practice in the last decade, the over-prescription and subsequent widespread adverse events and 'therapeutic' dependence on benzodiazepines is perhaps a good illustration of the dangers of drug promotion by the pharmaceutical industry and under-regulation or over-reliance on industry self-regulation.

Benzodiazepines, which include Valium, Librium, Mogadon and Ativan, were introduced as a replacement for barbiturates, which were found to cause dependence, were associated with severe withdrawal symptoms (such as seizures and hallucinations) and lethal in overdose. Benzodiazepines were first marketed in the early 1960s and were widely prescribed until the 1980s for a variety of conditions, including anxiety and panic disorders and insomnia.

Despite anecdotal evidence and some clinical trial data to the contrary, most large-scale (industry-sponsored) trials led people to believe that benzodiazepines did not cause dependence and that they were much safer overall, particularly in overdose, than barbiturates. More and more anxious or sleepless patients were therefore prescribed them as a treatment. In 1979, 30 million prescriptions for benzodiazepines were written in the UK.[194]

A report in 1980 by the Committee on the Review of Medicines (a body since abolished) stated that benzodiazepines tended to lose their sleep-promoting properties after approximately two weeks of continuous treatment and to lose their anti-anxiety properties after approximately four months' treatment. However, the results of short-term trials were extrapolated and many patients continued being prescribed them for years on end. There is also evidence that the dosages used were far above those necessary to treat the conditions intended.

The side-effects of benzodiazepine treatment are now known to include excessive sedation, decreased attention, amnesia and sometimes intractable dependence. Abrupt cessation can lead to severe withdrawal symptoms, including convulsions in some patients. Short-term treatment and a long tapering period is now recommended to limit these risks.

It has been estimated that around 500,000 people in the UK were dependent on benzodiazepines in the mid-80s. High current levels of addiction (up to 1.5 million) have also been suggested. According to Mr Barry Haslam, who was addicted to benzodiazepines for 10 years:

> 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.[195]

[194] HC Deb 31 March 1988, Cols 657-8W; 27 February 1990, 121-2W

[195] PI 64

A large-scale legal action was brought against the manufacturers of Ativan (John Wyeth) and of Valium, Mogadon and Librium (Roche) in 1986. By 1992, over 12,000 claimants were involved in this litigation. However, most claimants were funded under the Legal Aid scheme and the Board withdrew this funding in 1996. To date, no redress against the companies involved has been made, and the legacy of an influential promotional campaign in the 1960s continues.

There is a lack of support and rehabilitation services available for people still addicted to benzodiazepine drugs, many of whom may have been first prescribed them in the 1970s or 1980s. Not a single NHS benzodiazepine rehabilitation clinic exists in the UK to this day.

Patients

235. There is much contact between the pharmaceutical industry and the general public and the extent is increasing. The industry is obliged by law to provide information to the public in the form of the patient information leaflet (PIL) supplied with all medicines. OTC drugs may be advertised directly to the public; prescription-only medicines may not. However, we were informed that promotional campaigns for prescription-only medicines were also targeted to patients.

236. In this section we examine the information that is received by patients, in the form of the PIL, through direct-to-consumer advertising (DTCA), disease awareness campaigns and other promotional campaigns. We also look at the relationship between industry and patient organisations and charities.

Information to patients: the Internet and PILs

237. Patients (and their carers) clearly wish to be informed about their condition but find it difficult to obtain independent specialist information. The wealth of information available on the Internet reflects this demand. The mental health charity Mind summed up the situation:

> Research with users of medication consistently shows a demand for information, which is often not met by the prescriber. For example, 61 per cent 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.[196]

238. Many companies stressed frustration at their inability to provide information directly to patients through their information service when much unofficial and unchecked information is on the Internet and elsewhere. According to AstraZeneca:

> 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

[196] PI 27

> 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.[197]

239. PILs should be the most straightforward way for the industry to provide patients with the information they require. Unfortunately, they are rarely in a comprehensible form. Dr Iona Heath, from the RCGP, commented:

> A definite problem is that people are frightened by these things and the fact is that [a] huge list of potential side effects is written to defend the company legally with no indication of prevalence. … They are not contextualised in any sort of way about how likely that is to happen to you and that information is available. In the actual way it is presented, nothing is done to mitigate the fear which comes with information.[198]

240. The problem is widely recognised and the MHRA has set up a Patient Information Working Group to address the matter. There are concerns that too few lay people are involved in this group, however. There may need to be a change in the legal requirements for PILs. A design firm provided the Committee with an impressive example of a PIL which was clear and patient-friendly but, as the designers admitted, it did not meet the existing legal framework.[199]

Direct-to-consumer advertising

241. Direct-to-consumer advertising of prescription-only medicines is currently only permitted in the US and New Zealand. Advertising medicines in this way is clearly effective in increasing sales of medicines. A US study published in August 2002 by *PharmTrends*, a marketing service for the industry that monitors purchasing of prescription-only and OTC drugs, reported that one in five of 25,000 respondents said DTCA prompted them to visit their family doctor to discuss a drug they had seen advertised. In total, 22% said DTCA had made them aware that there were drug options to treat their condition and 12% had been prompted to ask their doctor about an advertised drug.[200]

242. The increase in the number of drugs reclassified from prescription-only to OTC status has implications for advertising. Zocor, for example, is now widely advertised on television and in publications such as the *Radio Times* and national newspapers. The *Daily Mail's* medical correspondent reported that the newspaper now carries full-page advertisements for this drug.[201]

243. While increased awareness of the availability of treatment options is desirable, sharp increases in annual spending on medicines have been observed in the US and New Zealand following successful advertising campaigns. Overall, the proportion of expenditure on

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[197] PI 33

[198] Q283

[199] PI 127

[200] PI 16e. Direct-to-consumer advertising (DTCA) of prescription medicines: third quarterly update - July to September 2002, Colin Meek November 2002. Commissioned by the RPSGB.

[201] Q609

advertised drugs, and number of prescriptions written, is significantly higher than for non-advertised drugs (see Figure 8).

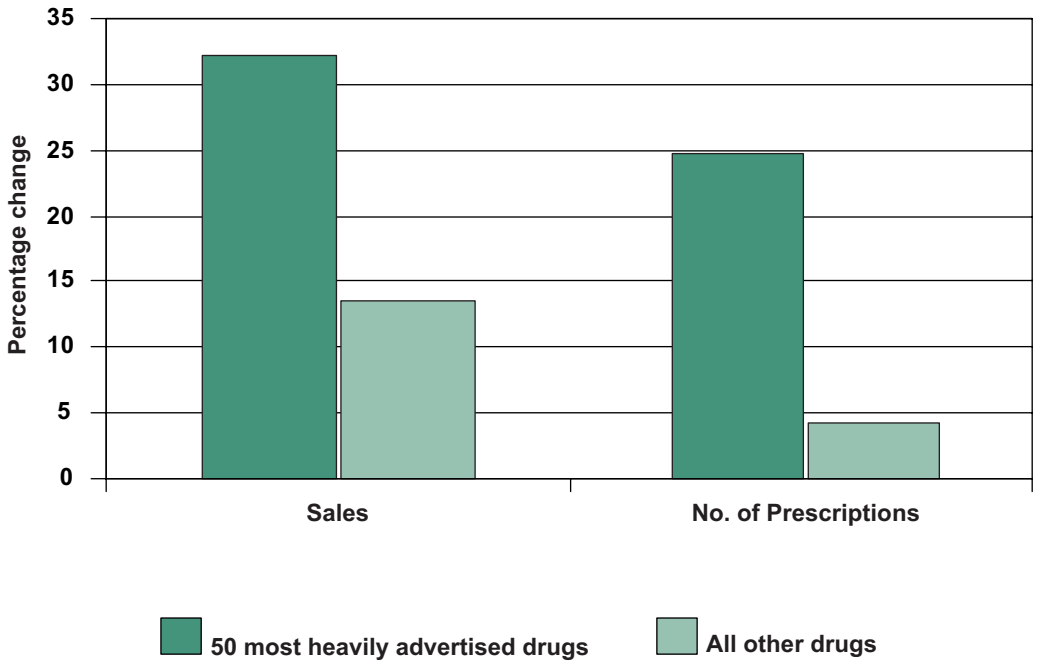

Figure 8: Change in sales and number of prescriptions 1999–2000 (US).

Data from US NIHCM Report 2001

244. Studies of this kind have led to concern that DTCA encourages the unnecessary and inappropriate use of medication. Distorted prescribing behaviour, due to doctors and other prescribers being 'talked into' prescribing the drug of the patients' choice, has also been reported. Healthcare professionals are more likely to prescribe a brand-name drug when a patient asks directly for it rather than another, possibly generic, version of the same medicine.[202]

245. In the UK (and Europe) the industry has emphasised that it is not intent on introducing DTCA of the kind seen in the US, which now attracts expenditure about $4 billion/year.[203] We were told by Ms Margot James, European President, Ogilvy Healthworld:

> 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

[202] PI 53

[203] The Henry J. Kaiser Family Foundation, Daily Health Policy Report, 21 March 2005

> few years ago. …There is no appetite among pharmaceutical companies for bringing that kind of advertising to the UK.[204]

246. However, the industry is determined to communicate directly with patients; the ABPI argues that, "no one knows more about a medicine than the people who discovered, developed and made it available". The ABPI's Informed Patient Initiative Task Force (whose remit is to work with the ABPI to make recommendations to the MHRA on patient information) 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."[205] It seems anomalous that others can provide information about drugs on the Internet but pharmaceutical companies cannot do so officially. However, there are concerns about relaxing the rules, not least because a suitable format for PILs has not been established.

Disease awareness campaigns

247. Disease awareness campaigns encourage individuals to seek advice or treatment from their doctor for previously undiagnosed conditions. We received allegations that disease awareness campaigns can act as advertisements for prescription-only drugs, particularly where there is a particularly well-known brand of treatment.[206] Such campaigns, which may be established by a drug company with or without the endorsement of a patient group or charity, often take place at the same time as the drug's launch and may involve aggressive promotion of a particular medicine to prescribers. Mr Graham Vidler, from Which? told us:

> What those awareness campaigns will do is encourage the public to go and see their GP, often in quite strong terms, saying, "Go and see your GP. Be forceful. There is something that can be done." Simultaneously, the companies will be advertising specific drugs to those GPs, and … quite often it [is] easiest for them to take the path of least resistance.[207]

248. Witnesses argued that the use of disease awareness campaigns, which in the past have involved conditions including depression, anxiety and obesity, play a major part in the "medicalisation" of our society; in short:, "where disease awareness campaigns end and disease mongering begin is a very indistinct line".[208] Dr Des Spence, representing the group 'No Free Lunch', asserted that the bombardment of the general public and patients served, "to undermine our collective sense of well being".[209] Dr Spence was especially concerned about the 'Defeat Depression Campaign' and its effect on prescribing patterns and the public's perception of depression:

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[204] Q619

[205] PI 35

[206] PI 53, Q250, PI 16i: Letter to MCA from RPSGB in July 2002, commenting on draft disease awareness campaign guidelines: "One of the problems with [disease awareness campaigns] is that if there is only one product (or a clear brand leader) to treat a particular condition then promoting the condition equates to promoting the product."

[207] Q92

[208] Q651

[209] PI 05

> [That campaign] 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 ten 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.[210]

249. The 'Defeat Depression Campaign' (1992–1997), which was run through the RCGP and the Royal College of Psychiatrists, and sponsored by the manufacturers of antidepressants (who provided approximately one-third of the funding) targeted doctors as well as patients, in particular to emphasise that these drugs did not cause addiction or dependence. These claims have since been disputed and a warning about withdrawal symptoms is now included in the SPC. The Royal College of Psychiatrists provided supplementary evidence emphasising that the Defeat Depression Campaign had been intended to make it clear "that antidepressant treatment was not appropriate for mild to moderate depression, but effective only for severe or clinical depression".[211] This important message evidently got lost; indeed there remains much confusion on this point today.[212] The Royal College also told us it had recently reviewed its policies on accepting commercial sponsorship, and now aims to keep total income from these sources at around 5% of the College's annual turnover. Commercial sponsorship accounted for under £500,000 (5.5% on turnover of £9m) in 2003.

250. According to the Royal Pharmaceutical Society of Great Britain (RPSGB), disease awareness campaigns may hide potentially adverse consequences. Those seeking screening, diagnosis or treatment might, for instance, receive a false-positive result that leads to the individual undergoing an unnecessary procedure. Witnesses said that the guidelines, which were drawn up between the MHRA and the ABPI, are inadequate.[213] The guidelines state that the risks associated with treatment and the fact that treatments are not always suitable or effective for every individual should be made clear[214] but, we are told, the industry does not always adhere to these recommendations.

251. No witness suggested that all disease awareness campaigns were cynical attempts to increase drug sales, but many doubted that they were simply aimed at improving the lives of those with unmet medical needs. It is not acceptable for such campaigns to be veiled advertising for branded prescription-only medicines.

Promotional campaigns: targeting patients and the general public

252. Documents requested from drug companies were analysed to determine whether promotional campaigns also targeted non-professionals[215]. The pharmaceutical industry is

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[210] Q91

[211] PI 103a

[212] See boxed text after Paragraph 305

[213] PI 05, Q89, Q651

[214] PI 16

[215] PI 125

prohibited by law and by the ABPI Code of Practice from not only targeting but from aiming to target patients and the general public with marketing and promotional activity relating to prescription-only drugs. In many of the documents, however, patients and the general public emerged as key targets in internal literature (which is not covered by the Code of Practice). Detailed and continuous market research, for example, is conducted with these groups to uncover their emotional drivers and motivations, which are then exploited to encourage presentation to medical services with the overall aim of benefiting the pharmaceutical company in question. PR activity is also used to encourage media coverage with the clear intention of targeting patients, patient groups and the general public. As Ms Jenny Hope, medical correspondent with the *Daily Mail*, told us:

> I do not feel that I am being used but I feel I am a target for promotional and marketing activity.[216]

253. There is clear evidence that the industry is concerned with identifying populations who are not currently presenting for diagnosis. In one document relating to the "strategic planning process," these patients, who, "do not currently present to their GP or take prescription medications," are referred to as "the missing millions" and are estimated to comprise almost 2 million people in the UK. This population is viewed as providing a "significant opportunity" for the company.[217]

254. Research is then conducted on behalf of the company that aims to understand what barriers exist to prevent these people from presenting and to identify factors, both rational and emotional, that will overcome these barriers and encourage patients to seek professional advice. The following example comes from the company's brief for a PR firm:

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 with [the condition]
- Explore their rationale/belief systems that inhibit them from presenting
- Identify hooks and drivers to encourage them to seek advice both emotional and rational.

255. The documents make it clear that the companies are concerned with using the results of such research to design strategies that are able to "target these customers" and go as far as identifying which of these customers will be most "receptive" to their communications. Research is also conducted with the general public to "evaluate and communicate channels that could be used to target customers" and highlights more general communication principles that need to be considered when targeting such groups. The outcomes of the

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[216] Q560

[217] PI 125

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.

256. 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.

257. These company documents suggest that the pharmaceutical industry intends to manipulate marketing principles, such as the perceived source of communications and distribution outlets, in order to make the general public more receptive to its marketing activity.

Examples of PR activity targeting patients and general public:

258. A considerable number of documents described PR activity targeting patients and the consumer press. It is clear that PR activity is vital and part of a coherent strategy, both reactive and proactive, for many pharmaceutical companies. Specifically, this activity is consistently designed to tap into and exploit the target audience's emotions and deliberate efforts are made to build emotional elements into campaigns. One document mentions the specific targeting of consumers, while another mentions the use of "patient case studies for use in articles/press and media interviews", with a view to targeting patients and patient groups.

259. The use of 'key opinion leaders' for such purposes was recognised by two witnesses from the press, though both were somewhat sceptical about their effectiveness. Ms Hope told us:

> The PR industry sets great store by opinion leaders which slightly mystifies me…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 Lois Rogers, medical editor at the *Sunday Times*, added:

> Even the expression "opinion leader" to me is a deterrent [it] would immediately tell me that that person is in the pocket of that drug company.[218]

[218] Q562

4. Medicalisation: future risks of genetic testing

The introduction of gene-based therapy, which targets pre-disposition to disease rather than disease itself, is a recent development in medical research. Gene sequences can be patented and genetic tests developed on the basis of these groups of genes. There is currently no regulatory assessment of clinical data relating to genetic testing in the EU, although the UK Genetic Testing Network has developed procedures and criteria for evaluation of genetic tests for use within the NHS.[219]

There has been a surge in recent years in the use of genetic tests in medicine. Genetic testing has, for example, led to increased numbers of women with a strong family history of pre-menopausal breast cancer undergoing genetic screening for mutations in the BRCA1 and BRCA2 genes. Testing is only suitable for a small number of women who are particularly at risk. Options to reduce this risk include elective mastectomy. Inherited, or familial, forms of breast and other types of cancer represent approximately 5–10% of all cancers. In addition to genetic testing for several inherited types of cancer, testing for other conditions is increasingly common. Examples of predictive diagnostics include genetic tests for Tay-Sachs disease and cystic fibrosis.

The WHO recently announced the approval of the first international standard for a human genetic test, for a genetic mutation known as Factor V Leiden. This mutant gene induces a defect in the blood clotting system and is a major risk factor for venous thrombosis, and also increases risk of miscarriage and pre-eclampsia.

A further positive aspect of genetic research is the determination of those patients likely to respond to treatment on the basis of their genetic make-up. So-called pharmacogenetics are being increasingly used by industry and drug companies have been keen to point out the benefits of individualised treatment based on this type of research.

The concept of 'genetic predisposition to disease' is therefore one that has gained widespread acceptance in recent years. However, being genetically predisposed to a disease does not mean that it will actually develop – there is an environmental component that interacts with other biological factors, such as the presence of particular disease antibodies. According to GeneWatch:

> 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 [and are also now available over the counter][220]

We were told that it is in the pharmaceutical industry's interest to classify as large a proportion of the population as possible as 'abnormal'.[221] Genetic susceptibility to disease is an additional means of classifying a significant percentage of the general 'well' population

[219] PI 22

[220] PI 18

[221] PI 19

in this way. The proportion of individuals classified as genetically susceptible to particular types of disease seems likely to rise dramatically in the future. The availability of genetic tests, some of which are already advertised and may be purchased directly by the consumer in the US, has grown.

Pre-emptive treatment of 'predisposed individuals' is likely to target the healthy in Western countries, to promote the use of supplements, lifestyle advice or preventative medication and increase the proportion of the population taking medicines regularly. Roche is the world leader in the market of medical tests. It already plans to market a genetic test for heart attack risk in the next 2–3 years.

Additional fears surrounding genetic testing include causing a reduction in positive lifestyle changes in the absence of 'genetic susceptibility'. For example, smokers tested for a predisposition to smoking-related disease (such as lung cancer or chronic obstructive pulmonary disease) who receive negative results may be persuaded that they need not give up. Worryingly:

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.[222]

Patient organisations

260. Over 200 national patient organisations and support groups exist in the UK today. Such groups provide information and a range of services to their members and the general public and often campaign for increased access to particular treatments. A goal of many patient organisations is to influence healthcare policy for the benefit of patients; as the MS Society described, this aim often coincides with that of the pharmaceutical industry:

> 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.[223]

261. Pharmaceutical companies may provide direct funding of a charity or valuable contributions in kind, such as distributing leaflets to GPs' surgeries. CancerBACUP, for example, stated:

> 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 10 major companies. There is no branding…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.[224]

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[222] PI 18

[223] PI 25

[224] PI 07

262. Most charities claim that they remain independent despite involvement with the pharmaceutical industry, but stress that they simply could not survive without financial input from this source. According to Depression Alliance: "The simple fact is that the strength of the mental health charity is its independence. Without that independence, our voice would hold no sway."[225]

263. The Long-term Medical Conditions Alliance (LMCA) indicated the advantages of close contact between industry and patient groups. In particular, it argued, it ensures that the information needed by patients is provided by the manufacturers of the products in question. Charities are able to influence the workings of the pharmaceutical industry through identifying patient-centred outcomes, ensuring treatment regimes meet patients' needs and that information provided by manufacturers is balanced and appropriate for users of the product.[226]

264. The benefit to the industry of close associations with patient groups was illustrated in a survey of US executives from 14 pharmaceutical and biotechnology companies: 75% of respondents cited patient education as the top-ranked marketing activity necessary to bring a brand to number 1.[227] Drug companies benefit further when charities agree to endorse their products by allowing their logo to appear alongside an advertisement for the drug or details of a sponsored disease awareness campaign.

265. However, many witnesses told us of the disadvantages of close relationships between patient groups and the industry. We received evidence that some groups receive substantial sums from the industry and campaign to increase the availability of medicines for their members in the absence of strong supporting evidence. Dr Tim Kendall, from the Royal College of Psychiatrists, commented:

> I am aware that there are some…like Depression Alliance, which have very substantial funding at times from drug companies. 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.[228]

266. Charities can be harmed by working closely with the industry. Dr Ike Iheanacho, the Editor of the *DTB*, told us:

> 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 character - here it is - and it is 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. In terms of the charity, the charity did not know about the problem, that this was bad behaviour, until they were alerted by the media, who pointed it out:

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[225] PI 54

[226] PI 36

[227] *The Pharmaceutical Journal* 2004, 272: 635-636

[228] Q296

> "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.

267. Paul Flynn MP described fears that pharmaceutical companies use patient organisations as "conduits to promote their products in a subtle form of marketing". This leads to a situation in which, instead of representing the interests of patients, groups "become marketing tools for the pharmaceutical companies".[229] Referral by the pharmaceutical industry to patient organisations as "ground troops" for lobbying Government to increase access to new drugs is further evidence of this.[230]

268. The need for charities' relationship with the industry to be transparent was repeatedly made. At present, however, there is no requirement for such groups to declare to the general public the names of donors or the type or amount of support received. A report by *Health Which?* found that, of 125 patient organisation websites, donors were listed on 32. Only two groups (Diabetes UK and the Alzheimer's Society) explained their funding policy.[231] Furthermore, links between charities and industry may be interpreted differently by patients and the charities themselves, with the sponsors products seen as, "preferable by the charity associating itself with the company".[232]

269. The LMCA publishes guidelines for patient groups on issues relating to relationships with the pharmaceutical industry. These cover the primacy of patients' interests, transparency regarding funding, the expectation of benefit to both sides, and the need for equality between both partners. In addition, limits on the amount or proportion of funding from any individual source, the importance of diluting the influence of any one donor by accepting donations from different commercial organisations, and commitments not to endorse specific products (or to do so only in specified circumstances) are stressed.

270. The Charity Commission also monitors charities' financial activities and requires that all charities make their accounts available on request to the public. The Commission may take action if it feels that undue commercial influence over a charity was giving rise to financial, reputational or governance issues. However there is no common definition for what would constitute "undue commercial influence".[233]

271. **The pharmaceutical industry's promotional efforts are relentless and pervasive. The evidence presented showed the lengths to which the industry goes to ensure that promotional messages reach their targets, and that these targets include not only prescribing groups, but patients and the general public.**

272. **There is an urgent need for a comprehensive and informative PIL, preferably one which indicates the role of the drug in overall management of the disease. We were advised that patients themselves should be involved in the process of developing such a**

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[229] PI 38

[230] This reference was made in an article , 'The Mark of Zorro', published in *Pharmaceutical Marketing* in May 2000. It cited the need 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."

[231] *Health Which?* April 2003

[232] PI 36

[233] PI 38

PIL. The MHRA's Patient Information Working Group is addressing this issue but the group is dominated by professional interests.

273. **DTCA is inappropriate and unnecessary in the UK. The evidence reviewed above on the targeting of prospective patients, and the central emphasis on emotional appeals, leads us to believe that great caution should be exercised in any relaxation of the rules relating to provision of consumer drug information by drug companies.**

274. **The existing guidelines on disease awareness campaigns are weak and unmonitored. Drawn up after limited public consultation, they make no strict demands apart from a requirement not to mention brand names. The effectiveness of future guidelines will depend on interpretation, monitoring and enforcement.**

275. **We often do not know what funds or support in kind patient groups receive from pharmaceutical companies. Limiting or legislating against such support is not appropriate; this would disadvantage both the charities that rely on industry funding and the industry itself, by cutting off a source of valuable feedback from the eventual consumers of its products. Measures to limit the influence of industry on patient groups are needed, however. Patient groups should declare all significant funding and gifts in kind and the Government should seek to make appropriate changes to charity law to ensure this. It would in any case be greatly preferable if patient groups were funded by companies' charitable arms, rather than by companies themselves.**

The drug regulatory system

276. The presence of a strong, independent drug regulatory system, committed to improved health outcomes, is not only vital to the public interest, but is also fundamental to the development of a healthy pharmaceutical industry. Without an effective regulator in place, licensing standards and operating procedures will not be maintained and inadequately tested medicines will enter the market. The pharmaceutical industry is a business, with obligations to its shareholders. The regulator should expect it to use any legal means to provide a return on investment.

277. The UK regulator, the MHRA, is in a potentially powerful position. Companies need to market new drugs, and benefit from drug approval. The industry has previously expressed concerns that excessive drug regulation and slow approval procedures are impediments to drug innovation, but we heard no strong complaint from its representatives on this score. The evidence presented to us indicated that the UK-based industry has confidence in the MHRA, and vice versa.

278. The pharmaceutical industry in turn exerts a strong influence on drug regulatory policy and process. This influence can be expected to increase because the EU will take more responsibility for drug licensing and because of the trend to global development of regulatory standards and protocols.

279. Globally, the ICH is becoming increasingly important. Its secretariat is run by the International Federation of Pharmaceutical Manufacturers & Associations. ICH standards which are adopted by the EU become binding on the MHRA, and determine the procedures and standards applied by the MHRA. Importantly, these may include restrictions on regulatory scrutiny. During the first oral evidence session, Prof Kent Woods

was questioned about one such restriction. A recently introduced ICH requirement prevents the MHRA from accessing the audit report required with each clinical trial – a critical document in assessing standards of compliance with GCP, including the quality of patient care. Under ICH-generated regulations, the MHRA may request sight of an audit report only if it suspects "serious non-compliance", otherwise it receives only a certificate confirming that the audit has taken place. This amounts to a Catch 22 position: the primary evidence of serious non-compliance would be in the audit report, but regulators may ask to see that report only if they suspect serious non-compliance. Surprisingly, the MHRA expressed no concerns about the issue. [234]

280. In its own interests, the Agency needs to keep a close eye on its market share of regulatory business: increasingly it competes with other European drug regulatory agencies to scrutinise drug licence applications. Like any other regulatory agency, the MHRA walks something of a tightrope, trying to strike a balance between support for the industry and effective medicines control. The MHRA Chairman, Prof Sir Alasdair Breckenridge emphasised:

> You have to balance each of these…systems of funding which we do have against the [health] incentives … 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[235]

281. There was little doubt that, even in the best-resourced regulatory bodies, the pressure on individual employees may become intense when problems arise. While our inquiry was taking place, Dr David Graham, Associate Director for Science and Medicine in the FDA's Office of Drug Safety, gave relevant evidence to the US Senate Committee on Finance in hearings following the withdrawal of Vioxx [236] and subsequently spoke about the relationship between regulators and industry:

> The FDA has become an agent of industry. I have been to many, many internal meetings and, as soon as a company says it is not going to do something, the FDA backs down. The way it talks about industry is 'our colleagues in industry'… it is rather because the body is entirely geared towards concentrating on approving drugs, doing little once they are on the market[237]

282. The relationship between the industry and the MHRA is naturally close. There are regular interchanges of staff, common policy objectives, agreed processes, shared perspectives and routine contact and consultation. Many of the senior staff of the MHRA have previously worked with the industry, the main exception being Prof Woods, who became chief executive of the MHRA in 2004. Overwhelmingly, the different parties appeared to speak the same language, with companies determined to observe the letter of the law and the regulators determined to uphold it. Dr Herxheimer stated:

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[234] Qq24-25

[235] Q862

[236] US Senate Committee on Finance. Hearings: FDA, *Merck and Vioxx: Putting Patient Safety First?* 18 November, 2004. See: http://finance.senate.gov

[237] Griffiths K; The Interview - Drug tsar who took on the system: David Graham, FDA whistleblower. *The Independent*, 12 February 2005

> …when the agency was hived off from the Department of Health…the culture became confirmed that the industry is the client and the client must be looked after: quick service, good service, easy contact, etcetera - so it is a closed community in a sense.[238]

283. Such closeness provides the basis of the trust that the MHRA said it relied on as an integral part of the regulatory process.[239] The MHRA Chairman suggested that trust underpinned the stance of the MHRA towards the companies they regulate. We inferred that this extended to the routine acceptance of companies' summaries of the results of tests on their drugs as true reflections of the raw data on which they were based.

284. Trust is critical in the relationship between regulators and industry. However, at the heart of this inquiry are the concerns of those who believe that the MHRA is too trusting. Trust should be based on robust evidence; it should be earned rather than presupposed. The evidence indicated that the MHRA examined primary (raw) data on drug effects only if it suspected some misrepresentation in the summary data supplied. It was argued that such trust in regulated companies goes too far: reliance on company summaries is neither sufficient nor appropriate, in the absence of effective audit and verification of data that companies provide. The secrecy surrounding this information is also unacceptable, as Sir Iain Chalmers commented:

> Denial of access to information held by the [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.[240]

285. Regulatory inertia was clearly illustrated through publication of the findings of the UK's first ever public investigation into a drug safety problem: the December 2004 report of the CSM's Expert Working Group (EWG) into the safety of SSRI antidepressants. The Group's main findings pointed to lack of evidence of risk (rather than risk itself) not least because a number of essential studies had never been performed. Some 10–15 years after licensing the major SSRIs, and in spite of several earlier reviews of the same drug problems, the MHRA had received no convincing evidence of:

- Drug efficacy in mild depression, accounting for some two-thirds of all SSRI prescriptions in the UK;[241]
- Any benefit to be gained with most SSRIs from increasing the dose above the recommended daily dose;
- The incidence of SSRI withdrawal reactions, a common and sometimes disabling side effect and the subject of much complaint.

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[238] Q169

[239] Q822

[240] PI 29

[241] Martinez et al, *BMJ* 2005; 330:389-393

Reputation of the regulator

286. The formal aims and objectives of the MHRA set out the commitment to "support industry and scientific innovation" but otherwise give little indication of the extent to which collaboration with the pharmaceutical industry affects the style and content of the Agency's work. The MHRA describes its responsibilities as:

> …protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely[242]

287. The reference to "promoting health", and ensuring drugs are "used safely" implies some recent and significant shift in the definition of regulatory responsibilities or, at least, the determination to communicate that public confidence in the present regulatory system is justified. A report by the National Audit Office (NAO) in January 2003[243] highlighted the lack of public profile and impact of the MHRA and stated that it ought to strengthen these aspects in order to fulfil its mission to provide information to contribute to the safe and effective use of medicines.[244] It is clear that some progress has been made in this regard. The new emphasis on the safe use of drugs both alters the Agency's regulatory interpretation and departs from the long-established tradition of not challenging the clinical freedom of prescribing doctors.

288. The MHRA claims to have made other changes and we received some convincing evidence of this. The MCA's original leadership responsibilities were defined, not in relation to health outcomes, but in terms of organisation. Dr Keith Jones, the MCA's previous director, has stated: "My role is primarily that of a medically, scientifically informed manager: I am there to oversee the running of the MCA and since July 1991, to advise Ministers on matters of medicines control."[245] However, in evidence to this inquiry, the MHRA Chairman emphasised the changes that had recently taken place, to distance the new MHRA from its predecessor.[246] Sir Alasdair stated:

> …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.[247]

289. The MHRA's proposed reorganisation of the Advisory Committee structure, for example, has signalled its awareness of the need to take greater account of patient and consumer perspectives and to avoid conspicuous potential conflicts of interest. The decision to accept reports from patients of suspected ADRs and publication on the Internet of this and other information gleaned from the Yellow Card Scheme is also notable. Such developments represent a significant advance on policies favoured only a few years ago.

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[242] See http://www.mhra.gov.uk

[243] NAO, *Safety, Quality, Efficacy: Regulating Medicines in the UK*

[244] PI 27

[245] See http://www.bseinquiry.gov.uk/files/ws/s447.pdf

[246] Qq775-776, Q779, Qq808-809

[247] Q779

290. In addition, a new Director of Communications and additional staff were appointed in February 2005 in response to implementation of the Freedom of Information Act and other pressure to improve levels of transparency and access to drug information:

> …setting up communications…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.[248]

291. For all such evidence of commitment to change, however, the reputation of the regulator ultimately stands or falls on its success in avoiding problems, especially those leading to drug withdrawals and giving rise to adverse publicity. Since it was formed, in April 2003, the MHRA has been involved in a succession of problems and seen unprecedented levels of concern (See Table 2, below).

292. The major safety problems related to SSRI antidepressants (notably Seroxat) and COX-2 inhibitors (notably Vioxx). Publicity has subsequently focused not only on the drugs involved, but on the quality of the regulatory system and its relationship with the pharmaceutical industry.

Date	MHRA safety-related announcements
2003	
04-Apr	Oral contraceptives and cervical cancer
10-Jun	Safety of Seroxat in children and adolescents
08-Aug	Hormone replacement therapy (HRT) and breast cancer
19-Sep	Safety of Efexor (venlafaxine) in children and adolescents
03-Dec	Use of HRT in the prevention of osteoporosis
10-Dec	Use of SSRIs in children and adolescents with major depressive disorder
2004	
09-Mar	Atypical antipsychotic drugs and stroke
11-Mar	Seroxat: reminder to use the recommended dose
09-Jun	New prescribing advice for the 40mg dose of Crestor (rosuvastatin)
30-Sep	Immediate withdrawal of Vioxx
14-Oct	Chiron flu vaccine: quality and safety concerns lead to closure of major vaccine plant
18-Nov	Updated guidance on the use of Depo-provera contraceptive
06-Dec	SSRI antidepressants: findings of the CSM Expert Working Group
17-Dec	New data on cardiovascular risk with celecoxib (Celebrex)
21-Dec	Advice on the use of Celebrex and other selective Cox-2 inhibitors in light of concerns about cardiovascular safety
22-Dec	Dynastat (parecoxib) and Bextra (valdecoxib): new information on cardiovascular safety and serious skin reactions
2005	
31-Jan	Co-proxamol to be withdrawn from the market (dangers of overdose)
03-Feb	MHRA issues new advice (relating to liver problems) on use of Strattera (atomoxetine)
17-Feb	MHRA issue updated advice on the safety of selective COX-2 inhibitors
18-Feb	MHRA highlights its recent advice on SSRIs

Table 2.

293. The timing of these problems was unfortunate for the reputation of the MHRA. It might be claimed that they were simply inherited from the old MCA, but the basis of drug licensing and regulation remains essentially unchanged. The new MHRA and old MCA do

[248] Q778

not differ in core regulatory activities, but, we are told, are rather concerned with image, reputation and questions of presentation.[249]

294. There was evidence of change in the CSM/MHRA report on the safety of SSRI antidepressants. For the first time, the regulators publicly summarised the clinical trial evidence on which their recommendations were based, and systematically identified the extent of data missing. We were told that the MHRA had taken prompt and effective action to investigate this case, whereas the MCA had repeatedly failed to do so. However, we also had significant concerns about the resulting conclusions and recommendations, including several unresolved issues.[250]

295. In setting up the review of SSRI antidepressants, the MHRA/CSM responded to another long-standing concern about regulatory activity: the possible conflicts of interest of regulators. Members of the EWG, which was set up in May 2003, were required to have no personal interests in any of the companies being investigated. This was the first time this requirement had applied; in previous investigations, conflicts of interest were not debarred, but were required to be disclosed. In future, Lord Warner assured us, the merged Medicines Commission and CSM will require "the chairs and members of the commission and the new statutory committees to have no financial interest in the industry," and "a stronger code of practice on declarations of interest".[251]

Post-marketing surveillance

296. The MHRA puts its main regulatory emphasis on scrutiny of pre-marketing data. It was argued that it gives too little attention to post-marketing surveillance to evaluate the effects of medicines in normal clinical settings. Sir Richard Sykes told us:

> 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.[252]

297. Both companies and regulators overwhelmingly rely on pre-licensing data, based on industry-sponsored clinical trials that measure drug effects in selected populations of patients in tightly controlled settings. Because these data are regarded as scientific, they routinely 'trump' much of the data collected through post-marketing surveillance, most of which is regarded as anecdotal. The net result is that data from clinical trials may provide the bedrock of understanding of a drug's benefit : risk profile, often years after approval.

298. Lord Warner appeared to dismiss concerns about weakness in the post-marketing surveillance system. He pointed out the "good track record" of the CSM on taking serious post-licensing evidence of drug safety issues:

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[249] Q778

[250] See boxed text after Paragraph 305

[251] Q915

[252] Q434

> You could argue that some of the high profile examples [e.g. SSRIs] 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.[253]

299. Others questioned whether waiting for 10 years before undertaking a thorough review of SSRIs represented a good track record. Prof Healy argued:

> 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 SSRI or other drugs.[254]

300. There was perhaps a degree of complacency in the Minister's view of the Yellow Card Scheme.[255] This system is widely considered to be failing and was described to us as "worthless"[256] and "bit of a pup"[257], but Lord Warner maintained:

> I do not think there was any evidence from [the review of the system] 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.[258]

301. In addition, the 5-year renewal procedure has not been used to good effect, and appears to have become an automatic process focussing on safety issues rather than an opportunity to review both efficacy and safety data rigorously.

302. Several witnesses expressed concerns not only about the relatively weak emphasis on post-marketing investigations, but also about possible conflicts of interest that might arise when the same Agency is responsible for both pre- and post-marketing drug evaluation: if problems arise once a drug is on the market, it might indicate flaws in the original assessment and require the regulators to examine their own earlier failings. Such concerns have also been expressed in the US. Witnesses forcefully argued for more robust post-marketing drug surveillance, proper assessment of the extent and cost of drug-induced illness, and the need to avoid basic conflicts of this kind.[259]

The patient voice

303. The MHRA paid the price of the MCA's earlier failures to get to grips with the problem of SSRI antidepressants. During six previous investigations, user reports of often serious problems had been systematically discounted or ignored. The MHRA has since responded to this problem, but the users' voice in the drug regulatory system as a whole remains very weak. The MHRA's proposal to set up a patients' committee in its new structure was welcomed, but previous experience gives rise to concern that it will not

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[253] Q914

[254] Q168

[255] See Paragraph 104 for a description of the Yellow Card Scheme

[256] Q168

[257] Q168, 403

[258] Q953

[259] PI 19, PI 65, PI 113, Q102, Q189, Q434

fundamentally change the situation. Richard Brook, who was one of two lay members originally on the EWG examining SSRI antidepressants, told us:

> 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.[260]

304. The MHRA is seeking to communicate more effectively with the public. Sir Alasdair Breckenridge admitted that communication had been poor in the past, but that better standards were now in place. Lord Warner also stated that it will become more common for evidence supporting the MHRA licensing decisions to be placed in the public arena:

> 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…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.[261]

305. Witnesses stressed that improved communication must involve publication of all benefit : risk assessments produced by the MHRA and documents relating to the withdrawal of medicines.[262]

[260] Q162. Mr Brook was commenting on the late submission of information regarding the anti-depressant Efexor to the MHRA.

[261] Q931

[262] PI 29, Q195, Q439

5. Problems with Seroxat and other SSRIs

Prozac and Seroxat are the best-known examples of SSRI and related antidepressants, but others are widely used. The introduction of SSRIs led to a threefold increase in antidepressant prescriptions between 1990 and 2000. Prescriptions for antidepressants now match those of the benzodiazepine tranquillisers at their peak, 25 years ago.

Almost from the outset, there was concern about two main problems with SSRIs. First, there was suspicion (initially centred on Prozac) that these drugs could induce suicidal and violent behaviour – infrequently, but independently of the suicidal thoughts that are linked to depression itself. There was also concern (centred on Seroxat) about a risk of dependence; some users found it impossible to stop taking SSRIs because of severe withdrawal symptoms.

The MCA/CSM formally reviewed these problems on several occasions. The suicidality problem was first investigated in 1990/1; withdrawal reactions were investigated in 1993, 1996 and 1998. In 2002, the MCA organised a further intensive review of both problems. This review was abandoned in April 2003, following criticism about conflicts of interest involving key figures on the review team.

Expert Working Group report on SSRI safety

The MHRA set up another enquiry in May 2003, an independent review by an Expert Working Group (EWG) of the CSM. None of its members had personal interests in companies whose drugs were under investigation, and they included two consumer representatives. The appointment of lay members was unprecedented; their contribution to the work of the EWG was subsequently warmly acknowledged. However, one of the two lay members left soon after the review began. The other was Richard Brook, the chief executive of Mind, who resigned in protest half way through. A third lay member was appointed to the EWG eight months later, by which time the report was virtually complete.

In evidence to this Committee, Mr Brook expressed concerns about the influence of the industry on drug regulation, specifically the perceived threat by MHRA staff of legal entanglement resulting from regulatory action:

> …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 the whole time of that dimension, to my view, more than the dimension of public health and public responsibility of the public.[263]

The EWG was originally expected to report within three months. In the event, the EWG held 20 meetings over as many months and its final report was released in December 2004. This initiative was overtaken by events from the outset.

[263] Q162

Very soon after the appointment of the EWG, GSK submitted evidence to the MHRA to support a licensing application for Seroxat use in children. Suspecting a problem, the MHRA requested further data from GSK and, in June 2003, unexpectedly issued a warning to advise against the use of Seroxat in children. A similar warning was issued for another antidepressant, Efexor, three months later and, in December 2003, the warning against use in children was extended to all of the drugs reviewed bar Prozac. The underlying reason was not only the evidence of a small but statistically significant increased risk of drug-induced suicidal behaviour, but lack of evidence of effectiveness.

The EWG was therefore unable to focus on its original brief, relating to withdrawal problems and possible suicidality in adults, until the end of 2003. Its final report identified a significant lack of important data, a clear and substantial risk of sometimes severe withdrawal reactions, and no clear evidence of a greater risk of SSRI-induced suicidal behaviour compared with older drugs (notably tricyclic antidepressants). The final report concluded that the benefit : risk profile of SSRIs was positive in adults; it also somewhat softened the earlier warnings about using SSRIs for children.

There appears to have been a lack of effective warnings relating to the frequency of withdrawal symptoms experienced with Seroxat. Both the manufacturers[264] and the regulators[265] claimed they had acted promptly and appropriately in this respect. However, working papers seen by the EWG state that the original licence application recorded Seroxat withdrawal reactions in 30% of patients. The regulators denied this. Three separate reviews conducted by the MCA/CSM in the 1990s were all based on Yellow Card counts, and produced misleadingly low estimates of the risk level:

> **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 per cent.
>
> **Professor Sir Alasdair Breckenridge**: When a drug is licensed and for the first few years until there is good clinical trial evidence, one cannot say what the incidence of an adverse reaction is. You cannot tell that from yellow card reports ... [266]
>
> The MHRA/CSM failed to warn of the lack of evidence (since the early 1990s) of SSRI effectiveness in mild depression, suggesting that most users might expect minimal benefit when exposed to significant risks.[267]

There was a lack of basic data identified in the EWG, and a number of other shortcomings:

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[264] Q713

[265] Qq801-803, Qq806-808

[266] Q802

[267] Qq798-799

[268] Risk:Benefit Evaluation of Paroxetine (Article 31 Referral), October 2003, p 53

[269] Article 31 Referral for paroxetine – Assessment of the MAH's response to the list of outstanding issues, February 2004, p 23

[270] Q987

- The data on Prozac suicide-related events provided by Eli Lilly excluded large numbers of controlled trials performed outside the US. The EWG report commented: "Lilly have provided a proposal for retrieving these data, but this cannot be completed in the required time-frame for the report. Report to be updated when data are available."

- The Dutch company, Organon, "excluded many seemingly relevant studies" from the data on suicidality with Zispin (mirtazepine). The report notes that Organon "has been requested to provide these data. A response is awaited."

- Three companies (Lilly, Solvay, Wyeth) were unable to produce any clinical trials specifically designed to establish the prevalence and severity of withdrawal reactions.

Further concerns, relating to the MHRA's reliance on company summaries of data, rather than raw data are discussed elsewhere. The EWG did not make clear to what extent its findings were based on re-examination of data held by the regulators for years. To a significant extent this appears to be the case.

The EWG working papers suggested that companies may not comply with requests for relevant information, and that the MHRA is often in no position to require them to. One example involved GSK, the Marketing Authorisation (MA) Holder, arguing first, that it had fully investigated Seroxat withdrawal problems, then later resisting the regulators' proposal to warn that Seroxat withdrawal appeared particularly troublesome, on the grounds that no clinical trials had been done to establish this. From October 2003:

> The MA holder considers that the clinical trials already conducted … have allowed the nature, frequency and severity of withdrawal reactions to be comprehensively characterized. They do not consider that further studies would add appreciably to the knowledge of events and consequently do not plan to conduct any further studies in this area.[268]

From February 2004:

> They are of the opinion that there are no data from well designed, comparative clinical trials that would support the conclusion that the true frequency of withdrawal reactions is higher for paroxetine than other SSRIs as a class and that such statement in the SPC should not be based on spontaneous reporting data.[269]

All the available evidence pointed to a singular risk with Seroxat, but the warnings eventually proposed by the MHRA/CSM did not mention it.

Wider significance of the SSRI experience

The antidepressant controversy is not yet over, but it has already had a profound effect on shape of drug regulation as well as on the reputation of the industry. The lasting impact of the antidepressant controversy relates to greater recognition of:

- The limitations of clinical trials in predicting the benefits and risks of drugs in routine clinical practice;

- The prevalence and significance of bias resulting from non-publication of negative trial

results;

- The limitations of existing post-marketing surveillance systems, and of lack of data relating to the effects of drugs in routine use;
- The essential importance of feedback on drug effects from users, and the importance of the Internet in facilitating this;
- The significance of intensive drug promotion and PR management in shaping perceptions of drug benefit and risk;
- The pervasiveness of conflicts of interest of all kinds, and their significance as factors that affect the quality of drug prescribing; and
- The need for greater transparency of data and clarity in regulatory warnings and communications.

We look forward to hearing the results of the investigation into the withholding of information by the manufacturers of Seroxat, currently underway by the MHRA.[270]

Medicines reclassification

306. We heard evidence of "serious concerns", notably from Which? and the *DTB*, about the MHRA's current programme of de-regulation of prescription-only medicines (POMs), making them available over-the-counter. For a description of the reclassification procedure see Part 6.

307. There was a reasonable number of POM to P switches throughout the 1990s, but due to some regulatory hurdles, the frequency decreased. Numbers of POMs being reclassified has accelerated following the agreement between the industry and Government reached in PICTF. The two parties "agree[d] that a market for medicines not reimbursed by the NHS, which involves NHS prescribers, should be developed."[271] To this end, Government made commitments for "streamlining the processes for reclassifying medicines", and quickly introduced new legislation to do so. Government would also gain from this, because only prescription drugs are reimbursed by the NHS. In its 2001 annual report, the MCA said that the new law had:

> …resulted in a complete redesign of the process by which medicines are reclassified …cut dramatically the time taken between an application and a product reaching the shelves, while maintaining essential safeguards.[272]

308. These changes were introduced following public consultation. The consultation document began by saying: "Within the NHS Plan the government aims by 2002 to make more medicines available over the counter to widen access and patient choice…" Comparing this to the previous statement by PICTF suggests that the MHRA has been

[271] PICTF, section 2.61, March 2001

[272] This information is taken from the MHRA's annual report, available at http://medicines.mhra.gov.uk/aboutagency/annualreports/2001/maintaining.pdf

giving out different messages to different stakeholders, honed to what the regulators perceive to be the stakeholders' particular preferences and needs.

309. Evidence from Which? proposed that the process of selecting and approving medicines for reclassification "is driven by inappropriate targets and without due consideration to public health need or a satisfactory level of safety and efficacy data".[273] The *DTB* emphasised this was not a wholesale objection, however:

> There are many drugs which are available over the counter which do bring great benefits to patients, but … 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.[274]

310. The efficacy of some reclassified drugs is questionable but the MHRA's reclassification procedure makes no provision for taking efficacy alone into account. Oral Buscopan (hyoscine butylbromide) was mentioned in this respect. This medicine, which has recently been reclassified from P to GSL status, was mentioned by Dr Iheanacho when he was asked for examples of a drug that had been reclassified and for which there was essentially no evidence of efficacy for the condition it was licensed to treat:

> I suppose the most prominent example of a drug which has undergone reclassification … is a drug called hyoscine or Buscopan, which is a treatment for a condition known as 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.[275]

311. In their evidence, Which? also suggested that there were both safety and efficacy concerns about the drug Zocor, whose reclassification from POM to P status was approved by the Secretary of State for Health in 2004. A key issue was that the indications for the use of the product in the doses provided OTC relied on the extrapolation of trial data generated using higher doses in individuals at high risk of developing coronary heart disease. No large scale trials of the drug as a preventative in individuals at 'moderate risk' of coronary heart disease have been conducted and there is some uncertainty about the risks of these drugs in this population; yet the drug is now available for individuals to purchase if they are at moderate risk.

312. **Post-marketing surveillance in the UK is inadequate. This has several causes: the lack of effective post-marketing investigation of drug benefits and harms in real life situations, and institutional indifference to the experience and reports of medicine users. In addition, the focus on drug licensing and on the safety profiles of individual drugs has contributed to a dearth of information about the overall impact of drug-induced illness in the community.**

313. **The reputation and credibility of the MHRA depends on its ability to communicate uniformly with its different stakeholders. These diverging messages contribute to confusion between health and trade priorities.**

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[273] PI 53

[274] Q110

[275] Q114

6. Generic medicines

Generic medicines are an important resource for the NHS and cost much less than branded drugs. We heard allegations that, over the past decade, major companies have developed, and now systematically employ, a range of product- and legal-based strategies intended to subdue or delay competition from generic manufacturers (known as 'life cycle management'). Strategies to extend the life of branded products include:

a) Direct entry into the generics markets or developing an exclusive partnership with an existing manufacturer;

b) Seeking reclassification to obtain OTC status;

c) Defensive pricing strategies;

d) Intensified promotion before patent expiry to enhance brand name 'outreach, compliance and retention';

e) Longer times to process licence applications for generics compared to brand-name products; and

f) A variety of minor product modifications, collectively known as product 'evergreening'.

Evergreening involves extending the patented life of a branded product, typically by reformulating the drug, for instance by using a different drug delivery system, changing a dosage form, or presentation (e.g. from tablet to capsule). Evergreening, in one common form, occurs when the brand-name manufacturer stockpiles patent protection by obtaining separate patents on multiple attributes of a single product. These patents can cover everything from aspects of the manufacturing process to tablet colour, and may extend to intermediate compounds produced in the body when the drug is ingested and metabolised. The significance of evergreening is underlined by the increased range of drug attributes eligible for patent protection. In the 1980s, the list of relevant drug properties was relatively limited. In the 1990s, the list extended protection in relation to range of use, methods of treatment, mechanism of action, packaging, delivery profiles, dosing route, regimen and range, drug combinations, screening and analytical methods, drug chirality, biological targets and field of use.

The British Generic Manufacturers Association (BGMA) listed five examples in which the originating company had employed evergreening methods, resulting in little or no therapeutic gain, but at a cost to the NHS estimated between £164m and £369m.[276]

NICE

314. The relationship between NICE and the pharmaceutical industry is one in which some degree of conflict is inevitable. NICE acknowledges this:

[276] PI 48

> 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. [277]

315. The fact that manufacturers do not attend meetings of the technology appraisals advisory committee, whereas patient and carer groups and healthcare professionals are present at these meetings, in NICE's view is, "an important part of minimising the risks associated with the potential conflict of interest".[278]

316. NICE has great influence on the industry. A key problem articulated by witnesses from the industry was that an evaluation by NICE of the comparative value of a new drug treatment might not be completed until several years after the drug is launched.[279] Furthermore, implementation remains patchy and slow. Industry stressed that this presented a significant additional cost in marketing medicines in the UK. GSK, among others, told us that it was, "disappointed to date by the lack of progress" in delivering the goals of "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."[280] There are many factors which may contribute to this time lag, including:

a) Lack of relevant data before a drug is licensed and widely used;

b) Lack of access to such clinical data before a drug is licensed;

c) Lack of NICE resources to undertake fast-tracked evaluations; and

d) Delays resulting from the evaluation process (including time needed for consultation with stakeholders).

317. As we have previously indicated, the UK has one of the slowest uptake rates of new drugs in the world. We do not know the health significance of this slow uptake, but several submissions from the industry argue that patients suffer as a result of "NICE blight", in which uptake is slowed until NICE guidance is compiled or medicines not evaluated by NICE are not prescribed. Further concerns about NICE regulation were expressed by the BioIndustry Association (BIA):

> NICE has an emphasis on mainstream drugs, whereas the bioscience industry often has niche products where the patient numbers involved fall below NICE's economic threshold.[281]

318. In our review of the organisation in 2002, we urged the MHRA to provide NICE with the confidential information held by pharmaceutical companies. We also recommended that NICE publish all the information on which it based its decisions, a recommendation which was reiterated by the WHO in its review of NICE published in 2003. According to

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[277] PI 32

[278] PI 32

[279] Q729, PI 33, PI 35

[280] PI 51

[281] PI 47

NICE, an agreement between NICE and the ABPI in May 2004, "acknowledge[d] the importance of putting relevant information into the public domain to ensure the credibility of NICE guidance" but that unrestricted access to and publication of all relevant data for the development of guidance has yet to be achieved.[282]

319. The industry therefore also influences NICE, through access to its information. It provides the data on which the Institute bases its guidelines. The creation of such guidelines and algorithms may be compromised by publication bias and the proportion of articles that are ghost-written. A consistent lack of reporting of drug safety effects in the literature means that such effects will not show up in reviews and will therefore not be highlighted in the guidelines. Management of the medical literature may result in a drug that has not been proven to be more efficacious than its older (cheaper) rivals, being preferentially prescribed, which imposes a financial cost on the NHS and might put patients at risk.

320. Industry also influences the topics that are chosen for NICE review. Cancer Research UK stressed its concern over the influence of the industry on the topics considered by NICE for appraisal and suggested a need for increased transparency in this area and in the process by which certain drugs are prioritised by the Institute.[283]

321. Several improvements were suggested by witnesses. The BIA argued that a system for the provisional licensing of drugs should be introduced to provide early access (and reimbursement) to drugs where real need exists and no alternative is available. Such a scheme exists, for example, in France (the Autorisation temporaires d'Utilisation system) where medicines deemed highly likely to be effective are available often before the completion of Phase III clinical trials. AIDS, some types of cancer and neurological diseases are the conditions most commonly involved.

322. NICE could play a role in determining the research agenda by defining targets for new treatments in a limited number of disease areas. For example, it could prospectively define the type and size of benefit in the treatment of heart failure that would be considered an advance likely to merit inclusion in a local formulary, and fast-track subsequent guidance. Prof Patrick Vallance argued:

> 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.[284]

323. The need for closer working and ongoing dialogue between NICE and drug manufacturers was reiterated by the industry, "to reduce duplication of effort and to accept regulatory evidence".[285]

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[282] PI 32

[283] PI 59

[284] PI 106

[285] PI 28

324. Improved and transparent communication between the MHRA and NICE and the pharmaceutical industry at an early stage in medicines development would encourage the provision of truly innovative and beneficial treatments to the public. The regulators could, for example, outline the type of clinical trial and size of patient benefit proven that would be likely to lead to marketing approval or positive NICE guidance While many of the criticisms that have been levelled against both industry and the regulators have involved perceived 'cosiness' and exclusion of the public, the public would not be served by forcibly separating these entities. **Instead, we urge transparency in process and access to data for all.**

Government

325. Government has a number of areas of responsibility for medicines. It must act as sponsor for UK-based drug companies to encourage a thriving and competitive industry, it must maintain oversight of the regulatory system and ensure that mechanisms and incentives are in place so that the industry acts in a way that is consonant with the Government's public health aims.

326. In particular, the Government must ensure that areas of research that are not addressed by the pharmaceutical industry are resourced. Non-drug approaches, for example, are rarely investigated. Sir Iain Chalmers told us that most clinical trials relating to osteoarthritis of the knee are commercial studies of drugs whereas patients, rheumatologists, physiotherapists and GPs have made clear that what they need, instead of more drug trials, are rigorous evaluations of physiotherapy, surgery and educational/coping strategies.[286]

327. Government has been slow to see the importance of these areas, perhaps because the pharmaceutical industry funds such a great proportion of other medical research. The industry cannot be expected to fully fund areas of research that are not directly in its interest, however, and so it falls to Government to address areas of need such as non-drug treatments, combination studies and iatrogenic illness.

328. **Areas of research that are not of direct interest to the pharmaceutical industry but may significantly benefit patients, such as non-pharmacological treatments, should be funded by Government.**

329. The Government is in a position to determine the ultimate balance between the interests of the industry and its requirement to look after health, but its task in doing this must be seen in the context of the growing influence of the industry.

330. The industry's influence internationally is underlined by the growing intensity of world trade; through strong support for companies by governments of the leading drug producing nations; and by the developing trend to Public-Private Partnerships. The close connection between the industry and Government is strong in the EU, where the European Commission's directorate for trade (DG Enterprise), not the directorate for health (DG Sanco), is responsible for drug policy and the operation of the EMEA. At the invitation of

[286] Q408

DG Enterprise, industry representatives were directly and prominently involved in the recent, major review of EU pharmaceutical regulation.

331. The close contact between the UK Government and the pharmaceutical industry in formulating health policy was illustrated by Ms Margot James:

> 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 vaccine 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 our clients] 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.[287]

332. Lord Warner mentioned that he had been struck by the "detachment" of health ministers from other EU countries regarding issues concerning the pharmaceutical industry, but added that "we have kept the balance pretty well" between public health interests and the interests of the pharmaceutical industry,[288] arguing against the separation of responsibility for the two within the Department of Health:

> **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 would be the impact if the commercial aspects, the competitive task force aspects of your role were actually within DTI and the regulatory remained within Health? ….
>
> **Lord Warner**: Once you separate those two functions it would be far more difficult to get the right balance. You set up a scope for conflict departmentally within government if you go down that path.[289]

333. Yet a distinguished witness with a wealth of experience in the industry and in academic life argued that the DTI would be much better placed than the Department of Health to promote the industry's commercial interests. He suggested the main reason for the present arrangements was more to do with the perceived threat of abuse arising from the monopoly power of the NHS in purchasing drugs:

> **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

[287] Qq643–644

[288] Q912

[289] Q998

> 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![290]

334. Other witnesses have forcefully argued that the right balance between health and trade interests has not been achieved. The UK Government has established PICTF, which is not concerned with health yet is co-chaired by the health minister responsible for the MHRA and drug licensing. The lack of national medicines policy, as recommended by the WHO, is also a source of concern, despite Lord Warner's acceptance of the need for a policy of this kind:

> 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 [UKCRC]…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.[291]

335. **The interests of patients, the NHS and industry can be at odds and we have no confidence that the Department is capable of achieving the balance required. The 'cross-dressing' role of the Department in this regard does not serve the public as well as it should.**

[290] Q454. Sir Richard later explained that the pharmaceutical industry are "the chickens" and the NHS "the fox" due to its power as monopoly purchaser.

[291] Q917

7. Over promotion and prescription of drugs: Vioxx

The COX-2 inhibitor Vioxx was launched in 1999 and was widely promoted and prescribed to arthritis patients in the UK and elsewhere. It was withdrawn by its manufacturers (Merck) in September 2004 following the revelation that it had probably caused many thousands of heart attacks and strokes. A report in *The Lancet* in January estimated that there are 140,000 people with serious heart disease in the US caused by use of the drug.[292]

There have been suggestions that Merck might have been aware of potential heart problems with the drug much earlier, but that the results of these trials were not publicised. The 1999 Vioxx Gastrointestinal Outcomes Research study of 8,000 patients, for example, showed heart attacks to be five times as common in patients taking Vioxx compared to a conventional, non-selective non-steroidal anti-inflammatory drug (NSAID). This was attributed by the company to the protective effect of the NSAID, however.[293] A 1998 trial (Study '090') involved 978 patients. Serious cardiovascular events were found to be approximately six times more common in patients taking Vioxx than in patients taking another arthritis drug or a placebo.[294] This study was never published. A recent meta-analysis comparing Vioxx to another arthritis drug or placebo in 20,742 patients has showed increased risk of heart attack in both short- and long-term trials. The Swiss and UK researchers concluded that Merck should have withdrawn the drug when this data was first available, in 2000 (four years earlier).[295]

Another COX-2 selective inhibitor, Celebrex, manufactured by Pfizer, has also similarly been linked with cardiovascular problems, although it remains on the market. Pfizer originally stated in October 2004 that no completed study had shown an increased risk of heart attack or stroke. A colon cancer prevention study, released in December 2004, however, showed a higher risk of heart attacks and strokes compared to placebo. A study conducted in 1999 showed a 3.6-fold increase in cardiovascular problems in older patients with Alzheimer's compared to those receiving a placebo. This latter study was not published and was submitted to the FDA only in June 2001.[296] Questions have also been raised about the validity of licensing Celebrex based on 6-month safety data because no significant advantage over comparator NSAIDs was observed in the same group at 12 months.[297]

A statement to the effect that heart problems were associated with Celebrex was issued by the MHRA in December 2004. In the statement, the Agency made it clear that it had not seen the actual data from the drug company but that its advice was based on information from Pfizer's website.

A promotional letter sent to healthcare professionals in November 2004 regarding the

[292] Graham D et al. *The Lancet* 2005; 365: 475-81

[293] Bombardier C et al. *New England Journal of Medicine*. 2000 Nov 23;343:1520-8

[294] FDA memorandum. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf

[295] Juni et al, *The Lancet* online, published 5 November 2004; http://www.thelancet.com

[296] Public Citizen's Health Research Group, http://www.citizen.org/hrg

[297] PI 49

safety of Celebrex was the subject of a complaint investigated by the MHRA. The complainant argued that the information given was not balanced or accurate. The complaint was upheld by the regulator and a corrective statement, highlighting the limitations of the research previously cited, was to be sent to the original letter's recipients. However, in the interim period, updated safety advice from the CSM on Vioxx and other selective COX-2 inhibitors was issued by the MHRA, publication of which would have coincided with the corrective letter from Pfizer. The MHRA therefore decided "health professionals would be aware of current advice on prescribing celecoxib and that a further corrective letter would not serve a useful purpose."[298]

9 Conclusions and recommendations

Conclusions

336. The UK-based pharmaceutical industry is large, profitable and highly competitive; it has understandably been described as "world class and a jewel in the crown of the UK economy".[299] The industry has an outstanding record in developing new medicines, and is a major source of funding of medical research. The industry's products include many life-saving and important drugs which greatly benefit many people and contribute substantially to national health.

337. The commercial success of the industry is not in doubt, nor is its ability to produce excellent science and important drugs; however, its ability to put the health of the nation consistently before the needs and expectations of its shareholders may be questioned. The evidence to this inquiry indicated that, in recent years, large pharmaceutical companies have become ever more focused on a marketing-based approach. In our view, this is the source of many of the problems we have identified. However, these problems are global and we received no evidence that the situation in the UK was worse than in other countries.

338. In Chapter 8 we examined the overall influence of the pharmaceutical industry. It is widely welcomed and relied on, but it is also pervasive and persistent. Our over-riding concerns are about the volume, extent and intensity of the industry's influence, not only on clinical medicine and research but also on patients, regulators, the media, civil servants and politicians. This makes it all the more important to examine critically the industry's impact on health and to guard against excessive and damaging dependencies. In some circumstances, one particular item of influence may be of relatively little importance. Only when it is viewed as part of a larger package of influences is the true effect of the company's activity recognised and the potential for distortion seen. The possibility that certain components of any such campaign are covert and their source undeclared is particularly worrying.

[298] http://medicines.mhra.gov.uk/ourwork/advertpromed/complaints/celebrex_1204.htm

[299] PICTF Report 2002

339. However, other factors have contributed to the excessive influence this report describes. In many ways, the industry may be seen as a scapegoat for failings elsewhere. For many years it has been left to its own devices. It is worth noting that there has been no Select Committee investigation of the industry since the Select Committee report on patent medicines in 1914. The regulatory system, the medical profession and Government have all failed to ensure that industry's activities are more clearly allied to the interests of patients and the NHS.

340. Our over-arching conclusion is that the UK pharmaceutical industry is in many ways outstanding: it conducts much excellent research, produces products which make a vital contribution to the health of the nation and is of great economic importance; however, for want of critical scrutiny by, and lack of deference and accountability to, the public and public bodies, the industry lacks the discipline and quality control that it needs but cannot itself provide. In particular:

- The influence of the pharmaceutical industry is such that it dominates clinical practice, to an extent that deprives it of independent and constructively critical feedback; this is a discipline it needs and which can help it to improve.

- The industry's complaints of excessive regulation are understandable but self regulation is not at present effective. It could take on greater responsibility for regulation when its activities are fully transparent and effectively audited.

- The regulatory authority, which is responsible for controlling much of the behaviour of the industry has significant failings. Lack of transparency has played a major part in allowing failings to continue. The traditional secrecy in the drug regulatory process has insulated regulators from the feedback that would otherwise check, test and stimulate their policies and performance. Failure can be measured by the MHRA's poor history in recognising drug risks, poor communication and lack of public trust. Regulatory secrecy also underpins publication bias, and other unacceptable practices. The closeness that has developed between regulators and companies has deprived the industry of rigorous quality control and audit.

- Other bodies are in a position to provide feedback and quality control. They include academic, research, clinical and professional institutions, as well as the media and patient groups. However, representatives of these interests have had only limited success in containing excessive industry influence. This can be partly attributed to lack of transparency, limited resources, significant dependency on industry funding, and some conflicts of interest.

- The Government and the EU appear to believe that trade imperatives and health priorities are as one. The evidence received from the Department of Health was remarkable for its denial that any significant conflict between commercial and health objectives might arise that was not properly addressed through existing process and systems. We do not doubt the legitimacy of commercial objectives, the contributions of the pharmaceutical industry to health and the overlap of commercial and health interests, but this inquiry left us in no doubt that the scope for conflict between health and trade interests is huge. We firmly believe that the Department and the MHRA should focus on health priorities.

341. The failings we have described have consequences, in particular:

- The unsafe use of drugs; and
- The increasing medicalisation of society.

These problems have existed in many countries. The UK may have a better record than many others. Drugs have been used unsafely in every country and we have no doubt that the drift towards medicalisation is a global phenomenon.

Unsafe use of drugs

342. Unfortunately, a number of drugs which have been licensed and widely prescribed, have produced severe adverse reactions, and in some cases death, in large numbers of people. In this report we have highlighted the problems with SSRIs antidepressants, notably Seroxat, and the COX-2 inhibitors, Vioxx and Celebrex.

343. Problems with these and other drugs have revealed major failings not just in the pharmaceutical industry relating to the design and presentation of clinical trials and the supply of data to the regulator, but also in the regulatory system. The regulator's analysis of trial data and advice to prescribers and patients have been inadequate and its responses to indications of adverse reactions slow. Moreover, some doctors' prescribing habits and their reaction to promotional activity have been unsatisfactory.

344. The regulatory system relies mainly on scrutiny of clinical trials as a condition of drug approval. By emphasising the dominant, distinctive and more appealing characteristics of drug products, this output is inevitably focused on drug use under model and optimal conditions. The evidence overwhelmingly suggests that, under 'normal' conditions, drug problems mainly arise because of failures to understand the significance of their established effects, lack of information and transparency and flaws in communications – often closely related to (quantitatively and qualitatively) excessive promotion.

345. We know that, in the US, the manufacturers of Vioxx and Celebrex did not act in good faith in that they failed to supply all the data in their possession to the regulator at the time of licence application. This may also have been the case in the UK. Whether the MHRA effectively evaluated the benefit : risk profile of these drugs is unclear, as we cannot be certain that all studies were provided during the licensing application.

346. We can be sure, however, that the clinical trials of Seroxat and other SSRI antidepressants were not adequately scrutinised. The failings of Seroxat and other SSRIs should have been picked up by a more careful examination of the evidence presented in the Phase III clinical trials and suitable prescribing advice should have been issued on this basis.

347. Although the case of Seroxat has been described in greater detail elsewhere in this report, it is worth noting here that, in additional information provided to the Committee on the basis of the EWG's report on SSRIs, it has been shown that suicidal thoughts and hostility are twice as common in patients receiving Seroxat in the month following drug withdrawal as in those receiving placebo. Data contained in the licence application itself cited studies in which withdrawal symptoms were common. Yet for years the MHRA

maintained that withdrawal symptoms were rare, affecting of the order of 0.1–0.2% of patients. The Agency now acknowledges that 20–30% of patients might experience withdrawal symptoms when stopping SSRIs.

348. **Prescribers must take their share of the blame for the problems that have resulted from the prescribing of SSRI antidepressants and COX-2 inhibitors. There is no doubt that these medicines have been indiscriminately prescribed on a grand scale. This is partly attributable to intensive promotional activity, especially around the time of drug launch, but also the consequence of data secrecy and uncritical acceptance of drug company views. It seems that intensive marketing has worked to persuade too many professionals that they can prescribe with impunity. There is a huge variation in prescribing, even within a limited area. That many acted cautiously makes those who did not more open to criticism. There is a lack of any effective mechanism for tempering the prescribing explosion often seen in the months following a product launch. We have been told time and again that this is the most important period in drug promotion terms, but is also the time when least is known about the product (see Recommendations in Paragraph 358).**

349. Such problems are compounded by an excessive reliance on results from pre-marketing clinical trials, together with a failing system of pharmacovigilance. The lack of pro-active and systematic monitoring of drug effects and health outcomes in normal clinical use is worrying. Improvements in post-marketing surveillance are clearly needed and would, no doubt, have led to the earlier detection of problems with SSRI antidepressants, COX-2 inhibitors and other drugs.

Medicalisation of society: 'a pill for every ill'

350. A major and recurring issue raised during the inquiry is the increased 'medicalisation' of our society – the pill for every problem. With over-the-counter statins now promoted for all men over the age of 55, for example, and a vast array of preventative treatments and supplements, it is easy to believe that everybody will be self-medicating every day in the near future. We were pleased that Lord Warner seemed to share our concerns in this regard:

> 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 parcel of the human condition[300]

351. The belief that every problem may be solved with medication seems particularly relevant in the context of antidepressants. While we readily accept that antidepressants can be effective medicines and have been successfully used by many patients, it is also clear that SSRIs, in particular, have been over-prescribed to individuals, often with mild forms of depression, who may be distressed by difficult life circumstances. Unhappiness is part of the spectrum of human experience, not a medical condition.

352. This trend has not been created by the pharmaceutical industry but it has been encouraged by it. The industry has acted, in the words of some witnesses, as a "disease-

[300] Q970

monger", with the aim of categorising an increasing number of individuals as 'abnormal' and thereby requiring (drug) treatment. This process has led to an unhealthy over-reliance on, and an over-use of, medicines. It also diverts resources and priorities from more significant diseases and health problems.

Recommendations

353. The Committee was impressed by the evidence from Sir Richard Sykes. He acknowledged problems, emphasised the industry's underlying strengths and the commitment of its employees, and defined solutions in terms of greater transparency of data and in relationships:

> 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.[301]

354. In making our recommendations we are conscious of Sir Richard's comments. We trust that they will both benefit health and encourage the development of a more successful and effective pharmaceutical industry. We consider these recommendations under the following headings:

The industry;

The regulatory system;

Prescribers;

Government and the EU.

The industry

Research

355. As we have seen, the industry undertakes much excellent research. However, there are failings which make an objective assessment of the efficacy and safety of drugs more difficult. The situation would be much improved by more transparency. We therefore welcome the pharmaceutical industry's acceptance of the need to establish a register of all clinical trials. The details of the proposed register are not yet clear, but it is essential that it encourages genuine transparency and accountability. We have been told that the results of trials relating to medicines that receive a licence will be posted on the register within a year of launch. We see no reason why such data should not be posted immediately. We are also concerned that the maintenance of the clinical trials register by the pharmaceutical industry itself will not inspire confidence from either the public or healthcare professionals. **We recommend that the clinical trials register be maintained by an independent body and the results of all clinical trials data, containing full trials information, be put on the register at launch as a condition of the marketing licence.**

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[301] Q455

356. There are other deficiencies in both the conduct and value of clinical trials. We are particularly concerned that the results obtained in clinical trials do not mimic those likely to occur in routine clinical practice. Thus the true therapeutic value of drugs is hard to assess. **Clinical trials have significant limitations. We recommend that the MHRA work with the pharmaceutical industry and outside experts to design clinical trials that establish the real therapeutic value of new medicines using measures that are relevant to patients and public health. Trials should be designed to more accurately predict the performance of drugs in routine clinical settings. We recommend that research ethics committees encourage, where appropriate, the inclusion of comparator drugs and non-drug approaches in the evaluation of proposed clinical trials. Ethics committees should also require applicants to prove that the trial does not duplicate previous research and that results will be published in full.**

357. More could be done assist pharmaceutical companies undertake research in the UK. Although the NHS has made progress in facilitating the conduct of medical research by the industry, notably through the UK Clinical Research Collaboration, it does not make it easy enough to conduct clinical trials and may be contributing to the movement of clinical research abroad. **We recommend that the NHS take further steps to facilitate the conduct of clinical trials, with each Trust having a single point of contact for the pharmaceutical industry to approach when considering a trial.**

Marketing

358. The marketing of medicines is strictly regulated, and sometimes excessively so, but, nevertheless, there are failings. Three are of particular concern. The first relates to the volume of promotional material. The quantity of promotional material that may be given to prescribers is limited only indirectly by the PPRS. Doctors are already deluged with promotional messages following the release of a new medicine, and nurses and pharmacists will increasingly be so in future. In the absence of information from alternative, non-industry sources, prescribing levels of new drugs may be unjustifiably high. The quality of promotional material provided to prescribers is already regulated. **We recommend that, in addition, limits be set as to the quantity of material prescribers receive, particularly in the first six months after launch. Less experienced and non-specialist doctors are ill-equipped to cope effectively with the promotional material. The pressure on nurses and pharmacists is likely to intensify as their prescribing powers are further extended. Stricter controls are needed in respect of drug company representatives' promotion of their products to junior doctors and to nurses or pharmacists with new prescribing powers.**

359. The second concerns the reporting of illegal marketing practices. **Marketing practices that appear to be illegal should be reported by the pharmaceutical industry and others to the MHRA.**

360. Thirdly, procedures for investigating complaints about breaches of regulations are too slow, poorly enforced and weakly sanctioned. **We recommend a major review of the investigation of complaints to ensure the process is far quicker and that effective sanctions are enforced.**

361. One of the few levers the Government has to influence the actions of the pharmaceutical industry is the Pharmaceutical Pricing Regulation Scheme (PPRS). The Scheme makes provision for allowances to companies for marketing, R&D and information. It could be used by the Government to encourage improvements in the behaviour of the industry. **The PPRS should be used more effectively to influence the actions of the pharmaceutical industry in the public's interest. When companies are found to be in breach of advertising regulations or to have published misleading findings, the allowance for promotion and research, respectively, provided under the Scheme should be reduced. In addition, rewards for innovation should be limited to those drugs that are proven to offer clinical advantage.**

The regulatory system

362. Our inquiry revealed major failing in the regulatory system. The organisation, process and techniques of the MHRA are focussed on bringing drugs to market fast. The stated rationale, that patients benefit from new drugs, is insufficiently qualified by considerations of relative merit or value, or therapeutic need. We have concerns about the licensing process, including the evaluation of clinical trials; the control of marketing; staffing levels, particularly in relation to post-marketing evaluation; the withdrawal of drugs; the Yellow Card system; and licensing related to generics.

363. The process by which drugs are licensed is far from transparent. There is no public access to the data presented by the pharmaceutical companies nor to the assessments undertaken by the MHRA. There is not enough involvement of patients, the public and the wider scientific community, and the Agency does not listen or communicate well. After years of intense secrecy surrounding UK drug regulation, we welcome the MHRA's commitment to improve external communications, and to give patients a greater voice, but we are not convinced that these changes will be sufficient to counter the current inadequate state of affairs. **We recommend that the MHRA publishes, in some form of useable database, the material it receives from drug companies and the assessments it sends to advisory bodies at the time it sends them. We welcome the MHRA's plans to include lay members on every MHRA advisory committee, and recommend that these members receive sufficient training and support to allow them to fully contribute to decision making.**

364. **We are concerned that the MHRA is not permitted to routinely inspect audit reports for compliance with standards of Good Clinical Practice (GCP). The Department of Health should reconsider its agreement to waive powers to inspect, on a routine basis, audit reports of compliance with GCP standards, including standards of patient care. The Department should review all current and proposed standards developed by the International Conference on Harmonisation that impose restrictions on MHRA staff relating to inspection of company-held data and records**.

365. The MHRA does not routinely examine raw data submitted with the licence application but is dependent on summaries provided by the applicant. The Expert Working Group on SSRI's report of December 2004 showed that summaries of information may not provide the detail required to assess drug risks adequately. The licensing process relies excessively on the results of trials designed and presented by companies, in the absence of independent input. Trial design and the way in which results

are evaluated and reported can obscure negative results. More checks and balances on the part of the regulator would serve to reassure the public of the stringency of the licensing procedure. **The MHRA should put in place systematic procedures to randomly audit raw data. The results of such audits should be published. We also recommend that, like the US Food and Drug Administration, the MHRA play a greater role during the early stages of drug development. Guidance should be provided by the MHRA to the industry as to the types of clinical trial likely to prove the degree of therapeutic gain. NICE should also be involved in this process to provide advice on the type of data more likely to lead to the drug being included in NICE guidance.**

366. **The adverse drug reactions reported in the clinical trials that are considered in the medicines licensing process typically prove unreliable as a guide to routine clinical practice. Moreover, the adverse effects that may be linked to stopping treatment are insufficiently investigated. The MHRA should focus more intensely on updating drug benefit:risk profiles in the Summary of Product Characteristics, following systematic post-marketing review.**

367. Despite Prof Kent Woods' dismissal of suggestions that staffing of the MHRA was "woefully under-resourced" we do not believe that the MHRA has sufficient resources for effective post-marketing surveillance. The current process seems to be extremely passive. **We therefore recommend that the MHRA employ sufficient numbers of staff to monitor effectively drugs which have been recently licensed. Given the limited value of clinical trials in predicting drug impact in naturalistic settings, the MHRA should investigate options for the development of more effective post-marketing surveillance systems. Consideration should be given to the establishment of post-marketing surveillance and drug safety monitoring systems independently of the Licensing Authority. We also recommend that the MHRA enhances its relicensing procedures five years after launch. During the renewal procedure, the MHRA should again assess in detail the product's efficacy, safety and quality.**

368. Drug manufacturers provide less funding for Phase IV trials than for pre-marketing trials, possibly because such avenues of research are not profitable. The types of thorough, comparative studies needed to determine long-term efficacy, tolerance and risk of side-effects in large populations are therefore not undertaken. Independent research into these areas is limited.

369. Overwhelming evidence is required by the regulator before drug warnings are proposed or when drugs may be withdrawn, Only 19 drugs have been withdrawn between 1993 and 2004. On the other hand, medicines can be licensed in the absence of adequate data or investigation into possible adverse reactions and with proof of only limited therapeutic value. We agree that it is in the public interest to allow access to potentially life-saving therapy as quickly as possible, but timely withdrawal or provision of strict guidance on medicines that are dangerous if inappropriately prescribed is an equally life-saving pursuit. **We recommend that the MHRA is given the same authority to propose restrictions on drug use as it has when approving drugs.**

370. The recent review of the Yellow Card Scheme has led to a welcome increase in public access to information gleaned from the system and to the introduction of pilot schemes of patient reporting of suspected adverse reactions. However, we are concerned that these

measures will not address the main failings of the Yellow Card Scheme. The rate of adverse drug effects reported by healthcare professionals is inadequate, and when they are reported they are not always investigated or pursued with sufficient robustness. **We recommend that:**

- **the system of patient reporting to the Yellow Card Scheme be put in place country-wide as soon as possible;**
- **steps be taken to improve rates of healthcare professional reporting of adverse drug reactions;**
- **greater efforts be made to investigate signals of possible problems; and**
- **that maximum transparency be combined with concerted efforts to explain the uncertainties of risk**.

371. After a drug is withdrawn for health reasons, there are often a number of questions in the public mind, not least because such cases typically leave behind victims injured by the drug or bereaved relatives of people who suffered fatal reactions to the drug, as well as people who are denied access to a drug they may have found beneficial. A public inquiry could answer such questions as: should the safety problems have been better predicted from the pre-market testing data? Did the regulators get full and appropriate safety and efficacy data from the manufacturer? Was the right judgement made in balancing the risks and benefits of the drug? Could the health problem with the drug have been identified and acted upon earlier? Could and should the drug have been withdrawn earlier? Was sufficient consideration given to the continued provision of the drug for patients who uniquely benefited from it after withdrawal? Such a public inquiry could not only provide understanding and a sense of justice for the public, but equally importantly would ensure that the drug regulatory agency can learn effectively from mistakes and avoid them in the future. **We recommend that there should be a public inquiry whenever a drug is withdrawn on health grounds.**

372. As we mentioned earlier, Lord Warner told us that he was considering, "some kind of restrictions around the class of doctors who could prescribe particular products for a period of time".[302] We welcome such restrictions. They need to be combined with curbs on the promotion of such products. **The intensive marketing which encourages inappropriate prescribing of drugs must be curbed. Present methods of supplying independent information, as described by Lord Warner, are inadequate. We recommend that all the promotional material for a new product be pre-vetted by the MHRA prior to publication, and that consideration be given to limiting those who can prescribe a new drug in the two years following launch. Drug and Therapeutics Committees would be well-placed to implement this. Wider prescribing rights would be permitted once comparative studies, and trials investigating the potential adverse effects of the medicine in large populations, had been undertaken and after formal evaluation of the value of the product in clinical practice had been confirmed by the Licensing Authority and/or NICE.**

[302] Q916

373. The PMCPA and MHRA do not effectively co-ordinate their work in the assessment and approval of medicines advertising and promotional material. The defences in place against the inappropriate or misleading promotion of medicines are weak. The MHRA, which has admitted it cannot vet all such material, seems reluctant to punish companies that commit offences in the promotion of medicines in a swift and effective manner. Publishing upheld complaints on the MHRA website is an inadequate response; so is forcing companies to make minor changes to their advertising catchphrases. **We recommend that the MHRA and the PMCPA better co-ordinate their work relating to the promotion of medicines to avoid duplication. Complaints should be investigated swiftly, particularly when claims for new drugs are involved. When the PMCPA has evidence that a company has breached the regulations it should inform the MHRA of their findings. When companies are found to be in breach of advertising or marketing regulations by the MHRA, we recommend that corrective statements always be required and that such statements are given as much prominence as the original promotional piece. The publication of misleading promotional material is a criminal offence and the punishment should befit such a status.**

374. **A healthy generics market is important for the NHS and patients. We recommend a systematic review of so-called evergreening and other practices that impede the entry of generic drugs on to the market.**

375. The MHRA, like many regulatory organisations, is entirely funded by fees from those it regulates. However, unlike many regulators, it competes with other European agencies for fee income. This situation has led to concerns that it may lose sight of the need to protect and promote public health above all else as it seeks to win fee income from the companies. No evidence was submitted with proposals for a better system for funding the MHRA, but it is important to be aware of the dangers of the present arrangements. These dangers make our other recommendations for improving the regulatory system all the more important.

376. During this long inquiry we became aware of serious weaknesses in the MHRA. Worryingly, in both its written and oral evidence the Agency seemed oblivious to the critical views of outsiders and unable to accept that it had any obvious shortcomings, except those that could be remedied by more transparency. The Agency's attitude to its public health responsibilities suggested some complacency and a lack of requisite competency, reducing our confidence in its ability to undertake the reforms needed to earn and deserve public trust. Nor did we conclude that the MHRA provides the discipline and leadership that this powerful industry needs. **We recommend that there be an independent review of the MHRA. The earlier review by the National Audit Office was designed expressly to assess the public expenditure aspects of the work of the agency; a more wide-reaching and in-depth review needs to be carried out to determine whether the processes now used for decision-making are adequate and reflect patients' health needs and society's expectations. The following principles should govern the review:**

- **The need for greater independence from Government**
- **The need for greater independence from the pharmaceutical industry**

- **The need for policies of greater transparency and accountability in light of recent freedom of information legislation**
- **The effectiveness of the post-licensing department and the need for the MHRA to become pro-active rather than re-active**
- **Scrutiny of the regulatory standards underpinning clinical and non-clinical new drug review**
- **The reporting and evaluation of adverse drug reactions**
- **The prioritisation of new marketing applications**
- **Inclusion of the public in policy-making and implementation**

377. Major changes in the functioning of the MHRA after the review has been conducted and its findings implemented should enable it to make the improvements that we have recommended in this report.

Medical practitioners

378. Prescription rates and prescribing quality vary considerably between GPs and between clusters of GPs. Although positive changes have occurred since the establishment of PCTs, over-prescribing and inappropriate prescribing are still common in some areas. This has several causes including the difficulty in getting accurate information about the merits of medicines, the influence of promotional material, and failings in education. It is a matter of concern that some GPs and other prescribers are unable to evaluate information independently, recognise and report adverse reactions to drugs, deal with drug company marketing techniques and take evidence-based decisions about drugs. Some medical schools run relevant courses, but we understand that this approach is not widespread. This implies a major deficiency in the education of healthcare professionals. **We recommend that all medical students be taught how to judge clinical trial results effectively, recognise adverse drug reactions and deal with drug company representatives. There should be mandatory post-graduate training for all prescribers to keep up-to-date with prescribing changes. In addition, stricter regulation of individual prescriber's practices is required.**

379. We recognise the important work done by the *Drug and Therapeutics Bulletin*, the Cochrane Collaboration, the BNF and the James Lind Library in providing unbiased and independent information on medicines, but we are concerned that there is little independent and easily digestible information reaching (and influencing) busy GPs and other prescribers. Some Drug and Therapeutics Committees create formularies that are used by all hospitals in the relevant Trust and affiliated PCTs. Inclusion in the formulary is strictly controlled by careful evaluation of clinical trials data divided according to an evidence hierarchy. Guidance that is sensitive to local imperatives is needed, which can be provided soon after drug launch and be distributed widely and easily accessible. Such guidance may take the form of leaflets that are produced to explain why caution may be required. The prescription rates of COX-2 inhibitors was far lower in the UCLH Trust we visited and the affiliated PCTs than the national average, and this may be ascribed to the

guidance given. This impressive set-up should be replicated in all hospitals where it does not exist as effectively, including those without clinical pharmacologists.

380. **There is a lack of consistent and reliable independent advice, information and oversight of prescribers. We recommend that the Department of Health look into ways of making Use of Medicines Committees/Drug and Therapeutics Committees of a uniformly high standard, so that they can reliably carry out this vital educational role. Wherever possible, clinical pharmacologists and specialist pharmacists should be included on such Committees, as should lay representatives. Formularies established in hospital Trusts should be shared with affiliated PCTs with a view to adoption by the entire local health community. Ideally, new drugs should not be prescribed until they have been approved by such a committee. New drugs that might represent significant advances should be fast-tracked through these committees.**

381. During our inquiry some witnesses blamed the pharmaceutical companies for giving hospitality to prescribers and for paying what are sometimes significant sums to 'key opinion leaders'; less attention was paid to the fact that the beneficiaries of the hospitality and payments willingly accepted it. Prescribers' evaluation of the merits of drugs may be influenced by the hospitality they receive from pharmaceutical companies. Moreover, in the evaluation of clinical trial information, it may be highly relevant to know of particular investigators' affiliations with the company sponsoring the trial. We were dismayed to find that there is no register of interests to record gifts, hospitality or honoraria received by prescribers. The Royal Colleges and other professional bodies should take greater responsibility for the prescribing standards of their members. **We recommend that a register of interests be maintained by the relevant professional bodies (General Medical Council, Royal College of Nursing, Royal Pharmaceutical Society of Great Britain etc), detailing all substantial gifts, hospitality and honoraria received by members. The register should be made available for public inspection. Individual practitioners should be responsible for maintaining their entry on the register. Professional bodies should provide advice to their members about the levels of hospitality and payments that are acceptable.**

Patients

382. Many patients want more information about diseases and their treatment. Patient organisations and disease awareness campaigns can be important vehicles for providing such information. In the absence of alternative sources of funding many depend on funding from pharmaceutical companies. Some smaller charities could not survive without it. However, some disease awareness campaigns act as a form of advertising to patients. Guidelines are already in place to ensure that individual medicines are not mentioned in material produced in relation to such campaigns, but the promotional material we requested from several pharmaceutical companies shows that targeting of patients may be a prime objective. Material relating to one brand highlighted the "missing millions" and the need to render them "open to change beliefs" so that they present to their GP. While disease awareness campaigns may be valuable, the presence of company logos and use of tactics such as those described in the marketing campaign analysed for us clearly suggests that these are not merely health promotion tools. **We recommend that the current guidelines on disease awareness campaigns be strengthened. When a campaign is**

sponsored by a company that is developing or marketing a product to treat the condition that is the subject of the campaign, any related literature should carry a statement to this effect.

383. Patient groups, which often depend on funding from the pharmaceutical industry, are not required to make their sources of income, or funding policies, public. **We recommend that patient groups be required to declare all substantial sources of funding, including support given in kind, and make such declarations accessible to the public.**

NICE

384. NICE carries out valuable work, but it acts too slowly and covers only a proportion of the drugs available. Prescribers may be cautious in prescribing new drugs until guidance has been issued, or they may over-prescribe in the absence of sufficient supporting evidence. There would be great advantages if NICE guidance were issued promptly. The Institute needs to be better informed of medicines that are in the pipeline with a view to directing resources appropriately to accelerate the publication of its guidance. We recognise, however, that the current system of consultation and evaluation is not conducive to speed. We were also pleased to hear from Lord Warner that a more "holistic picture of what is the best therapeutic approach to particular sets of disease conditions" is being encouraged.[303] **We recommend increased funding of NICE to allow it to evaluate more medicines more quickly. Consequent improvement in prescribing standards should make such investment cost-effective.**

Government and EU

385. The Government and European Commission see the maintenance of a large and profitable pharmaceutical industry as vital. There are additional measures that the Government could take to encourage it. We have already made recommendations to facilitate clinical trials in the UK. It is also important that it ensures that there are sufficient staff with the right variety of skills needed by the pharmaceutical industry. There is a shortage of chemists, yet some university chemistry departments are closing or under pressure to close. **The Government should look at the levels and range of expertise required by the pharmaceutical industry and, with universities, take action to ensure that appropriate numbers and quality of staff are trained.**

386. The Government has had considerable success in maintaining a profitable and effective pharmaceutical industry. However, it should also give equal priority to health. This it has not done. Drugs have been too readily licensed and prescribed and iatrogenic disease is an increasing problem. The Government has also done little to curb the increasing 'medicalisation' of society. Indeed it may have encouraged it. There is not and cannot be a pill for every difficulty we face. The prospect of ever more sophisticated drug development implies some urgent need to define the limits of medical intervention.

387. We know too little about the optimal uses and effects of existing drugs and in-depth investigation of existing (off-patent) treatments is uncommon. Considering, for example, the myriad uses of aspirin, many of which were discovered long after the drug was

[303] Q981

originally available, greater investigation of existing medicines is a worthwhile venture. There is also too little independent research into the use of drugs compared to non-drug approaches. Neither the illness caused by drugs nor the health effects of medicalisation have been adequately investigated.

388. Pharmaceutical companies cannot be expected to undertake in-depth research into these areas. In the absence of other sources of funding this research must be financed by the Government. **We recommend that the Government fund**:

- **A multi-disciplinary investigation of existing medicines, combinations of medicines and medicines use where there is a reluctance of the industry to fund such research;**
- **Research into the adverse health effects of medicalisation;**
- **Trials of non-drug approaches to treatment.**

389. **We recommend that the extent, cost and implications of illness resulting from the use of medicines be systematically investigated by the Department of Health in conjunction with the MHRA.**

390. There are a number of specific measures which may help to focus on health priorities. The World Health Organization has recommended that all countries adopt a National Drugs Policy to encourage the availability of medicines to all types of patients, the safety and efficacy of these medicines and their rational use. **We recommend that the Government adopt a National Drugs Policy to encourage the availability of medicines to all types of patients, the safety and efficacy of these medicines and their rational use and to ensure that medicines are compared to non-drug approaches.**

391. The NHS, despite its size, has no policy on the evaluation of drugs in treatment relative to non-pharmacological approaches. **We recommend that the NHS adopt a policy regarding the role of drug treatment in relation to non-drug treatment, emphasising the importance of both approaches.**

392. During this long inquiry we have become concerned that there is a fundamental weakness in the Government's dealings with the pharmaceutical industry: that is the Department of Health's dual role in promoting health and acting as 'sponsor' of the industry. These roles have not proved compatible. Health and trade priorities are not always identical and their combination leads to a lack of clarity of focus and commitment to health outcomes. We need a Secretary of State for Health who is not saddled with dual responsibilities, who is not a 'cross-dresser' but who puts health priorities first. **We recommend that responsibility for representing the interests of the pharmaceutical industry should move into the remit of the Department of Trade and Industry to enable the Department of Health to concentrate solely on medicines regulation and the promotion of health.**

Annex: contributions from pharmaceutical companies to All-Party Groups

Group	Contribution (£)	Company
Africa All-Party Parliamentary Group	500	GlaxoSmithKline
All-Party Parliamentary Group on AIDS	5000	Merck Sharpe and Dohme
All-Party Parliamentary Group on Asthma	Reception	Novartis
Associate Parliamentary Health Group	6000	AstraZeneca
Associate Parliamentary Health Group	6000	GlaxoSmithKline
Associate Parliamentary Health Group	6000	Novartis
Associate Parliamentary Health Group	6000	Pfizer
Associate Parliamentary Health Group	6000	Sanofi-Synthelabo
Associate Parliamentary Health Group	6000	Wyeth
Associate Parliamentary Health Group	6000	Bristol-Meyers Squibb
Associate Parliamentary Health Group	6000	NAPP
Integrated and Complementary Healthcare	1000	Weleda (UK) Ltd.
Integrated and Complementary Healthcare	1000	Nelsonbach
Pharmaceutical Industry	Secretarial support	ABPI
Parliamentary and Scientific Committee	664	Amersham plc
Parliamentary and Scientific Committee	614	ABPI
Parliamentary and Scientific Committee	622	GlaxoSmithKline
Parliamentary and Scientific Committee	516	Globepharm Ltd
Parliamentary and Scientific Committee	816	Merck Sharpe & Dohme
Parliamentary and Scientific Committee	960	Novartis
All-Party Parliamentary Group on Skin	750	LEO Pharmaceuticals
All-Party Parliamentary Group on Skin	750	Galderma UK Ltd
All-Party Parliamentary Group on Skin	750	Roche Products Ltd
All-Party Parliamentary Group on Skin	750	Serono Limited
All-Party Parliamentary Group on Skin	750	Schering-Plough Ltd
All-Party Parliamentary Group on Skin	750	Wyeth Pharmaceuticals

Source: Compiled on 14 March 2005 from the House of Commons Register of All Party Groups on the Parliamentary website: http://www.publications.parliament.uk/pa/cm/cmparty/050211/memi01.htm.

The table shows direct contributions to all party groups from pharmaceutical companies. Some groups may receive funding from subject related charities who receive monies from pharmaceutical companies – this information is not held on the register of interests.

List of Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse drug reaction
BGMA	British Generic Manufacturers Association
BMA	British Medical Association
BNF	British National Formulary
CRO	Contract research organisation
CSM	Committee on the Safety of Medicines
DTCA	Direct-to-consumer advertising
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good clinical practice
GMC	General Medical Council
ICH	International Conference on Harmonisation (on technical requirements for registration of pharmaceuticals for human use)
KOL	Key opinion leader
NICE	National Institute for Clinical Excellence
MHRA	Medicines and Healthcare products Regulatory Agency
NCRN	National Cancer Research Network
OTC	Over-the-counter
PCT	Primary Care Trust
PICTF	Pharmaceutical Industry Competitiveness Task Force
PIL	Patient Information Leaflet
PPRS	Pharmaceutical Price Regulation Scheme
RCGP	Royal College of General Practitioners
RCN	Royal College of Nursing
RPSGB	Royal Pharmaceutical Society of Great Britain
SPC	Summary of Product Characteristics (the drug data sheet)

SSRI	Selective Serotonin Re-uptake Inhibitor (anti-depressant drug)
UMC	Use of Medicines Committee
WHO	World Health Organization

Glossary

Carcinogenicity	The capacity to cause cancer or increase the risk of developing cancer
Clinical end-point	A clinical measure used to determine the effect of an intervention (e.g. mortality rate after a heart attack)
COX-2 inhibitor	A drug that acts to reduce the action of the enzyme cyclo-oxygenase-2, which produces natural substances that cause or enhance inflammation
Evergreening	Tactics used to extend the duration of a drug's patent
Herceptin	Drug used to treat breast cancer. Generic name trastuzumab
Human Genome Project	A long-term project to identify all the genes present in human DNA. Coordinated by the US Department of Energy and National Institutes of Health, with major input from the UK and other countries, the project was completed in 2003.
Iatrogenic illness	Ill-health induced by the use of medicines
Life-cycle management	Activity carried out to ensure a drug remains protected by its patent for as long as possible
Naturalistic setting	A clinical environment that closely mirrors routine practice or normal life
Orphan drugs	Medicines used to treat patients with rare diseases, for which no sponsoring company could be found under normal commercial conditions because of a small potential market.
Pharmacovigilance	The process of detecting and assessing unwanted effects of medicines once they are on the market
Suicidality	Suicidal feelings, thoughts or actions
Surrogate end-point	A measure that is used as a substitute for a clinically meaningful outcome
Venous thromboembolism	A blood clot in the veins that breaks off and subsequently lodges in (and usually blocks off) vessels at a distant site

Conclusions and recommendations

1. The industry's ability to compete internationally requires a legislative and organisational framework for research that protects the interests of all stakeholders – patients, researchers and pharmaceutical companies. (Paragraph 43)

2. Priorities for research into medicines inevitably reflect the interests of the pharmaceutical companies and are not necessarily well aligned with the medical needs of all patients. The industry will continue to undertake the bulk of research in this area, but there are improvements which could be made. We welcome Lord Warner's recognition of this and look forward to his proposals to align more closely the drug companies' research strategies with the public health aims of the NHS. (Paragraph 189)

3. However it occurs, the presence of many 'me-too' drugs on the market creates difficulties for prescribers and the NHS. Although this is a considerable problem, we were given no obvious solution. We expect that there will continue to be a large number of me-too drugs. The National Prescribing Centre and others should particularly consider issuing independent advice in areas where many 'me-toos' exist. (Paragraph 190)

4. Much excellent clinical science takes place within the industry and elsewhere, but the current system of clinical testing provides ample opportunities for bias. Too many of these problems appear to persist unnoticed or unacknowledged by the organisations that are central to the co-ordination, conduct and review of the clinical trials. There is a need for more transparency and we welcome the contribution that the proposed clinical trials register should make to this approach. The regulators must check that research is designed to provide objective evidence of a drug's efficacy and safety at the time of licensing. (Paragraph 191)

5. The aggressive promotion of medicines shortly after launch, the sheer volume of information that is received in its many forms by prescribers and the "promotional hospitality masquerading as education", in the absence of effective countervailing forces, all contribute to the inappropriate prescription of medicines. (Paragraph 232)

6. Ghost-writing, in conjunction with suppression of negative trial results, is harmful. If prescribers do not have access to fair and accurate accounts of clinical trials they cannot be expected to make informed prescribing decisions. The guidelines on the subject of authorship and the role of professional medical writers quoted in Paragraph 199 must be followed. (Paragraph 233)

7. The blame for inadequate or misinformed prescribing decisions does not only lie with the pharmaceutical industry, but with doctors and other prescribers who do not keep abreast of medicines information and are sometimes too willing to accept hospitality from the industry and act uncritically on the information supplied by the drug companies (Paragraph 234)

8. The pharmaceutical industry's promotional efforts are relentless and pervasive. The evidence presented showed the lengths to which the industry goes to ensure that

promotional messages reach their targets and that these targets include not only prescribing groups, but patients and the general public. (Paragraph 271)

9. There is an urgent need for a comprehensive and informative PIL, preferably one which indicates the role of the drug in overall management of the disease. We were advised that patients themselves should be involved in the process of developing such a PIL. The MHRA's Patient Information Working Group is addressing this issue but the group is dominated by professional interests. (Paragraph 272)

10. DTCA is inappropriate and unnecessary in the UK. The evidence reviewed above on the targeting of prospective patients, and the central emphasis on emotional appeals, leads us to believe that great caution should be exercised in any relaxation of the rules relating to provision of consumer drug information by drug companies. (Paragraph 273)

11. The existing guidelines on disease awareness campaigns are weak and unmonitored. Drawn up after limited public consultation, they make no strict demands apart from a requirement not to mention brand names. The effectiveness of future guidelines will depend on interpretation, monitoring and enforcement. (Paragraph 274)

12. We often do not know what funds or support in kind patient groups receive from pharmaceutical companies. Limiting or legislating against such support is not appropriate; this would disadvantage both the charities that rely on industry funding and the industry itself, by cutting off a source of valuable feedback from the eventual consumers of its products. Measures to limit the influence of industry on patient groups are needed, however. Patient groups should declare all significant funding and gifts in kind and the Government should seek to make appropriate changes to charity law to ensure this. It would in any case be greatly preferable if patient groups were funded by companies' charitable arms, rather than by companies themselves. (Paragraph 275)

13. Post-marketing surveillance in the UK is inadequate. This has several causes: the lack of effective post-marketing investigation of drug benefits and harms in real life situations, and institutional indifference to the experience and reports of medicine users. In addition, the focus on drug licensing and on the safety profiles of individual drugs has contributed to a dearth of information about the overall impact of drug-induced illness in the community. (Paragraph 312)

14. The reputation and credibility of the MHRA depends on its ability to communicate uniformly with its different stakeholders. These diverging messages contribute to confusion between health and trade priorities (Paragraph 313)

15. Areas of research that are not of direct interest to the pharmaceutical industry but may significantly benefit patients, such as non-pharmacological treatments, should be funded by Government. (Paragraph 328)

16. The interests of patients, the NHS and industry can be at odds and we have no confidence that the Department is capable of achieving the balance required. The 'cross-dressing' role of the Department in this regard does not serve the public as well as it should (Paragraph 335)

17. Prescribers must take their share of the blame for the problems that have resulted from the prescribing of SSRI antidepressants and COX-2 inhibitors. There is no doubt that these medicines have been indiscriminately prescribed on a grand scale. This is partly attributable to intensive promotional activity, especially around the time of drug launch, but also the consequence of data secrecy and uncritical acceptance of drug company views. It seems that intensive marketing has worked to persuade too many professionals that they can prescribe with impunity. There is a huge variation in prescribing, even within a limited area. That many acted cautiously makes those who did not more open to criticism. There is a lack of any effective mechanism for tempering the prescribing explosion often seen in the months following a product launch. We have been told time and again that this is the most important period in drug promotion terms, but is also the time when least is known about the product. (Paragraph 348)

18. We recommend that the clinical trials register be maintained by an independent body and the results of all clinical trials data, containing full trials information, be put on the register at launch as a condition of the marketing licence. (Paragraph 355)

19. Clinical trials have significant limitations. We recommend that the MHRA work with the pharmaceutical industry and outside experts to design clinical trials that establish the real therapeutic value of new medicines using measures that are relevant to patients and public health. Trials should be designed to more accurately predict the performance of drugs in routine clinical settings. We recommend that research ethics committees encourage where appropriate the inclusion of comparator drugs and non-drug approaches in the evaluation of proposed clinical trials. Ethics committees should also require applicants to prove that the trial does not duplicate previous research and that results will be published in full. (Paragraph 356)

20. We recommend that the NHS take further steps to facilitate the conduct of clinical trials, with each Trust having a single point of contact for the pharmaceutical industry to approach when considering a trial. (Paragraph 357)

21. We recommend that limits be set as to the quantity of material prescribers receive, particularly in the first six months after launch. Less experienced and non-specialist doctors are ill-equipped to cope effectively with the promotional material. The pressure on nurses and pharmacists is likely to intensify as their prescribing powers are further extended. Stricter controls are needed in respect of drug company representatives' promotion of their products to junior doctors and to nurses or pharmacists with new prescribing powers. (Paragraph 358)

22. Marketing practices that appear to be illegal should be reported by the pharmaceutical industry and others to the MHRA. (Paragraph 359)

23. We recommend a major review of the investigation of complaints (of marketing and advertising practices) to ensure the process is far quicker and effective sanctions are enforced. (Paragraph 360)

24. The PPRS should be used more effectively to influence the actions of the pharmaceutical industry in the public's interest. When companies are found to be in breach of advertising regulations or to have published misleading findings the

allowance for promotion and research, respectively, provided under the Scheme should be reduced. In addition, rewards for innovation should be limited to those drugs that are proven to offer clinical advantage. (Paragraph 361)

25. We recommend that the MHRA publishes, in some form of useable database, the material it receives from drug companies and the assessments it sends to advisory bodies at the time it sends them. We welcome the MHRA's plans to include lay members on every MHRA advisory committee, and recommend that these members receive sufficient training and support to allow them to fully contribute to decision making. (Paragraph 363)

26. We are concerned that the MHRA is not permitted to routinely inspect audit reports for compliance with standards of Good Clinical Practice (GCP). The Department of Health should reconsider its agreement to waive powers to inspect, on a routine basis, audit reports of compliance with GCP standards, including standards of patient care. The Department should review all current and proposed standards developed by the International Conference on Harmonisation that impose restrictions on MHRA staff relating to inspection of company-held data and records (Paragraph 364)

27. The MHRA should put in place systematic procedures to randomly audit raw data. The results of such audits should be published. We also recommend that, like the US Food and Drug Administration, the MHRA play a greater role during the early stages of drug development. Guidance should be provided by the MHRA to the industry as to the types of clinical trial likely to prove the degree of therapeutic gain. NICE should also be involved in this process to provide advice on the type of data more likely to lead to the drug being included in NICE guidance. (Paragraph 365)

28. The adverse drug reactions reported in the clinical trials that are considered in the medicines licensing process typically prove unreliable as a guide to routine clinical practice. Moreover, the adverse effects that may be linked to stopping treatment are insufficiently investigated. The MHRA should focus more intensely on updating drug benefit:risk profiles in the Summary of Product Characteristics, following systematic post-marketing review. (Paragraph 366)

29. We recommend that the MHRA employ sufficient numbers of staff to monitor effectively drugs which have been recently licensed. Given the limited value of clinical trials in predicting drug impact in naturalistic settings, the MHRA should investigate options for the development of more effective post-marketing surveillance systems. Consideration should be given to the establishment of post-marketing surveillance and drug safety monitoring systems independently of the Licensing Authority. We also recommend that the MHRA enhances its relicensing procedures five years after launch. During the renewal procedure, the MHRA should again assess in detail the product's efficacy, safety and quality. (Paragraph 367)

30. We recommend that the MHRA is given the same authority to propose restrictions on drug use as it has when approving them. (Paragraph 369)

31. We recommend that: the system of patient reporting to the Yellow Card Scheme country-wide be put in place as soon as possible; that steps be taken to improve rates

of healthcare professional reporting of adverse drug reactions; that greater efforts be made to investigate signals of possible problems; and that maximum transparency be combined with concerted efforts to explain the uncertainties of risk. (Paragraph 370)

32. We recommend that there should be a public inquiry whenever a drug is withdrawn on health grounds. (Paragraph 371)

33. The intensive marketing which encourages inappropriate prescribing of drugs must be curbed. Present methods of supplying independent information, as described by Lord Warner, are inadequate. We recommend that all the promotional material for a new product be pre-vetted by the MHRA prior to publication, and that consideration be given to limiting those who can prescribe a new drug in the two years following launch. Drug and Therapeutics Committees would be well-placed to implement this. Wider prescribing rights would be permitted once comparative studies, and trials investigating the potential adverse effects of the medicine in large populations, had been undertaken and after formal evaluation of the value of the product in clinical practice had been confirmed by the Licensing Authority and/or NICE. (Paragraph 372)

34. We recommend that the MHRA and the PMCPA better co-ordinate their work relating to the promotion of medicines to avoid duplication. Complaints should be investigated swiftly, particularly when claims for new drugs are involved. When the PMCPA has evidence that a company has breached the regulations it should inform the MHRA of its findings. When companies are found to be in breach of advertising or marketing regulations by the MHRA, we recommend that corrective statements always be required and that such statements are given as much prominence as the original promotional piece. The publication of misleading promotional material is a criminal offence and the punishment should befit such a status. (Paragraph 373)

35. A healthy generics market is important for the NHS and patients. We recommend a systematic review of so-called evergreening and other practices that impede the entry of generic drugs on to the market. (Paragraph 374)

36. We recommend that there be an independent review of the MHRA. The earlier review by the National Audit Office was designed expressly to assess the public expenditure aspects of the work of the agency; a more wide-reaching and in-depth review needs to be carried out to determine whether the processes now used for decision-making are adequate and reflect patients' health needs and society's expectations. The following principles should govern the review: the need for greater independence from Government; the need for greater independence from the pharmaceutical industry; the need for policies of greater transparency and accountability in light of recent freedom of information legislation; the effectiveness of the post-licensing department and the need for the MHRA to become pro-active rather than re-active; scrutiny of the regulatory standards underpinning clinical and non-clinical new drug review; the reporting and evaluation of adverse drug reactions; the prioritisation of new marketing applications; and inclusion of the public in policy-making and implementation (Paragraph 376)

37. We recommend that all medical students be taught how to judge clinical trial results effectively, recognise adverse drug reactions and deal with drug company representatives. There should be mandatory post-graduate training for all prescribers to keep up-to-date with prescribing changes. In addition, stricter regulation of individual prescriber's practices is required. (Paragraph 378)

38. There is a lack of consistent and reliable independent advice, information and oversight of prescribers. We recommend that the Department of Health look into ways of making Use of Medicines Committees/Drug and Therapeutics Committees of a uniformly high standard, so that they can reliably carry out this vital educational role. Wherever possible, clinical pharmacologists and specialist pharmacists should be included on such Committees, as should lay representatives. Formularies established in hospital Trusts should be shared with affiliated PCTs with a view to adoption by the entire local health community. Ideally, new drugs should not be prescribed until they have been approved by such a committee. New drugs that might represent significant advances should be fast-tracked through these committees. (Paragraph 380)

39. We recommend that a register of interests be maintained by the relevant professional body (General Medical Council, Royal College of Nursing, Royal Pharmaceutical Society of Great Britain etc), detailing all substantial gifts, hospitality and honoraria received by members. The register should be made available for public inspection. Individual practitioners should be responsible for maintaining their entry on the register. Professional bodies should provide advice to their members about the levels of hospitality and payments that are acceptable. (Paragraph 381)

40. We recommend that the current guidelines on disease awareness campaigns be strengthened. When a campaign is sponsored by a company that is developing or marketing a product to treat the condition that is the subject of the campaign, any related literature should carry a statement to this effect. (Paragraph 382)

41. We recommend that patient groups be required to declare all substantial sources of funding, including support given in kind, and make such declarations accessible to the public. (Paragraph 383)

42. We recommend increased funding of NICE to allow it to evaluate more medicines more quickly. Consequent improvement in prescribing standards should make such investment cost-effective. (Paragraph 384)

43. The Government should look at the levels and range of expertise required by the pharmaceutical industry and, with universities, take action to ensure that appropriate numbers and quality of staff are trained. (Paragraph 385)

44. We recommend that the Government fund: a multi-disciplinary investigation of existing medicines, combinations of medicines and medicines use where there is a reluctance of the industry to fund such research; research into the adverse health effects of medicalisation; and trials of non-drug approaches to treatment. (Paragraph 388.)

45. We recommend that the extent, cost and implications of illness resulting from the use of medicines be systematically investigated by the Department of Health in conjunction with the MHRA. (Paragraph 389)

46. We recommend that the Government adopt a National Drugs Policy to encourage the availability of medicines to all types of patients, the safety and efficacy of these medicines and their rational use and to ensure that medicines are compared to non-drug approaches. (Paragraph 390)

47. We recommend that the NHS adopt a policy regarding the role of drug treatment in relation to non-drug treatment, emphasising the importance of both approaches. (Paragraph 391)

48. We recommend that responsibility for representing the interests of the pharmaceutical industry should move into the remit of the Department of Trade and Industry to enable the Department of Health to concentrate solely on medicines regulation and the promotion of health. (Paragraph 392)

Formal minutes

Tuesday 22 March 2005

Members present:
Mr David Hinchliffe, in the Chair

Mr Keith Bradley	Dr Doug Naysmith
Jim Dowd	Dr Richard Taylor
Mr Jon Owen Jones	

The Committee deliberated.

Draft Report (The Influence of the Pharmaceutical Industry), proposed by the Chairman, brought up and read.
Paragraphs 1 to 392 read and agreed to.
Summary agreed to.
Text in boxes agreed to.
Annex agreed to.
Resolved, that the Report be the Fourth Report of the Committee to the House.
Ordered, That the Chairman do make the Report to the House.
Several papers were ordered to be appended to the Minutes of Evidence.
Ordered, That the Provisions of Standing Order No. 116 (Select Committees (reports)) be applied to the Report.
Ordered, That the Appendices to the Minutes of Evidence taken before the Committee be reported to the House.—(*The Chairman.*)
Several Memoranda were ordered to be reported to the House.

[Adjourned till Tuesday 5 April at 10.00am.

Witnesses

Thursday 9 September 2004 *Page*

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. Ev 19

Thursday 14 October 2004

Dr Des Spence, UK Spokesperson, No Free Lunch, **Mr Graham Vidler,** Head, Policy, Consumer's Association (Which?), **Dr Ike Iheanacho,** Editor, Drug and Therapeutics Bulletin, and **Dr Peter Wilmshurst,** Consultant Cardiologist, Royal Shrewsbury Hospital Ev 57

Mr Richard Brook, Chief Executive, Mind**, Professor David Healy,** Cardiff University, and **Professor Andrew Herxheimer,** Emeritus Fellow, UK Cochrane Centre, Oxford Ev 93

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* Ev 115

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 Ev 145

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 Ev 171

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 Ev 198

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 Ev 225

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* Ev 243

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, Deveopment, AstraZeneca Ev 293

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 Ev 337

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 Ev 347

Professor Sir Michael Rawlins, Chairman, and **Mr Andrew Dillon CBE,** Chief Executive, National Institute for Clinical Excellence Ev 366

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 Ev 389

Reports from the Health Committee since 2001

The following reports have been produced by the Committee since the start of the 2001 Parliament. The reference number of the Government's response to the Report is printed in brackets after the HC printing number.

Session 2004-05

First Report	The Work of the Health Committee	HC 284
Second Report	The Prevention of Venous Thromboembolism in Hospitalised Patients	HC 99
Third Report	New Developments in Sexual Health and HIV/AIDS Policy	HC 252

Session 2003–04

First Report	The Work of the Health Committee	HC 95
Second Report	Elder Abuse	HC 111 (Cm 6270)
Third Report	Obesity	HC 23 (Cm 6438)
Fourth Report	Palliative Care	HC 454 (Cm 6327)
Fifth Report	GP Out-of-Hours Services	HC 697 (Cm 6352)
Sixth Report	The Provision of Allergy Services	HC 696 (Cm 6433)

Session 2002–03

First Report	The Work of the Health Committee	HC 261
Second Report	Foundation Trusts	HC 395 (Cm 5876)
Third Report	Sexual Health	HC 69 (Cm 5959)
Fourth Report	Provision of Maternity Services	HC 464 (Cm 6140)
Fifth Report	The Control of Entry Regulations and Retail Pharmacy Services in the UK	HC 571 (Cm 5896)
Sixth Report	The Victoria Climbié Inquiry Report	HC 570 (Cm 5992)
Seventh Report	Patient and Public Involvement in the NHS	HC 697 (Cm 6005)
Eight Report	Inequalities in Access to Maternity Services	HC 696 (Cm 6140)
Ninth Report	Choice in Maternity Services	HC 796 (Cm 6140)

Session 2001–02

First Report	The Role of the Private Sector in the NHS	HC 308 (Cm 5567)
Second Report	National Institute for Clinical Excellence	HC 515 (Cm 5611)
Third Report	Delayed Discharges	HC 617 (Cm 5645)

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