Paediatric Medicines: Proposed EU Regulation

Report with Evidence

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**NOTE:** References in the text of the report are as follows:

(Q) refers to a question in oral evidence

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Over 50% of all medicines given to children (and some 90% of those given to the newly-born) have never been tested or authorised for use on them. The European Commission want to stimulate the development of medicines for children and lay down rules for testing and approval. It is high time this was done and the framework proposed seems right. But ethical considerations on the implementation of the rules need to be carefully considered and the incentive mechanisms proposed are a leap of faith which will have to be examined rigorously after they have been tried out.
CHAPTER 1: INTRODUCTION

1. This Inquiry examines a Proposal by the European Commission to introduce a Regulation on medicinal products for paediatric use. It was carried out by Sub-Committee G of the European Union Select Committee which deals with Social Policy and Consumer Affairs.

Why are we carrying out this Inquiry?

2. We decided to hold this Inquiry because:
   - the European Commission stated that between 50–90% of all medicinal products used in the paediatric population had never been specifically studied or authorised for their use;
   - we were anxious to be sure that the Proposal satisfactorily addressed the ethical considerations involved and that the overriding priority was the protection of the health, welfare and rights of any children involved in paediatric trials;
   - we also wanted to find out whether the Proposals were soundly-based and would work well in practice; and,
   - we saw the need to draw wider Parliamentary and public attention to the significance of this Proposal and what it entailed.

Background

3. On 29 September 2004 the European Commission adopted a Proposal for a Regulation on Medicinal Products for Paediatric Use which was sifted to Sub-Committee G for scrutiny on 16 November 2004.

4. We gave our initial reactions to the Proposal to the Department of Health on 9 December 2004. The Department did not reply until 11 July 2005. We responded to the Minister on 21 July.

5. At the same time, we also decided to carry out a selective consultation with relevant professional organisations and other interested parties. We hoped to...

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1 The Members of the Sub-Committee and their declared interests are shown at Appendix 1
3 The European Commission use the term “paediatric population” in much of their documentation related to this Proposal, whereas the Government and other respondents have tended to use the term “children”. Article 2 of the draft Regulation defines “paediatric population” as that part of the population aged between birth and 18 years. The Government also confirmed that the Regulation would apply to anyone under the age of 18 years. (QQ 40-41).
5 p 31
6 pp 32-34
7 pp 34-35
this would give us a better understanding of the ethical and practical aspects of the Commission’s Proposal, for consideration after the Summer Recess.

6. We have drawn on the evidence contained in the responses to that consultation, as well as subsequent oral evidence from Professor Sir Cyril Chantler, the Chairman of the Great Ormond Street NHS Trust. The other main sources have been oral evidence and correspondence from the Minister of State and officials at the Department of Health and details provided by the Minister of a consultation on the Proposal carried out by the Medicines and Healthcare Products Regulatory Agency (MHRA). We are very grateful to all those who have assisted this short Inquiry.

7. Our Inquiry was carried out in this limited way in a very short timescale because we were aware that the Government were very anxious to try to secure political agreement on the Proposal before the end of the UK Presidency of the European Union. Moreover, the independent evidence demonstrated overwhelming support in principle for rapid progress in setting up the arrangements envisaged by the Commission Proposal.

8. Ideally, we would have preferred to have spent much longer studying this important and potentially sensitive proposal in greater depth. But we are satisfied, on the basis of the evidence we have had, that we have a sufficient understanding of the key issues to justify the Conclusions and Recommendations we make in this Report.

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8 The respondents are listed at Appendix 2

9 In the time available it was not possible to arrange for oral evidence to be given by more than one independent professional witness. Professor Chantler readily agreed to assist the Inquiry. Both his written and oral evidence are based not only on his own professional experience, but also on consulting a number of professional colleagues who are mentioned in the evidence.
CHAPTER 2: THE COMMISSION PROPOSAL

9. The Commission Proposal\(^{10}\) derives from a Resolution of the Council of Health Ministers of 14 December 2000\(^{11}\) calling on the Commission to make proposals for incentives, regulatory and other supporting measures to ensure through clinical research and development that new medicinal products for children, as well as those already on the market, should be fully adapted to the specific needs of children.

10. The Commission stated their general objectives were:
   - to increase the development of medicines for use in children;
   - to ensure that medicines used to treat children are subject to high-quality research and are appropriately authorised for use in children;
   - to improve the information available on the use of medicines in children; and,
   - to achieve these objectives without subjecting children to unnecessary clinical trials and in full compliance with the Clinical Trials Directive\(^{12}\).

11. The Proposal therefore combined procedures to regulate clinical trials of medicines for use in children with incentives designed to encourage the pharmaceutical industry to develop and submit for approval medicines specifically developed for the treatment of children.

Approvals Procedure

12. The approvals procedure proposed by the Commission for the Regulation is based on the use of the European Community’s Clinical Trials Directive\(^{13}\) and operated through the European Medicines Agency (EMEA)\(^{14}\), which is the European Union’s centralised body for authorising medicinal products.

13. The key elements of the Proposal\(^{15}\) are:
   - an expert Paediatric Committee should be set up by the EMEA to:
     (a) oversee the process by assessing and agreeing Paediatric Investigation Plans for the development of medicinal products intended for use in children;
     (b) assess compliance with Paediatric Investigation Plans from the results of studies;
     (c) advise the EMEA on data collection for surveys carried out under the Regulation and the adoption of an Inventory of Therapeutic Needs;
     (d) support and advise the EMEA in establishing a European Network for coordinating studies related to paediatric medicinal products and

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\(^{10}\) Commission reference 13880/04 COM (2004) 599 final
\(^{11}\) See http://ue.eu.int/ueDocs/cms_Data/docs/pressData/en/lsa/14517.en0.doc.html#_Toc503256039
\(^{12}\) See paragraph 12
\(^{13}\) Directive 2001/20/EC dated 4 April 2001
\(^{14}\) Established in 2004 by Regulation (EC) 726/2004
\(^{15}\) Commission reference 13880/04 COM (2004) 599 final
building up the necessary scientific and administrative competence throughout the EU; and,

ey give scientific and professional advice to the EMEA on documents to be issued under the Regulation or any other questions related to paediatric medicines.

- the Paediatric Committee should be composed of:
  
  (a) five members of the EMEA Committee for Medicinal Products for Human Use (CMPHU);
  
  (b) one person appointed by each Member State which is not represented on the CMPHU; and,
  
  (c) six persons appointed by the Commission, through a public call for expressions of interest, representing paediatricians and the interests of patient associations.

- no members of the Paediatric Committee should have financial or other interests in the pharmaceutical industry which could affect their impartiality.

- applications to the EMEA for marketing authorisation for new medicines, or the development of existing patent-protected products, would have to be accompanied by a Paediatric Investigation Plan approved by the Paediatric Committee, unless the Committee granted a waiver on the grounds that the medicines concerned were unlikely to benefit children.

- the Paediatric Committee may authorise requests for deferral of studies in children where initial experience of using a product in adults would be appropriate before use in children was authorised, or where studies in children might take longer to conduct than studies in adults.

- to avoid unnecessary studies in children, the Paediatric Committee may grant waivers from the requirements of the Regulation where the product concerned is likely to be ineffective or unsafe for all or part of the paediatric population, where the disease or condition for which the product is being developed occurs only in adult populations or where the product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

- details of trials carried out under paediatric investigation plans and data collected by Member States on existing uses of medicinal products in children should be entered by the EMEA on the European Clinical Trials Database established under the Clinical Trials Directive.

- the EMEA would coordinate the establishment of a European Paediatric Clinical Trials Network to encourage communication and collaboration between existing European networks of scientific expertise in paediatric studies.

- the Commission would also examine the possibility of setting up an independent paediatric study programme, entitled Medicines Investigation for the Children of Europe (MICE), to fund studies into the paediatric use of medicines.
Authorisation Procedures: Rewards and Incentives

14. To stimulate research and development on medicines suitable for use in children, the Commission propose to introduce the following rewards and incentives where studies have been carried out under an approved Paediatric Investigation Plan:

- new medicines and products covered by existing patents, or granted market exclusivity by Supplementary Protection Certificates (SPC) under existing EMEA authorisation procedures, shall be entitled to a six-month extension to the market exclusivity (known as the SPC extension); and,

- an addition of two years of market exclusivity to the ten years of market exclusivity to which to orphan medicinal products (those specifically designed to diagnose, prevent or treat a rare disease) are entitled under existing EMEA authorisation procedures (making 12 years of market exclusivity in all)

15. Ten years of data protection for new paediatric studies (but not market exclusivity) would also be granted to off-patent medicinal products developed specifically for use in children. Safety, quality and efficacy in children would need to be demonstrated. Products authorised under this provision would be granted Paediatric Use Marketing Authorisation (PUMA).

Product Identification

16. To identify suitability for the purpose, medicinal products granted marketing authorisation for paediatric use would have to display on the label, alongside the name of the product, the letter “P” in blue lettering surrounded by an outline of a star also in blue.

Review Procedures

17. The Commission would be required to publish annually a list of all the companies that have benefited from any of the rewards or incentives under the Regulation and those that have failed to comply with any of the obligations in the Regulation. This would be based on information supplied by Member States and the EMEA.

18. Within six years of entry into force of the Regulation, the Commission would also be required to publish a general report on the application of the Regulation, including a detailed inventory of all medicinal products authorised for paediatric use under the Regulation.

Legal Base

19. The Commission propose that the legal base for the Regulation should be Article 95 of the EC Treaty, which allows the Community to adopt measures for harmonising national laws. This Article requires co-decision by qualified majority.
Justification for the Proposal

20. In justifying the Proposal\(^{16}\) the Commission explained that:

- because between 50–90% of all medicinal products used in children have never been specifically studied or authorised for such use, prescribers have no alternative but to use either products authorised for adults which have not been tested or authorised for paediatric use or completely unauthorised products;

- the results of tests of medicines in adults cannot necessarily be extrapolated directly to children because they have different developmental, physiological and psychological characteristics than adults;

- many drugs are formulated in a way that is not suitable for administration to children, especially the very young;

- because of the relatively small size and complexity of the market, pharmaceutical companies often find it is not worthwhile to carry out the lengthy and expensive research and development needed to produce or adapt medicines specifically for children;

- attempts by Member States to encourage manufacturers to develop or adapt medicines for use in children voluntarily have largely been unsuccessful.

21. The Commission pointed out that similar voluntary initiatives in the USA had also been largely unsuccessful. The situation there had changed dramatically when legislation to encourage clinical trials in children had been introduced in 1997 and 1998. The combination of incentives and obligations in the US legislation had been extremely successful in stimulating the development of medicinal products for paediatric use.

22. The Community Regulation on orphan medicinal products\(^ {17}\), introduced in 2000, had similarly stimulated the authorisation of medicines to treat rare diseases.

23. The Commission concluded\(^ {18}\) that self-regulation by the industry to develop a Code of Practice would not provide the necessary stimulus for development of medicines specifically for children. Government intervention would be required to ensure that the right studies were done for the benefit of children, rather than because of anticipated market returns.

24. While Member States could help with research and training programmes, the regulation of medicines was a Community-based function and the problem required Community-wide co-ordination.

Consultation by the Commission

25. Following preliminary consultations and studies, the Commission launched a public consultation on a draft proposal for the Regulation in March 2004. This attracted 69 responses: 27 from health-care professionals, 18 from


\(^{17}\) Regulation (EC) 141/2000

industry, 15 from regulators, 3 each from insurance companies and patients’ associations and 3 from other sources\textsuperscript{19}.

26. The draft Proposal was generally welcomed. But changes were proposed to the composition of the Paediatric Committee. Industry representatives suggested that the SPC extension should be for 12 rather than 6 months. Some respondents favoured stronger incentives for off-patent medicines.

27. The central database was generally welcomed. But industry respondents were concerned about the confidentiality of information and wanted the information that would be accessible to the public to be clearly defined.

28. Some respondents regretted the lack of an explicit commitment to fund the proposed Medicines Investigation for Children of Europe (MICE) programme.

\textit{Impact Assessment}

29. The Commission engaged Rand Europe\textsuperscript{20} to assess the economic social and environmental impacts of the draft Regulation.

30. The Rand Europe Study Report (Rand Study)\textsuperscript{21} estimated that:

\begin{itemize}
  \item \textbf{(a)} To handle the expected increase in the number of applications the EMEA budget would have to be increased by between 67–150\%. In the worst case this would mean a rise of between €130–195 million.
  \item \textbf{(b)} The costs of developing paediatric investigation plans and the related studies in children would increase costs to the pharmaceutical industry by an average of €4 million per product.
  \item \textbf{(c)} The initial costs to industry for paediatric testing would be around €560 million in the first year, falling to between €160–360 million in subsequent years (bearing in mind that the average cost of developing new drugs was estimated in 2000 to be around US$802 million).
  \item \textbf{(d)} Marginal costs of testing passed on directly to consumers would be likely to increase drug prices between 0.1\% and 0.4\% (although it noted that in many EU Member States the price of medicines is controlled by Government).
\end{itemize}

31. The Commission admit that estimating the financial value of social savings through health improvement likely to result from the Regulation is “very difficult”. They quote Rand Study figures which would appear to indicate that hospital costs caused by unlicensed and off-label use of medicines in children could be between €140–252 million. But they urge caution in interpreting these figures.

32. The Rand study estimated that the incentives to the innovative pharmaceutical industry proposed in the Regulation could enable drug


\textsuperscript{20} Rand Europe is part of the US-based Rand Corporation, described on its website [www.rand.org] as a non-profit research organization providing objective analysis and effective solutions that address the challenges facing the public and private sectors around the World.

companies to cover the costs of testing and make a profit of between €63–205 million in ten years.

33. The six month SPC extensions available to the innovative pharmaceutical industry were predicted by the Rand study to cost generic drug manufacturers between €4–51 million through delayed market access. But the study calculated that the cost of adjusting to the new market conditions could be absorbed by the generics industry over a period of five years.

34. The Rand Study estimated the cost impact of these incentives on total European health care as between 0.01% and 0.04% in total European health care expenditure and between 0.06% and 0.25% of annual European pharmaceutical expenditure. But, because of the difficulty of accurately estimating potential costs and savings, the Commission concluded that these figures should be regarded as a “worst case scenario”.
CHAPTER 3: THE NEED FOR THE REGULATION

35. The need for an EU-wide regulatory framework to establish common standards for testing medicines in children and authorising products for them was already clear from the Commission Proposal and accompanying Staff Working Paper22. So was the need to stimulate the research and production of medicines specifically suitable for children.

36. Earlier correspondence from the Government to us strongly supported the Proposal in principle.23 The seven substantive responses we received from our selective consultation on the Proposal all welcomed it. Several endorsed it in strong terms.

37. While welcoming the Proposal, the Association of the British Pharmaceutical Industry (ABPI)24 expressed disappointment that it would be some six years after the original Council Resolution in 2000 before legislation based on the Regulation would be in place25.

38. Similarly strong support for the Regulation was also evident from the summary produced by the Minister of the 19 substantive responses to the MHRA consultation conducted between May and August 200526.

39. The urgent need for the Regulation was emphasised in evidence from Professor Sir Cyril Chantler, the Chairman of the Great Ormond Street NHS Trust (QQ 2–4, pp1–2). He told us about a study indicating that 36% of children admitted to hospital involved the use of unlicensed or off-label treatments. Unlicensed use in new-born babies, who were particularly vulnerable, could well reach 90%. Another study suggested that 40% of new medicines had the potential to be used in children but had no market authorisation for that use.

40. Professor Chantler explained that, without testing, it was not possible to know how a child’s body might absorb, distribute, metabolise and eliminate the drug (pharmacokinetics). Nor could it be known what effect the medicine might have on the child (pharmacodynamics). Post-operative pain for children was a major problem in hospitals throughout the country. Drugs in wide-spread use to relieve acute pain in children had not been licensed for that purpose.

41. The size and maturity of children affected the pharmacokinetics: simply scaling an adult dose based on body size dramatically oversimplified drug clearance from the body. Systems such as kidney function developed with age. The immunosuppressive effect of medicines given to prevent the rejection of transplanted organs was very different in children than in adults.

42. For example, over-dosage had led to some antibiotics causing deafness in children. Serious errors could occur in diluting dosages of medicines suitable for adults without specific test information. He had no doubt that the lack of suitable and properly-licensed medicine exposed children to significant mortality and morbidity.

23 pp 12-14 and pp 31-32
24 pp 25-26
25 pp 26-27
26 pp 48-56
43. Pharmaceutical preparations that were not made for children could be difficult to administer. They might need to be reformulated without adequate information on the consequences of reformulation, which could either make them dangerous or ineffective.

44. The need for clinical trials in children was borne out by experience in the USA and was supported by 90% of European paediatricians in a survey recently reported to the European Parliament. He believed that the Regulation was long overdue (Q 21).

45. The Minister told us that the proposed Regulation would be the key to addressing long-standing UK concern over the lack of medicines authorised and formulated specifically for paediatric use. The regulatory approach proposed by the Commission included incentives and requirements designed to ensure that new medicines for children, and those already on the market, met the specific needs of children. But it also ensured that children were not subjected to unnecessary clinical trials or that the authorisation of medicines for adults was needlessly delayed (Q 37).

46. We conclude, in principle, from the evidence we have had that there is an overwhelming and urgent need to take effective action at European level to govern clinical trials in children and the authorisation of medicinal products for paediatric use with the minimum of delay.
CHAPTER 4: ETHICAL CONSIDERATIONS

The Clinical Trials Directive

47. The Government acknowledged traditionally “wide-spread” resistance on ethical grounds to conducting clinical trials in children, but stated that this had to be balanced by the ethical issues related to giving medicines to a population in which they had not been tested. This reflected the view in the Commission’s original Explanatory Memorandum.

48. Professor Chantler (pp1–2, Q 5) also acknowledged the ethical arguments against carrying out studies in children. But he pointed out that in the UK no research in children could take place without permission from a properly-constituted ethical committee. Under the proposed Regulation, paediatric investigations in children would have to be agreed by the Paediatric Committee.

49. In many cases, he said the preparations would be researched in children who would be likely to benefit from their use. His personal view was that the Directive was sound so far as ethical issues were concerned. Most of his senior medical colleagues agreed (Q 5, Q 7).

50. The Minister told us that the Proposal “effectively” took account of ethical concerns. When we asked what this meant, the Minister said that the Regulation would be based on the Clinical Trials Directive which required all clinical trials to be designed, conducted and reported in accordance with good clinical practice. This ensured that the rights, safety and well-being of participants were protected, that the results of any trials were credible, and that all medicines used in trials complied with good manufacturing practice. The Directive had been implemented in the UK since 1 May 2000 and was inspected by the MHRA to ensure that the required standards were met.

51. The Directive also set out the requirements for obtaining agreement from an ethics committee for every trial conducted in Member States. The proposed Regulation had specific cross-references to the Directive making it clear that the control and monitoring of studies in children, and the development of medicinal products for them, must comply with the Directive.

52. The Directive also had specific requirements that:

- the ethics committee considering the trial must either have relevant paediatric expertise or take advice from persons involved in the relevant field of paediatric care;
- persons with parental responsibility or legal representatives must give informed consent to any trial involving a minor and may withdraw the minor from the trial at any time;
- the explicit wish of the minor to refuse participation in, or to be withdrawn from, a clinical trial at any time must be considered; and,

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27 pp 12-14 and pp 31-32
28 13880/04 COM (2004) 599 final
29 pp 31-32
30 pp 32-34
31 pp 35-56
• there must be no incentives or financial inducements, other than compensation, for those taking part in the trial.

53. Staff with experience with young persons must inform the minor involved of the risks and benefits of the trial. According to the minor’s capacity to understand, they must also consider his or her explicit wish to participate or to be withdrawn from the trial at any time.

54. The Directive also provides that:

• the clinical trial must relate directly to an illness from which the minor concerned suffers or that (sic) can only be carried out on minors;
• the trial must aim to provide some direct benefit for the group of patients involved; and,
• the interests of the patient must always prevail over those of science and society.

55. Moreover, the clinical trial must be designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the developmental stage of the child concerned.

56. The Minister strongly agreed with us that the health and welfare of children must be the overriding priority in conducting paediatric trials. She assured us that unnecessary trials would not be accepted by an ethics committee. All Member States shared the British Government’s view that the legislative provisions in the Regulation should be tightly drawn in this respect.

57. She pointed out that the Paediatric Committee, which included EU health professionals from the relevant paediatric disciplines, was required to waive the requirement to conduct trials where evidence showed that the product concerned was likely to be ineffective or unsafe in part or all of the paediatric population. Waivers could also be granted where the disease or condition for which the product was intended occurred only in adult populations (for example, Alzheimer’s disease). Where an appropriate product already existed, the Paediatric Committee might also decide no significant therapeutic benefit would be gained from undertaking clinical trials.

58. If the Paediatric Committee decided that clinical trials or studies on specific products should not take place, no financial or other incentive would be given for paediatric development work to be carried out on that product.

59. The Minister also reminded us about the deferrals procedure. This is designed to enable the Paediatric Committee to authorise products for use in adults where studies in children might take longer than studies in adults, and thus delay the introduction of the product for adults. Deferrals could also be granted where initial experience of use of the product in adults was recommended before it was studied in children.

60. The Paediatric Committee would also be required to consider carefully the timing of any trials in children, in accordance with agreed international guidelines.

61. Because the Regulation drew on experience gained in the USA, the Regulation would require studies undertaken under the US regime to be

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32 The Government have subsequently sent us a background note on paediatric legislation in the USA (pp 23-24). This also covers Australia and Canada where no legislative action has been taken so far, although in both countries responsible bodies have called for appropriate legislation.
PAEDIATRIC MEDICINES: PROPOSED EU REGULATION

submitted to the European Regulatory Authorities to avoid unnecessary participation of children in further trials in Europe.

62. Both the waiver and the deferral aspects of the Proposal had the full support of Member States. No modifications had been suggested during EU discussions. But the Minister pointed out that the details of how the procedure would operate would be set out in implementing texts (guidelines) to be drawn up by the Commission in consultation with Member States. These would take account of the relevant scientific and other criteria.

63. None of the responses to our own consultation or those to the MHRA consultation questioned the suitability of the Clinical Trials Directive as the basis for the Regulation.

64. **We conclude that the Clinical Trials Directive is an appropriate basis for this Regulation.**

Consent

65. We drew Professor Chantler’s attention to the Minister’s statement that the Clinical Trials Directive requires that a person with parental responsibility or a legal representative must give informed consent to any trial involving a minor, whereas the explicit wish of a minor to refuse participation or to be withdrawn from clinical trials “must be considered”.

66. Professor Chantler took the view that children should always be consulted. It was surprising how even very young children could understand what was in question, so long as imaginative ways of communicating with them were found. It was unacceptable to do something to any child that did not involve the child’s consent. The Medical Research Council had published guidance on medical research involving children and the Department of Health had also recently published relevant advice. He understood that the European Clinical Trials Committee were drafting new guidance on the ethics of studying children for the Clinical Trials Directive (Q 10, Q 11).

67. Asked about circumstances where a child’s lack of consent might need to be overridden, Professor Chantler said it was essential for the parents to be properly briefed and to give consent. If the parents agreed to a medical intervention and the child, although deemed able to give informed consent, did not, the issue would have to be referred to the Courts. He accepted that in medical intervention the essential criterion was that any action should be for the benefit of the child concerned. This did not necessarily apply to clinical trials. But where research was of no possible benefit to the child, the normal ethical requirement was to do something that was absolutely minimally invasive. He understood that the guidelines on ethical aspects of clinical trials in children which were being developed under the Clinical Trials Directive would cover such situations (QQ 13-14).

68. We asked the Minister about this. She did not see any inconsistency in the provision. The informed consent of a parent or person with parental responsibility was an essential pre-condition of any trials. But a distinction had to be drawn between a properly-informed decision by a child and one that might be no more than a “whim” on the day concerned. That was why

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33 *Seeking Consent: working with children*, published November 2001, reference 25752
the Government felt children should not have an automatic veto over participation in trials (Q 51).

69. The Minister assured us that the guidelines to be drawn up in the context of the Clinical Trials Directive would be very clear. The Government wanted to create an environment within which clinical trials would be conducted, for all the reasons that had been given, but in a very strong and robust ethical framework the details of which should become clear in the guidelines. Some decisions would probably have to be taken on a case-by-case basis (QQ 53–56).

70. Dr Dunne of the MHRA added that the Commission’s draft guidance on the ethics of conducting clinical trials with children was expected to be released for consultation by April 2006 so that it would be in place by the time that the Regulation was adopted (QQ 54).

71. The Minister hoped that the guidelines would also avoid the possibility that deference to children’s rights might undermine the randomness essential for successful trials (Q 55).

72. We are very troubled by this issue and not convinced from the evidence we have had that it has so far been given the necessary serious consideration. In the time available we have not been able to probe this further. But, as we see it, the ethical considerations which are likely to arise when conducting trials in children are not necessarily the same as those which arise in normal medical practice and we are not sure that the Clinical Trials Directive will cover them adequately. We accept that, where necessary, individual cases must be referred to the Courts. But we are not sure to what extent the existing law may be clear enough. The definition of informed consent and the distinction between consent and acquiescence must be interpreted clearly in relation to circumstances that are likely to arise during clinical trials.

73. We recommend that, in drawing up the guidelines underpinning the Clinical Trials Directive, the Government should ensure that particular attention is paid to the rights and capacity of children to give informed consent to trials. The guidelines must cover adequately and clearly the vulnerability of children, the possibility of conflict between the consent of parents and children involved in trials, the definition of informed consent and the distinction between consent and acquiescence in circumstances which are likely to arise during trials involving children, as well as the extent to which any trials concerned might benefit the child in question.

Ages of Children

74. Bearing in mind what we had been told by Professor Chantler about the differing reactions of children to medicines, depending on age and other factors (Q 23, pp1–2), we asked the Government and whether pharmaceutical companies would be required to carry out tests on different age groups.

75. Dr Dunne of the MHRA explained that a full programme of testing for each stage in the age range from newly-born to 18 year olds might not be necessary (QQ 40–42). Some products might well not be appropriate, for example, for the newly-born. Test information from one group might be extrapolated to other groups.
76. Dr Dunne recognised that the newly-born were particularly vulnerable. She confirmed that some 90% of medicines given to the newly-born had not been tested for use on them. When a product was authorised for use in the paediatric population a lower age limit for safe use was usually specified. It would be quite exceptional for a blanket statement to be made authorising use in children without having a clear lower limit. This would also be made clear in the dosing information (QQ 44–47).

77. The Minister confirmed that these aspects would be covered in the guidelines (Q 48). Dr Dunne added that the Regulation would make clear that appropriate age groups within the paediatric population should be studied. But the detail of how trials should be conducted could not be adequately covered in the Regulation. It would have to be covered by the guidelines which would be constantly revised to take account of technical advances (Q 50).

78. **We recommend that very careful consideration should also be given in the guidelines to the possible differences in the effects of medicines on children of different ages, and especially the vulnerability of the newly-born, as well other ways in which the reaction of minors may be markedly different from those of adults.**

**Other Aspects of the Guidelines**

79. It was clear to us from these exchanges that very careful attention will need to be paid in all other respects to getting the guidelines right, making sure they are properly understood by all the professionals concerned and kept up-to-date. We therefore asked the Minister for her officials to give us appropriate on-the-record briefing on progress in developing those guidelines after the Directive has been agreed in due course. She agreed to do so.

80. In this context we were interested to see a copy of the Royal College of Paediatrics and Child Health guidelines for the ethical conduct of medical research involving children. That document shows that considerable serious thought has already been given by the medical profession in this country to the ethical issues that have exercised us in this Inquiry. In our view, it will be most important to ensure that similarly serious and detailed professional consideration is given to the elaboration and updating of the guidelines related to the Regulation in a form that will be understood and implemented throughout the European Union.

81. The draft Regulation itself offers no more than a framework for decisions based on the Clinical Trials Directive. In an understandable desire to secure that framework, we are not convinced that the Government has given a sufficient lead during the UK Presidency in focusing attention at Council level on critical ethical aspects in preparation for drawing up the all-important guidelines by which the Clinical Trials Directive will be interpreted.

82. **We conclude that, in many other respects, the ethical validity and effectiveness of the Regulation will depend as critically on the guidelines to be developed as on the text of the Directive itself.**

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34 pp 57-60

35 Guidelines for the ethical conduct of medical research involving children as modified and updated in 1999 by the Ethics Advisory Committee of the Royal College of Paediatrics and Child Health (reprinted as Appendix 3)
detailed discussion of such aspects is appropriate for legal, medical and pharmaceutical experts, who must be adequately consulted, we recommend that the underlying issues of public policy should be given wider attention and political oversight. We therefore welcome the Minister’s agreement that the relevant officials should give us on-the-record briefing on the progress made in developing those guidelines at an appropriate time after the Directive has been agreed by the Council.

83. We recommend that once the guidelines are drawn up the Government should ensure that they are fully understood by the medical and pharmaceutical professions and explained to the general public.

84. We further recommend that the Government should ensure that the guidelines are kept fully up-to-date in line with changes in medical and scientific knowledge and practice.
CHAPTER 5: INFORMATION

Access to the Database

85. The Royal College of Physicians of Edinburgh drew our attention to the apparent limits on access to the Paediatric Clinical Trials Database in the proposed Regulation and supported the inclusion of access to information which was neither commercially nor scientifically confidential (pp 29–31). That view was supported by the Royal College of Paediatrics and Child Health (pp 28–29). They urged the MHRA and the Government to press for as much information as possible to be available for public access to prevent any unnecessary duplication of clinical trials in children. 36

86. In the MHRA survey 37 the ABPI supported the proposal to make parts of the Clinical Trials Database publicly available and stated that the UK pharmaceutical industry was already committed to registering new trials on a publicly available website. The ABPI hoped that the Paediatric Committee or regulatory authority would search the database for previous trials when considering Paediatric Investigation Plans. The Royal Pharmaceutical Society also agreed that parts of the database should be accessible.

87. Professor Chantler took the view that commercial confidentiality should not prevent public availability of information from clinical trials. (Q 28) He spoke of “real anxiety” about problems that had arisen with medicines that were not in the public domain. Commercial confidentiality could be protected by making certain information in the database anonymous for a limited period.

88. The Minister told us that access to some parts of the database might need to be restricted or delayed for reasons of commercial confidentiality (Q 62). But she thought it was for the Commission to draw up guidelines on which elements of the database should be made public.

89. In subsequent correspondence we noted that, although the Commission had apparently made some concessions over access to the database, it appeared to be less than the firm and unequivocal commitment to full access which we wanted to see. We asked the Government to press for clarification of the Commission’s position and to support the case for full access to the database vigorously at Council and in subsequent discussions on the guidelines. 38

90. The Minister replied 39 that the Council agreed that, at the very least, the results of all paediatric trials, whether terminated prematurely or not, should be publicly accessible. She said that the Government believed that to be a very positive development. We replied that we looked to the UK Presidency to ensure that clear and firm agreement was secured on that at the Council meeting 40.

36 It was also supported in the MHRA consultation by the Royal College of General Practitioners and by “Which?” (formerly known as the Consumers Association).
37 pp 48-56
38 pp 57-59
39 pp 59-60
40 p 60
91. We welcome the greater access to the database which has apparently been agreed at Council and the Government’s assurance that they will support the view that, at the very least, the results of all paediatric trials, whether terminated prematurely or not, should be publicly accessible.

92. **We recommend that the Clinical Trials Database should contain full details of all paediatric trials, whether terminated prematurely or not. The database should be publicly available as a vital safeguard not only for those who might be involved in clinical trials but also for the medical profession and the paediatric population of Europe as a whole. This principle must be assured in the Regulation itself and in any guidelines developed from it.**

*Product Information*

93. Concern was expressed in our own evidence, as well as in the MHRA consultation, about the proposals for identification of medicines licensed for use in children. Several respondents agreed with the Government that the Commission’s proposal to use the identifying letter “P” was unsuitable in the UK where that identifying letter was already used to denote medicines available for over-the-counter sale as distinct from on prescription.

94. The ABPI (pp 25–26) stressed that any labelling must be clear and unambiguous to enable medicines to be given to children safely. They and a paediatric research consultant suggested that a pictogram of a child would be better than the proposed letter “P”.

95. We asked Professor Chantler about the need for more clear and specific information, especially on suitability for use in differing ages of children. He agreed that the symbol “P” was unsuitable and saw clear risks, given the different likely reactions of children of different ages, in using a potentially misleading symbol denoting suitability for children. The label should direct users to the relevant product information (QQ 29–33).

96. We put this to the Minister (Q 74). She replied that following objections from several Member States, as well as the UK, the Council Working Group had accepted that all medicines authorised for paediatric use should bear an appropriate European symbol (other than the letter “P”). That symbol would be selected by the Paediatric Committee within one year of the Regulation coming into force. The meaning of the symbol would be explained on the package label, but it would not indicate suitability for a particular age group. The Government saw no danger of over-simplification.

97. We are not satisfied that adequate consideration has been given to this problem. We accept that a decision is not needed until after the Directive enters into force. But, despite the Minister’s assurance, we foresee a significant risk of dangerous confusion arising from over-simplification. Labelling a product as “suitable for use in children” appears to overlook the very real danger highlighted by Professor Chantler that a product suitable for use in mature children may be highly dangerous for use in younger ones.

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41 ABPI (pp 25-26), RCN (p 28), RCPCH (pp 28-29), as well as the Pharmaceutical Society of Northern Ireland, the Guild of Healthcare Pharmacists in the MHRA consultation (pp 48-56)

42 pp 39-48

43 Dr Jane Lamprill in the MHRA consultation (p 49)

44 pp 56-57
98. We recommend that the Government should give further and serious consideration to the proposal that the products should be labelled in a way which indicates their suitability for use in children.

99. It is abundantly clear from our evidence that children are not just young adults: their reaction to drugs varies considerably in relation to age and other factors and the newly-born are particularly vulnerable. We therefore recommend that any labelling scheme that is devised must take full account of this and make plain the risks of using products without consulting the relevant product information, especially for products which are available without prescription. Product information should also be summarised in clear, non-scientific language that leaves no doubt whatsoever about the risks of misuse and the need to follow carefully the dosage information.
CHAPTER 6: MECHANISM FOR IMPLEMENTING THE REGULATION

European Medicines Agency (EMEA)

100. As explained in Chapter 2, the Regulation would be operated through the European Medicines Agency (EMEA) which is the European Union’s centralised body for authorising medicinal products.

101. None of our respondents questioned the suitability of the EMEA for the role proposed. But, in response to the MHRA consultation\(^45\), the Royal College of General Practitioners questioned whether the EMEA was best-placed to provide the proposed scientific advice.\(^46\)

102. We asked the Minister whether the EMEA was the right body to oversee and co-ordinate the working of the Regulation and, if so, whether it would have enough capacity to do so properly. She replied (QQ 57–58) that the EMEA had a proven track record of over ten years in overseeing and coordinating pharmaceutical legislation, operating in close collaboration with all the competent authorities in the Member States and with their networks and experts.

103. She added that the role that the Member States would play was clearly set out in the Regulation, based on long experience, and the Government did not foresee any problem with it. The EMEA was funded by a mixture of state funding and fees and the EMEA budget took account of the extra work which the Regulation was expected to create.

104. We conclude that the European Medicines Agency (EMEA) is the appropriate body to oversee and coordinate the tasks envisaged by the proposed Directive. We welcome the Minister’s assurances that the EMEA should be sufficiently resourced to carry out this task and that experience suggests it will work smoothly and effectively with the health services and agencies of Member States in doing so. But we recommend that these aspects should be kept under close review by the Government once the Directive enters into force.

Paediatric Committee

105. As we see it, the Paediatric Committee will be the key to the success or failure of the ethical aspects of this Regulation. The Royal College of Physicians of Edinburgh (pp 29–31) stressed to us the need for Committee members to have the right mix of experience, including paediatricians with current hands-on experience of clinical trials. It would also be important to draw on European speciality organisations such as the European Respiratory Society and the European Academy of Allergy and Clinical Immunology, which had strong and well-established paediatric assemblies.

106. The ABPI (pp 25–26) argued that members of the Committee should include somebody with experience in the development of paediatric medicine, including work within the pharmaceutical industry.

\(^{45}\) pp 48-56
\(^{46}\) We deal with that point separately under the heading of Research (see paras 112-120)
107. In the MHRA consultation47 “Which?” welcomed the proposal to include patients’ representatives on the Committee. The Royal Pharmaceutical Society argued that experience in pharmacy must be included and that the Neonatal and Paediatric Pharmacies Group should be nominated as one of the paediatric learned societies to be consulted.

108. Professor Chantler suggested that the Committee should include someone with a background in clinical ethics (Q 17).

109. The Minister told us she was satisfied that the Committee, as proposed, would have the broadest range of experience needed to carry out its work effectively. It would comprise at least 31 members, five of whom would also be members of the EMEA’s Committee on Human Medicines, and could draw on other expert advice as needed. The scientific expertise available to the Committee should include pharmaceutical development, paediatric medicine, general medical practice, paediatric pharmacy and paediatric pharmacology.

110. We conclude from the evidence we have been given that the overall composition of the Paediatric Committee is about right. We fear that any increase in the size of its permanent membership might run the risk of making it unwieldy.

111. But, because the effective functioning of the Committee is crucial to the success of this Directive, we recommend that the Government should keep the composition of the Committee under review and ensure that it draws, where necessary, on relevant available ethical and practical expertise from Member States which may not be directly available through the Committee’s own membership.

Research

112. Under the Directive, the EMEA will also be responsible for developing a European Paediatric Clinical Trials Network. As noted in paragraph 94 above, the Royal College of General Practitioners questioned48 whether the EMEA would be best-placed to provide the proposed free scientific advice, which would be a significant undertaking.

113. The ABPI (pp 25–26) told us they supported the development of the proposed European Paediatric Clinical Trials Network, but doubted that the EMEA was the right organisation to coordinate that network. It suggested the work might be better left to one of the European paediatric societies and it was also concerned that no incentives were proposed for research taking place before the Regulation came into force.

114. The Royal College of Physicians of Edinburgh (pp 29–31) also stressed that setting up a truly functional network throughout Europe would require significant investment on the lines of that recently agreed in the UK which could provide a useful model to other Member States. They were also concerned about the apparent lack of funding of studies of off-patent medicines, without which adequate trials of such medicines were unlikely to be made.

47 pp 48-56
48 ibid
115. The Minister told us\textsuperscript{49} that the Government agreed that the EMEA should be the focal point to facilitate communication and collaboration between existing research networks (such as the UK Clinical Research Collaboration Network). It would also act as an information point for pharmaceutical companies looking to carry out multinational trials. The proposed network should not affect the individual integrity of existing national networks. It should help to disseminate good practice and communicate information on trials. The EMEA would receive the necessary funding to carry out this co-ordinating role.

116. Although we accept the Minister’s assurance that the EMEA would be the appropriate organisation to coordinate clinical research networks and that it would be adequately funded to carry out this task, we note expressions of concern we have had about this from some respondents. It is vitally important that this network should function effectively. We recommend that the Government give further consideration to ways in which the network might be improved and the extent to which UK practice might provide a useful model.

117. The Royal College of Paediatrics and Child Health (pp 28–29) told us that they were disappointed that the proposal for a European study (presumably the MICE programme mentioned in Chapter 2) had been excluded from the proposed Regulation and urged the Government to ensure that the Commission would set up such a programme through the seventh Framework.

118. The ABPI agreed (pp 25–26), as did the Royal College of Physicians of Edinburgh (see MHRA consultation)\textsuperscript{50}. The BMA (pp 27–28) also welcomed the MICE proposal\textsuperscript{51}.

119. We asked the Government about this. The Minister replied\textsuperscript{52} that, although the MICE programme which had been mentioned in earlier draft proposals was not included in the Commission’s formal Proposal, research into paediatric use of patent medicines could be funded through the Community’s research framework programmes. The Government believed that such funding was indeed needed, but was confident that the Community research framework programmes could meet the need.

120. \textbf{We are unable to judge from the limited evidence and time available to us whether the proposal for funding research into paediatric use of off-patent medicines through the Community’s research framework programmes will be adequate. Nor are we able to assess the need for a separate Community-funded research programme on the lines of the Medicines Investigation for the Children of Europe (MICE) proposal. But we recommend that the Government should ensure that both aspects are adequately addressed, in consultation with interested parties, when the Commission review the working of the Regulation.}

\textsuperscript{49} pp 56-57
\textsuperscript{50} pp 48-56
\textsuperscript{51} We have also seen a Press Release dated 29 September 2004 from the European Generic Medicines Agency regretting the “absence of an EU Paediatric Research Fund”
\textsuperscript{52} pp 56-57
CHAPTER 7: REWARDS AND INCENTIVES

121. Paragraphs 14 and 15 of Chapter 2 of this Report describes the rewards and incentives proposed under the Directive to stimulate the research and development of medicines:\(^\text{53}\):

- six months extension of market exclusivity known as the SPC extension;
- two years of additional market exclusivity for orphan medical products; and,
- ten years of data protection for off-patent medicinal products granted by the PUMA.

122. The ABPI told us (pp 25–26) that the incentives outlined in Article 36 (relating to the six month extension) were “essential to the whole process and must be supported” as a stimulus to research for licensed medicine. They also fully supported incentives for research into off-patent medicines through the PUMA procedure which should help European companies to develop niche markets. They added (pp 26–27) that if Europe was seen to be less competitive in this respect than the USA it would be very difficult to encourage ABPI members to carry out paediatric research in Europe. The ABPI also supported a robust review of the incentives after ten years.

123. The Royal College of Physicians of Edinburgh (pp 29–31) supported the SPC extension and orphan medicinal products proposals, but questioned how much of an incentive the six month SPC might be for industry.

124. The BMA (pp 27–28) agreed that the relatively small market for paediatric drugs was a disincentive to investment which might necessitate an extension to patent cover. It believed that the Commission’s Proposals struck the right balance between targeted investment in children’s health and commercial reward.

125. The Royal College of Paediatrics and Child Health questioned the two years of extended market exclusivity proposed for orphan medical products (pp 28–29).

126. In the MHRA consultation:\(^\text{54}\):

- A paediatric research consultant\(^\text{55}\) suggested that six months SPC extension might not be enough to cover research costs (except for certain products likely to be widely used) and suggested that 9 months might be more appropriate.
- The Guild of Healthcare Pharmacists also questioned whether the six months SPC extension would be sufficient in all cases and supported the Proposal for a full review of the proposed incentives.
- The Bio Industry Association believed that the six month SPC extension would be fair. A variable extension would be a significant barrier to innovative bioscience research.

\(^{53}\) See pages 4-5
\(^{54}\) pp 48-56
\(^{55}\) p 49
• “Which?” (formerly the Consumers Association) believed that the proposed incentives were appropriate but was concerned about the potential impact on the generics market, which would need to be reviewed.

• The National Patient Safety Agency was concerned that the proposed incentives would be insufficient to encourage development of paediatric formulations from established medicines. It suggested that the MHRA and NHS should collaborate to identify existing medicines of this type and to commission work to help to develop standard strengths and formulations for these proposals.

127. The European Federation of Pharmaceutical Industries and Associations (EFPIA) (p 62) sent us a position paper outlining their support for the Proposal, including the proposed fixed-term extension for intellectual property protection. But it pointed out that in some circumstances SPC protection might not be available or might expire before the approval process was completed. Consideration should be given to ways of overcoming potential anomalies.

128. Professor Chantler told us (Q 22) that price controls in Europe were a matter of great controversy within the pharmaceutical industry, and a cause of tension between the USA and the rest of the World. He understood that the generic pharmaceutical industry was unhappy about a six month extension. Having spoken to others, his view was that six months seemed appropriate. It had been shown to be sufficient in the USA.

129. He understood that the Government had suggested a variable extension, depending on the nature of the product and its use in children, but that this had failed to attract sufficient support in other Member States.

130. In his view, the data exclusivity offered by the PUMA proposal was also very important in his view and it would amount to marketing exclusivity where a new formulation could be produced.

131. He thought that the additional two years of market exclusivity proposed for orphan drugs was fully justified given the need to develop drugs to treat rare conditions (QQ 24–27).

132. The Minister told us that, in earlier discussions, the UK had put forward an alternative proposal which linked the SPC extension to sales. The Government believed that would be fairer to products with a low volume of sales and avoid excessive products profits for “block-buster” products. But this had attracted little support from other Member States and the Government were unable to find a workable way of implementing such a mechanism in 25 Member States.

133. The Government had therefore supported the fixed six months SPC extension at the Health Council, as had most Member States. But 5 Member States had favoured a shorter SPC extension, given the strength of generics market in their countries. The UK had also pressed for a review of the economic impact of the Regulation in ten years, which had been agreed.

134. We asked whether a review of the economic impact after ten years was adequate. The Minister replied that, having failed to secure support for the
Proposal for a variable SPC extension based on sales volume, the Government had had to re-examine their position. One of the major stumbling blocks to an alternative model was the lack of real information about the possible impact on the health budgets of Member States.

135. The review had been timed for “within ten years” of the introduction of the Regulation because it would be several years before products that were eligible for the incentives would be available on the market. Until a fair number had been marketed for a reasonable time it would not be possible to make a realistic assessment of the economic impact. On average, paediatric clinical trials could take three to six years, followed by about a year to complete the regulatory process.

136. In some Member States delays of up to three years could occur between the granting of market authorisation and the completion of negotiations for pricing and reimbursement between Governments and drug companies. The economic effect of the SPC extension could not be measured until the end of the patent life of the product concerned.

137. Consequently, the effect of the Regulation could not be adequately measured until a significant number of products on the market produced a sufficient volume of sales data. Nevertheless, the original review clause requiring the Commission to publish a general report within six years of the entry into force\(^\text{59}\) of the Regulation remained. If the volume of products eligible for incentives appeared by the time of that report to be more significant than the Government currently expected, Member States could call for a full economic review earlier than at the end of the ten year period. The Government would carefully consider that possibility when the Commission reported.

138. We pressed the Government further on the likely effectiveness of the proposed incentive arrangements. We were told (QQ 64–65) that incentives and rewards had been the most controversial aspect of the proposal. The length of the proposed SPC extension had been much debated and raised complex intellectual property issues. But the Government believed that these were the right kinds of measures: they were reasonable and implementable and were likely to command Council support. The six months SPC extension was measured and proportional. It was broadly supported by industry and by experience in the USA. The PUMA proposal was an adequate incentive for medicines that were no longer in patent. Nor was the requirement for paediatric testing likely to delay adult drug trials unduly (Q 66).

139. We asked the Government about generic products manufacturers\(^\text{60}\) and the position taken by some other Member States over generic products. We were

58 pp 35-56
59 Article 49 of the Regulation
60 We noted from the Government’s Partial Regulatory Impact Assessment of September 2005 that the British Generic Manufacturers Association had not responded to the MHRA consultation, although they had apparently told the Government informally that they wanted a shorter SPC extension, while the European Generic Medicines Association had argued that an extension of 3 or 4 months should be sufficient to cover the costs of paediatric clinical trials. On the other hand, we have seen a Press Release dated 29 September 2004 from the European Generic Medicines Association which says “although it may be acceptable in this case to grant an additional period of market exclusivity to compensate for additional costs, protection should be reasonable—reflecting the costs of the trials—and should not be unnecessarily expensive for health care budgets”.

We were
told (QQ 67–68) that Member States had differing views about the likely effect on generics producers. A balance had to be struck between downward pressure on medicines expenditure and the need to provide proper incentives and compensation for innovative producers who carried out tests. The Council had accepted by a very significant majority the Commission’s view that a six month SPC extension was “the right way to go”. The Government took the view that this was the most realistic and reasonable way forward through the European decision-making process.

140. On orphan medicinal products, the Government told us that only two Member States took issue with the additional exclusivity proposed (Q 67). Again this was because of the likely effect on generics producers. But the prevailing view was that six month extension would not be enough. Two years extension to market exclusivity was “the simplest and most workable way of giving them their incentives” (Q 70).

Assessing Benefits and Costs

141. In September 2005 the Government produced an updated Partial Regulatory Impact Assessment (PRIA)\(^{61}\) which attempted to analyse the probable benefits and costs arising from the Regulation.

Off-Label Prescribing

142. The PRIA’s assessment of benefits starts with the assumption that the Proposal would lead to less off-label prescribing. It argues that drugs that have not been tested as suitable for children run the risk of either causing adverse reactions or being ineffective.

143. The PRIA’s Risk Assessment quotes British Pharmacological Society estimates that 25–30% of all European children receive an off-label prescription every year. But it notes that these figures only relate to hospital in-patients and out-patients, an estimated 3.4 million of whom receive off-label prescriptions every year.

144. A table (unsourced) claims that in England an estimated 20,000 paediatric out-patients, and 11,000 paediatric in-patients, suffer adverse drug reactions each year. It is not clear whether this means total adverse reactions or only reactions to off-label drugs. But the PRIA cautions that clinicians are “generally” less likely to report adverse reactions to off-label prescriptions.

145. These figures appear to relate to patients of all ages. No breakdown is given for the proportion of adverse reactions in children. But the PRIA does point out that “children” (defined as those under 18) “can not be considered a single population”. No assessment is made of how serious (and thus costly) any of the adverse reactions recorded might be.

146. The PRIA mentions “evidence of a significant amount of off-label prescribing in a Community setting” (presumably meaning by GPs and Community health clinics). But no figures are given to indicate what is meant by “a significant amount” and the PRIA reports inability to find any assessment of associated adverse reactions.

\(^{61}\) pp 39-48
Cost/Benefit Assumptions

147. The PRIA suggests that it would be “somewhat optimistic” to assume that all the branded products currently regarded as suitable for children will be tested and labelled under the Regulation. Nor does it expect adverse reactions in children to drop to quite the same level as found with adults. (It does not specify that level or say why the child reaction would be different).

148. It also suggests that the Proposals should lead to more effective use of medicines because “currently it is possible that there is significant under-dosing in some situations leading to lack of efficacy, but there is no systematic evidence that allows us to quantify this”.

149. With these caveats, the PRIA sets out a series of possible cost/benefit assumptions. These take estimates of 50%, 25% and 10% effectiveness applied to Department of Transport figures for the average costs of treating mild and serious road accident victims as “a rough proxy” for the value of reductions in adverse reactions (presumably because no other relevant figures are available).

150. For England, the PRIA claims this methodology would yield estimated annual monetary benefits of £245 million (50% effectiveness) £122 million (25%) and £49 million (10%). Corresponding EU-wide results are estimated to be £2 billion, £1 billion and £0.4 billion respectively.

151. Quoting the Rand Europe study, on which the Commission’s own Impact Assessment was based, the PRIA estimates annual savings for hospitals in England of between £3–12 million (on the same basis of 50% effectiveness), £2–6 million (25% effectiveness) and £1–2 million (10% effectiveness). Corresponding EU-wide hospital savings are estimated to be £27–96 million, £13–48 million and £6–19 million respectively. No explanation is given for the wide variation between these figures. Nor is the wide difference between hospital savings and total cost benefits explained.

Benefits for Industry

152. The PRIA quotes the Rand study estimate that the proposed six-month SPC extension would enable the “innovative” (i.e.: research-based as distinct from generic) pharmaceutical industry to recover the costs of testing and make a profit of between 0.8 and 9.1 million euros per product, or between 63 and 205 million euros overall. The wide variation of the latter estimate is not explained.

153. In an attempt to demonstrate the impact on business, the PRIA states that the pharmaceutical industry employs some 73,000 people in the UK and generates another 250,000 jobs in related industries. The ABPI is quoted as estimating that the UK pharmaceutical industry invested £3.2 billion in research and development in 2002–3. But the PRIA does not relate these figures to the cost recovery and profit estimates quoted above.

Costs

EMEA

154. The PRIA again quotes Rand study estimates that processing applications under the Regulation would cost the EMEA an extra £126 million initially and between £12 million and £36 million a year in the longer run (as
demand for retrospective testing of drugs already on the market is expected to decrease).

Innovative Pharmaceutical Industry

155. It quotes Rand study estimates that initially the Regulation would cost the innovative pharmaceutical industry between £97 million and £676 million initially and between £28 million and £434 million a year in the longer run. But the PRIA comments that these figures probably underestimate testing costs. It quotes the ABPI as claiming that each Paediatric Investigation Plan would cost the UK industry between 20 and 30 million euros.62

Generics Sector

156. According to the PRIA, the six-month SPC extension proposed could cost “the generics sector” (whether in the UK or the whole EU is not stated) between £23 million and £410 million a year in lost sales.63 It adds, “we would not expect the SPC extension to result in fewer generic medicines”.

Costs to the National Drugs Bill/NHS

157. The PRIA estimates that the six-month extension would cost the “drugs bill” (undefined) for England between £30 million and £120 million a year. (The Minister subsequently quoted64 these figures as a cost to the NHS.) Non-NHS drugs purchases are not mentioned. No figures are given for Scotland and Wales (presumably because health services are the responsibility of the Devolved Administrations).

158. The PRIA comments that it is not possible to know which products might qualify for the SPC extension, nor what financial effect the delay in introducing generic alternatives might have.

159. We asked the Government about the reliability of some of these estimates and queried the utility of some of the very wide ranges of estimates quoted (Q 72). We were told that the Government had drawn on a variety of sources in compiling the figures. But it was impossible to tell how many medicines might “actually come through this particular gateway and how quickly”. Nor could the sales levels and the cost for health services be predicted (“we do not actually know anything about that at the moment”). The ranges were simply indicative and inevitably had to be quite wide.

160. But the UK, strongly supported by most of the Council, had demanded a robust review of the economic and beneficial impacts of the Regulation. The timing for that review had not been finally fixed, but it would be somewhere between six and ten years after the start of operations under the Regulation (Q 73).

161. We wrote to the Minister65 registering our concern over the uncertainties surrounding the initiative arrangements and our disappointment over the inadequacy of the cost and benefit estimates in the PRIA. We hoped that the

62 The ABPI also queried some of the Government’s estimates (pp 26–27)
63 As noted in footnote 49, the relevant UK trade association did not respond to the MHRA consultation, but has argued informally that the six-month extension is not justified.
64 pp 35–38
65 pp 57–59
Department would try to refine more reliable figures. But we accepted, to some extent, the difficulties in doing so and acknowledged that it might well be some years before a clear picture would emerge of how well the arrangements were working.

162. For that reason, we stressed that we attached great importance to the Government’s efforts in pressing for a full economic review of the Proposal as soon as feasible. We expected the Government, in its Presidency capacity, to focus attention on this aspect in Council and secure a firm and unambiguous commitment from the Commission that such a review should form part of the general report required within six years of implementation. Failing that, the Commission should be required to explain to the satisfaction of the Council why it would be premature to do so at that stage and to ensure that a review was undertaken as soon as possible after that.

163. The Minister replied reiterating that the UK had pressed hard in negotiations for a robust review of the incentives. A full economic analysis would be undertaken at six years, provided that sufficient data was available. If not, it would have to be undertaken within ten years of the Regulation coming into force. We welcomed this assurance.

164. We recognise the difficulties involved in trying to produce accurate estimates in these circumstances. But the ranges of figures given in the PRIA are so wide as to be meaningless, some of the assumptions are not fully explained and the validity of others is open to question.

165. We were surprised that the PRIA included data from the Department of Transport, rather than using hospital data from the Department of Health, in attempting to assess the costs and benefits to the NHS.

166. We recognise that the package of incentives and rewards proposed in the Regulation are a political compromise, based on the acknowledged need to provide incentives and the apparent success of the US model. But we conclude that they are essentially a leap of faith: it is impossible to judge from the information we have been given whether these arrangements are likely to provide the necessary incentives to industry, whether they are likely to be equitable and proportionate, or whether they may give rise to excessive profits, penalise the health services of Member States or create unacceptable disadvantages for the manufacturers of generic products.

167. We accept that a political compromise is necessary for the time being to launch the Regulation in the hope that it will bring the desired benefits for the children of Europe at a reasonable cost. But we recommend that the Government should continue to press the Commission to ensure that a full economic review of these proposals is made as soon as possible.

168. If the Commission are unable to provide such a review within six years of implementation, as required by Article 49 of the Regulation, we recommend that they should be required to explain to the satisfaction of the Council why it would be premature to do so at that stage and to ensure that it is done as soon as possible after that.

66 pp 59-60
67 p 60
169. **We also recommend that our successors should subject that review to very rigorous examination when it is submitted for Parliamentary scrutiny.**

170. **In the meantime, we recommend that the Government should make every effort to improve on the adequacy of the estimates of costs and benefits produced in the Partial Regulatory Impact Assessment as soon as it is practicable to do so and to submit the results to Parliamentary scrutiny.**
CHAPTER 8: LEGAL BASE

171. As stated in paragraph 19, the Commission proposed that the legal base for the Regulation should be Article 95 of the E.C Treaty. This allows harmonisation of national laws affecting the establishment and functioning of the internal market. The Government’s Explanatory Memorandum (EM)\(^{68}\) took the view that Article 95 was not appropriate for measures which established a centralised EC procedural body. Other Articles, in particular Article 308 which is subject to unanimous voting, should be used.

172. The EM also pointed out that the UK position on the use of Article 95 was being tested in two cases in the European Court of Justice. It added that the Department of Health would follow the procedure agreed with UK Law Officers where the UK supported proposals for policy reasons even though it was considered that the wrong legal base had been used.

173. We asked for clarification of this statement and drew attention to our concern about other instances where the Government had supported proposals which it regarded as otherwise worthwhile, despite having reservations about the proposed legal base\(^{69}\).

174. The Minister replied\(^{70}\) that, in the Government’s view, setting up bodies or procedures at Community level did not amount to the harmonisation of national law, as provided for by Article 95, because it was outside the scope of national law. The Government had raised these objections with the Commission.

175. The Minister also confirmed that the UK had mounted a legal challenge at the European Court of Justice to two other Regulations based on Article 95\(^{71}\). Until these challenges were resolved, the UK would continue to register concern about the inappropriate use of Article 95 by entering a Minute Statement recording disagreement with the legal base. That would not prejudice the UK’s approach to future challenges under this Article. The UK Presidency would also work with partners to help ensure that measures were adopted using legitimate and appropriate legal bases.

176. In subsequent correspondence\(^{72}\), the Minister told us that Denmark and Portugal had registered similar reservations on the legal base. Other Member States might follow suit, but it was highly unlikely but enough would do so to affect the outcome of any vote on the proposed Directive.

177. We replied\(^{73}\) pointing out that the centralised body concerned in the Regulation would be the Paediatric Committee which would function under the aegis of the European Medicines Agency (EMEA). But we noted that the Government did not appear to have challenged the use of Article 95 as a

\(^{68}\) pp 12-14  
\(^{69}\) pp 31-32  
\(^{70}\) pp 31-32  
\(^{72}\) pp 35-38  
\(^{73}\) pp 57-59
legal base for the EMEA itself. We found that surprising and seemingly inconsistent with the challenges mentioned in earlier correspondence.

178. In response the Minister\textsuperscript{74} reiterated that the Government intended to record disagreement over the appropriateness of Article 95 in a Minute Statement at the Council. But the Government believed that it would not be desirable to oppose every measure which used Article 95 inappropriately where they supported the underlying policy while awaiting the outcome of two UK challenges at the European Court of Justice.

179. Subsequently the Minister confirmed\textsuperscript{75} that, when the Government voted in favour of setting up the European Medicines Agency in 2003, it had submitted a Minute Statement registering objection to the use of Article 95 as the proposed legal base.

180. On 6 December 2005, the ECJ found against the UK in the case of United Kingdom v European Parliament and Council\textsuperscript{76} and held that Article 95 was an appropriate legal base for a Regulation which laid down a Community procedure for authorising smoke flavourings. This judgment suggests that Article 95 can be used as the legal base for proposals which establish centralised procedures in certain circumstances. The question of whether Article 95 is appropriate for the creation of centralised body remains before the Court in a case concerning the creation of the European Network and Information Security Agency. A judgment is expected shortly.

181. We are concerned about this and other instances where, in the Government’s view, the Commission has proposed an inappropriate legal base, (including one where the Government’s approach does not seem to be consistent\textsuperscript{77}). We support the Government in taking a robust line where the Commission puts forward a proposal with a legal base which is controversial. The recent ruling in the smoke flavourings case shows that Article 95 may be appropriate in relation to certain aspects of the current proposal but the issue of whether Article 95 can be used to establish a centralised body remains before the Court.\textsuperscript{78}

182. In principle, we continue to believe that the Government should take a robust and consistent line in opposing proposals by the Commission which are, in the Government’s view, brought forward on an inappropriate legal base. In this particular instance, in light of the overriding importance of the proposal and the need to make rapid progress in implementing it, we conclude that the Government is justified in agreeing to the present proposal with a Minute Statement recording its objection to the legal base.

\textsuperscript{74} pp 59-60
\textsuperscript{75} pp 60-61
\textsuperscript{76} Case 66/04
\textsuperscript{77} In the case of the Proposal for a Regulation to establish a European Institute for Gender Equality (Commission reference 7244/05 COM (2005) 328)) the Government felt on balance that the Articles proposed (Articles 13 (2) and 141 (3) EC) were a sufficient legal base. But in the case of the Proposal for creation of European Monitoring Centre for Drugs and Drug Addiction (Commission reference 12143/05 COM (2005) 399 final), the Government took the view that the Article concerned (Article 152 (EC) was not appropriate.
\textsuperscript{78} Case 217/04
CHAPTER 9: PARLIAMENTARY SCRUTINY

183. As noted earlier, the Government had been pressing us for some time\(^{79}\) to clear the Proposal from Parliamentary scrutiny in the hope that political agreement might be reached on it at the Health Council on 9 December 2005.

184. It is most unusual to lift the scrutiny reserve before publishing a Report on an Inquiry and we would normally be very reluctant to do so. In this case, we carefully considered the Minister’s request in the light of all the evidence we had received. We took particular note of the assurances the Minister had given us, especially about the protection of the health, welfare and rights of any children involved in paediatric testing.

185. We also took account of the overwhelming weight of professional opinion we had seen and heard which broadly supported the Proposal and was anxious to see it implemented as soon as possible. We also considered the indications of broad support from industry representatives, both in response to our own consultations and those of the MHRA. We also noted that the European Parliament had endorsed the Proposal\(^ {80}\) on First Reading in September 2005.

186. We told the Minister\(^ {81}\) that ideally we would have preferred to have spent more time considering the Proposal in greater depth. But in view of her assurances, the evidence we had been given and the widely-felt need to move forward in the interests of children, we said we would be willing exceptionally to grant her request to lift scrutiny so long as she was prepared to address the following principal outstanding concerns:

- The Government should press for clarification of the Commission’s position on the Clinical Trials Database and support the case for full access to the Database vigorously at the Council meeting and in subsequent discussion of the guidelines.

- Because so many important aspects of the safe and ethically-acceptable implementation of the Regulation would largely be determined by guidelines which had yet to be worked out, appropriate Departmental officials should give us on-the-record briefing in due course on the progress made in developing those guidelines.

- Because of the uncertainties surrounding the incentive arrangements, the impossibility of determining at this stage how they would work and what effect they might have, and the difficulty in providing meaningful estimates of the likely costs and benefits, the Government should strive to secure a firm and unambiguous commitment from the Commission for a full economic review of the Proposal.

- If the Commission was unable to include such a review in the general report required within 6 years of implementation, they should explain clearly to the satisfaction of the Council why it would be premature to do so at that stage and ensure that the review was undertaken as soon as possible after that.

\(^{79}\) Notably since the Minister’s letter dated 24 September 2005 to Lord Grenfell (pp 35-38)

\(^{80}\) Reported in Commission document 11956/05 CODEC 705 ECO 94 SAN 134

\(^{81}\) pp 57-59
187. We were also anxious to ensure that the Commission’s six year review would contain a full evaluation of all other aspects of the working of the Regulation which we would expect to be subjected to rigorous Parliamentary scrutiny.

188. We added that the Minister would be expected to report on the outcome of the December Council meeting and to set out in that report the remaining steps leading to implementation if the expected political agreement was secured.

189. We also made clear that, even if the scrutiny reserve was lifted as proposed, we could not guarantee that on such an important issue, with potentially far-reaching consequences for the welfare of children and with so many uncertainties inherent in the nature of the Proposal, a debate in the House might not be called for on publication of the Report.

190. The Minister replied accepting these conditions and pointing out that a full economic analysis would be undertaken within ten years of the Regulation coming into force, if not before. She also reiterated the Council’s view that, at the very least, the results of all paediatric clinical trials, whether terminated prematurely or not, should be publicly accessible. We acknowledged this acceptance and confirmed that scrutiny clearance had been lifted with effect from 25 November 2005 on that understanding.

191. The Government subsequently reported that political agreement had been reached at the Council on 9 December 2005.

192. We regard this as a satisfactory outcome. We will continue to follow developments closely. In the meantime, we make this Report to the House for information.

82 pp 59-60
83 p 60
84 pp 61-62
CHAPTER 10: CONCLUSIONS AND RECOMMENDATIONS

Chapter 3 – The Need for the Regulation

193. We conclude, in principle, from the evidence we have had that there is an overwhelming and urgent need to take effective action at European level to govern clinical trials in children and the authorisation of medicinal products for paediatric use with the minimum of delay.

Chapter 4 – Ethical Considerations

194. We conclude that the Clinical Trials Directive is an appropriate basis for this Regulation.

195. We recommend that, in drawing up the guidelines underpinning the Clinical Trials Directive, the Government should ensure that particular attention is paid to the rights and capacity of children to give informed consent to trials. The guidelines must cover adequately and clearly the vulnerability of children, the possibility of conflict between the consent of parents and children involved in trials, the definition of informed consent and the distinction between consent and acquiescence in circumstances which are likely to arise during trials involving children, as well as the extent to which any trials concerned might benefit the child in question.

196. We conclude that, in many other respects, the ethical validity and effectiveness of the Regulation will depend as critically on the guidelines to be developed as on the text of the Directive itself. While detailed discussion of such aspects is appropriate for legal, medical and pharmaceutical experts, who must be adequately consulted, we recommend that the underlying issues of public policy should be given wider attention and political oversight. We therefore welcome the Minister’s agreement that the relevant officials should give us on-the-record briefing on the progress made in developing those guidelines at an appropriate time after the Directive has been agreed by the Council.

197. We recommend that once the guidelines are drawn up the Government should ensure that they are fully understood by the medical and pharmaceutical professions and explained to the general public.

198. We further recommend that the Government should ensure that the guidelines are kept fully up-to-date in line with changes in medical and scientific knowledge and practice.

Chapter 5 – Information

199. We recommend that the Clinical Trials Database should contain full details of all paediatric trials, whether terminated prematurely or not. The database should be publicly available as a vital safeguard not only for those who might be involved in clinical trials but also for the medical profession and the paediatric population of Europe as a whole. This principle must be assured in the Regulation itself and in any guidelines developed from it.

200. We recommend that the Government should give further and serious consideration to the proposal that the products should be labelled in a way which indicates their suitability for use in children.
201. It is abundantly clear from our evidence that children are not just young adults: their reaction to drugs varies considerably in relation to age and other factors and the newly-born are particularly vulnerable. We therefore recommend that any labelling scheme that is devised must take full account of this and make plain the risks of using products without consulting the relevant product information, especially for products which are available without prescription. Product information should also be summarised in clear, non-scientific language that leaves no doubt whatsoever about the risks of misuse and the need to follow carefully the dosage information.

Chapter 6 – Mechanism for Implementing the Regulation

202. We conclude that the European Medicines Agency (EMEA) is the appropriate body to oversee and coordinate the tasks envisaged by the proposed Directive. We welcome the Minister’s assurances that the EMEA should be sufficiently resourced to carry out this task and that experience suggests it will work smoothly and effectively with the health services and agencies of Member States in doing so. But we recommend that these aspects should be kept under close review by the Government once the Directive enters into force.

203. We conclude from the evidence we have been given that the overall composition of the Paediatric Committee is about right. We fear that any increase in the size of its permanent membership might run the risk of making it unwieldy.

204. But, because the effective functioning of the Committee is crucial to the success of this Directive, we recommend that the Government should keep the composition of the Committee under review and ensure that it draws, where necessary, on relevant available ethical and practical expertise from Member States which may not be directly available through the Committee’s own membership.

205. We are unable to judge from the limited evidence and time available to us whether the proposal for funding research into paediatric use of off-patent medicines through the Community’s research framework programmes will be adequate. Nor are we able to assess the need for a separate Community-funded research programme on the lines of the Medicines Investigation for the Children of Europe (MICE) proposal. But we recommend that the Government should ensure that both aspects are adequately addressed, in consultation with interested parties, when the Commission review the working of the Regulation.

Chapter 7 – Rewards and Incentives

206. We recognise that the package of incentives and rewards proposed in the Regulation are a political compromise, based on the acknowledged need to provide incentives and the apparent success of the US model. But we conclude that they are essentially a leap of faith: it is impossible to judge from the information we have been given whether these arrangements are likely to provide the necessary incentives to industry, whether they are likely to be equitable and proportionate, or whether they may give rise to excessive profits, penalise the health services of Member States or create unacceptable disadvantages for the manufacturers of generic products.
207. We accept that a political compromise is necessary for the time being to launch the Regulation in the hope that it will bring the desired benefits for the children of Europe at a reasonable cost. But we recommend that the Government should continue to press the Commission to ensure that a full economic review of these proposals is made as soon as possible.

208. If the Commission are unable to provide such a review within six years of implementation, as required by Article 49 of the Regulation, we recommend that they should be required to explain to the satisfaction of the Council why it would be premature to do so at that stage and to ensure that it is done as soon as possible after that.

209. We also recommend that our successors should subject that review to very rigorous examination when it is submitted for Parliamentary scrutiny.

210. In the meantime, we recommend that the Government should make every effort to improve on the adequacy of the estimates of costs and benefits produced in the Partial Regulatory Impact Assessment as soon as it is practicable to do so and to submit the results to Parliamentary scrutiny.

Chapter 8 – Legal Base

211. In principle, we continue to believe that the Government should take a robust and consistent line in opposing proposals by the Commission which are, in the Government’s view, brought forward on an inappropriate legal base. In this particular instance, in light of the overriding importance of the proposal and the need to make rapid progress in implementing it, we conclude that the Government is justified in agreeing to the present proposal with a Minute Statement recording its objection to the legal base.
APPENDIX 1: SUB-COMMITTEE G (SOCIAL AND CONSUMER AFFAIRS)

The Members of the Sub-Committee which conducted this Inquiry were:

Lord Colwyn
Earl of Dundee
Baroness Gale
Baroness Greengross
Lord Harrison
Baroness Howarth of Breckland
Baroness Massey of Darwen
Lord Moser
Baroness Neuberger
Baroness Thomas of Walliswood (Chairman)
Lord Trefgarne

Declarations of Interest

Lord Colwyn
Practising Dental Surgeon  
President, All Party Group, Complementary and Integrated Healthcare  
President, National Medicines Society  
Chair, Campbell Montague International Ltd  
Chairman, Banbury Local Radio

Earl of Dundee
No relevant interests

Baroness Gale
Commissioner for Wales, Women’s National Commission

Baroness Greengross
Vice Chair, Britain in Europe  
President, Pensions Policy Institute  
Chief Executive, International Longevity Centre United Kingdom  
Chair, Experience Corps  
Board Member, HelpAge International

Lord Harrison
No relevant interests

Baroness Howarth of Breckland
Board Member, Food Standards Agency  
Board Member, CAFCASS (Children and Families Court Advisory and Support Service)  
Secretary, All Parliamentary Group for Children  
Patron and Trustee, Little Hearts Matter (health/care charity)
Baroness Massey of Darwen

Chair of the National Treatment Agency for Substance Misuse
Co. Chair of APPG for Children
School Governor

Lord Moser

Board of Governors, LSE
Board of Governors, Open Universities of Israel
Board Member of National Research and Development Centre for Adult Literacy and Numeracy

Baroness Neuberger

Member/Trustee of the British Council
Non-Executive Director, VHI (Irish health insurer)
Trustee, Imperial War Museum
Former Chancellor of Ulster University (1994-2000)
Advisor, Sainsbury Centre for Mental Health
Advisor, Jewish Community Centre for London

Baroness Thomas of Walliswood

No relevant interests

Lord Trefgarne

Chairman, SEMTA
Director, United Kingdom Skills
President, IIE
President, METCOM
APPENDIX 2: LIST OF WITNESSES

The following witnesses gave evidence. Those marked with * gave oral evidence and written evidence

Association of the British Pharmaceutical Industry (ABPI)
British Medical Association
Professor Sir Cyril Chantler *
Department of Health *
European Federation of Pharmaceutical Industries and Associations
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Physicians of Edinburgh
Royal Pharmaceutical Society of Great Britain (RSPGB)
APPENDIX 3: GUIDELINES FOR THE ETHICAL CONDUCT OF MEDICAL RESEARCH INVOLVING CHILDREN

Royal College of Paediatrics and Child Health: Ethics Advisory Committee

These guidelines are written for everyone involved in the planning, review, and conduct of research with children. The Royal College of Paediatrics and Child Health’s first guidelines (then the British Paediatric Association) were published in 1980. Since then, there has been significant progress in the understanding of children’s interests, in legal requirements, and in the proper regulation of research. The revised guidelines take account of such developments. General guidelines relating to all medical research provide an essential background to this document on research with children.85–94

These guidelines are based on six principles:

(1) Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner.

(2) Children are not small adults; they have an additional, unique set of interests.

(3) Research should only be done on children if comparable research on adults could not answer the same question.

(4) A research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal.

(5) All proposals involving medical research on children should be submitted to a research ethics committee.

(6) Legally valid consent should be obtained from the child, parent or guardian as appropriate. When parental consent is obtained, the agreement of school age children who take part in research should also be requested by researchers.

The special implications of fetal research are considered by the Polkinghorne Report.94

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Value of ethical research with children

Medical research involving children is an important means of promoting child health and wellbeing. Such research includes systematic investigation into normal childhood development and the aetiology of disease, as well as careful scrutiny of the means of promoting health and of diagnosing, assessing, and treating disease. It is also important to validate in children the beneficial results of research conducted in adults.

Research with children is worthwhile if each project:

- has an identifiable prospect of benefit to children
- is well designed and well conducted
- does not simply duplicate earlier work
- is not undertaken primarily for financial or professional advantage
- involves a statistically appropriate number of subjects
- eventually is to be properly reported.

Comprehensive registers such as the National Perinatal Epidemiology Unit’s register of perinatal research and the National Research Register help to promote high standards. They publicise worthwhile projects and good practice; they help to prevent unnecessary duplication; and by recording unpublished work they provide valuable information.

Children’s interests

Children are unique as a research group for many reasons. They are the only people, in British law, on whose behalf other individuals may consent to medical procedures. Many children are vulnerable, easily bewildered and frightened, and unable to express their needs or defend their interests. Potentially with many decades ahead of them, they are likely to experience, in their development and education, the most lasting benefits or harms from research.

To facilitate both the child’s health care and longer term research, general practitioners should be notified of all research on their paediatric patients. Long term follow up of research interventions may be of particular benefit to child subjects. Yet this means still more intrusion into their lives, as records are shared and computerised. Children may be less able than adults to challenge records about themselves. There is therefore a duty on researchers to respect confidentiality, and keep up to date with data protection and legislation on access to health records.

More needs to be known about how children are affected by their experiences as patients and research subjects, and what support they need. It is desirable to encourage psychosocial research conducted independently and in conjunction with physiological research. Research will then further the task of caring for the whole child within the family.

Research shares this task when it is more than research on children, and is research with them, learning from their responses and attending to their interests as perceived by the child and parents. (“Parents” in these guidelines refers to parents, guardians, or adults legally entitled to give consent on the child’s behalf.) This partnership should accord with the Declaration of Helsinki in that concern for the interests of the subject must always prevail over those of science and society.
Must the research involve children?

In principle, the informed and willing consent of human research subjects should be sought whenever possible. Yet there are complications in obtaining the consent of minors. Research and innovative treatment on humans should only be undertaken after adequate basic research. Research with children should be undertaken only if work with adults is clearly not feasible. When a choice of age groups is possible, older children should be involved in preference to younger ones, although much valuable research can only be done with younger children and babies.

Some treatments, such as organ transplantation, may involve a range of procedures. Each separate new procedure should be tested with informed willing adults when possible, with time to assess at least the medium term effects, before the procedure is attempted with children. The urgent desire to offer babies and children the potential benefits of medical innovation is laudable. Yet childhood is a vulnerable, formative time, when harms can have serious impact as well as being potentially long lasting. Potential harms should therefore be assessed carefully before children are put at risk.

Increasingly, research experience is regarded as an essential qualification for promotion in medicine. Research work can offer valuable training that may improve the quality of doctors’ clinical practice. An inquiring mind disciplined to test hypotheses by the approved canons of research while sensitive to the vulnerability of child patients should be seen as a valued professional asset in a paediatrician.

However, great care should be exercised by supervisory senior staff over the choice of research projects. The criteria for worthwhile research, listed above, must govern the selection of projects whether primarily undertaken as part of medical training or for the advancement of knowledge.

Potential benefits, harm, and cost

There are no general statutory provisions covering research on human beings. In the absence of relevant case law, earlier cautions against research on minors that offer no direct benefit to the child subject have been replaced by qualified support. This has not been challenged in the courts. The attempt to protect children absolutely from the potential harms of research denies any of them the potential benefits. We therefore support the premise that research that is of no intended benefit to the child subject is not necessarily unethical or illegal. Such research includes observing and measuring normal development, assessing diagnostic methods, the use of “healthy volunteers” and of placebos in controlled trials.

The importance of evaluating potential benefits, harms, and costs in research on human beings, and ways of doing so, have been discussed repeatedly. A summary of discussion points is included in these guidelines to illustrate how complex such evaluations can be. Our aim, rather than to provide answers, is to list questions for researchers and ethics committees to consider.


97 See footnote 91
Assessment of potential benefit includes reviewing estimates of:

**Magnitude**
- How is the knowledge gained likely to be used?
- In research into treatment how severe is the problem which the research aims to alleviate?
- How common is the problem?

**Probability**
- How likely is the research to achieve its aims?

**Beneficiaries**
- Is the research intended to benefit the child subjects, and/or other children?

**Resources**
- Will potential benefits be limited because they are very expensive, or require unusually highly trained professionals?

Assessment of potential harm included estimates of:

**Types of intervention**
- How invasive or intrusive is the research? (psychosocial research should be assessed as carefully as physical research)

**Magnitude**
- How severe may the harms associated with research procedures be?

**Probability**
- How likely are the harms to occur?

**Timing**
- Might adverse effects be brief or long lasting, immediate or not evident until years later?

**Equity**
- Are a few children drawn into too many projects simply because they are available?
- Are researchers relying unduly on children who already have many problems?

**Interim finding**
- If evidence of harm in giving or withholding certain treatment emerges during the trial, how will possible conflict between the interests of the child subjects and of valid research be managed?
Assessment of potential harm also includes reviewing personal estimates

Children’s responses are varied, often unpredictable, and alter as children develop, so that generalisations about risk tend to be controversial. A procedure that does not bother one child arouses severe distress in another. Researchers sometimes underestimate high risk of pain if the effects are brief, whereas the child or parents may consider the severe transient pain is not justified by the hoped for benefit. There is evidence that tolerance of pain increases with age and maturity when the child no longer perceives medical interventions as punitive.98–100

Some potential harms may not be obvious without careful consideration of their consequences. For example, with research into serious genetic disorders that present in adult life, presymptomatic diagnosis in a child, while it may be beneficial, may also have very harmful effects, and may affect the child’s opportunities and freedom of choice.101

Risks may be estimated as minimal, low or high

**Minimal** (the least possible) risk describes procedures such as questioning, observing, and measuring children, provided that procedures are carried out in a sensitive way, and that consent has been given. Procedures with minimal risk include collecting a single urine sample (but not by aspiration), or using blood from a sample that has been taken as part of treatment.

**Low** risk describes procedures that cause brief pain or tenderness, and small bruises or scars. Many children fear needles and for them low rather than minimal risks are often incurred by injections and venepuncture.

**High** risk procedures such as lung or liver biopsy, arterial puncture, and cardiac catheterization are not justified for research purposes alone. They should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned.

We believe that research in which children are submitted to more than minimal risk with only slight, uncertain or no benefit to themselves deserves serious ethical consideration. The most common example of such research involves blood sampling. Where children are unable to give consent, by reason of insufficient maturity or understanding, their parents or guardians may consent to the taking of blood for non-therapeutic purposes, provided that they have been given and understand a full explanation of the reasons for blood sampling and have balanced its risk to their child. Many children fear needles, but with careful explanation of the reason for venepuncture and an understanding of the effectiveness of local anaesthetic cream, they often show altruism and allow a blood sample to be taken. We believe that this has to be the child’s decision. We believe that it is completely inappropriate to insist on the taking of blood for non-therapeutic reasons if a child indicates either significant unwillingness before the start or significant stress during the procedure.

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Despite careful selection, children in clinical trials have social and emotional problems that are mainly unpredictable.\textsuperscript{102} Provision for necessary, continuing, emotional support should be built into the research design.

**Assessment of potential cost includes reviewing:**

**Resources**

- How much medical, nursing and other professional time is required for informing and supporting families, and for collecting data?
- Are sufficient staff available without prejudicing the care of patients?
- Are the costs of reducing and preventing harms included in the protocol (such as information material for staff and families, local anaesthetic cream (for example, EMLA), autolet)
- How much family time is required for collecting data, or attending clinics?
- How will their extra expenses be paid?
- Are reasonable costs allowed for collecting, collating, and analysing data, for writing and disseminating the reports, and for informing research subjects of the results?

**Statistics**

- Are enough children involved to make a statistically valid sample, and to allow for withdrawals during longer studies?
- Is the planned number of subjects unnecessarily high?

**Inconvenience**

- How much inconvenience to families is justified (such as extra visits to clinics)?
- All medical research, whether or not associated with therapy, requires careful evaluation, as well as the safeguards described in the next two sections.

**Research ethics committees**

As assessment of benefit and harm is complex, children are best protected if projects are reviewed at many levels, by researchers, funding and scientific bodies, research ethics committees, the research assistants and nurses working with child subjects, the children, and their parents. Everyone concerned (except young children) has some responsibility.

Ethics is about good practice, and each research ethics committee considering a project involving children should be advised by people with a close, practical knowledge of babies and children, such as a registered sick children’s nurse. They may be research ethics committee members, persons co-opted, or members of a sub-committee.

\textsuperscript{102} Kinmonth A, Lindsay M, Baum J. *Social and emotional complications in a clinical trial among adolescents with diabetes mellitus.* BMJ 1983; 286:952-4.
Given that valuable research can range from the descriptive using qualitative methods to that requiring statistical analysis, research ethics committees need to have or to co-opt members with a breadth of experience adequate to assess such research.

Multicentre research ethics committees (MRECs) have the task of reviewing all research taking place in five or more centres, and protocols approved by the MREC cannot be amended by a local research ethics committee (LREC). It is therefore particularly important that multicentre studies in children are always assessed after such advice and that LRECs are advised accordingly. LRECs considering multicentre protocols should ensure that there are no local objections to the study (for example, over researched groups, ethnic factors, research facilities, local investigators).

The duties of LRECs have been clearly described. Those of MRECs have also been outlined. It is important that committees are satisfied that each project:

- sets out to answer a useful question or questions
- is designed in the best possible way to answer the questions
- will work in practice (such as in the safety of drugs and techniques, age appropriate interventions, and prevention of too many studies being carried out in one ward).

Both MRECs and LRECs may also wish to know how researchers plan to monitor and respond to any signs of distress in child subjects. This may involve helping children to withdraw from the study. LRECs have the additional responsibility of monitoring the progress of studies.

Research ethics committees are faced with the paradox of trying to be both stringent assessors and an approachable forum for helping researchers to resolve problems. They have to compromise between aiming for the perfect protocol in advance and encouraging researchers to respond to families’ unpredictable responses, which may require changes in the research design later on.

**Consent and assent**

“Consent”, in this section, describes the positive agreement of a person; “assent” refers to acquiescence. The law relating to research on children (children defined by law as those under 18 years) has never been clearly established. The application of general principles indicates that, where children have “sufficient understanding and intelligence to understand what is proposed”, it is they and not their parents whose consent is required by law. A reasoned refusal by a child to participate in research is likely to be taken as evidence of such understanding, and it would be

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107 Gillick-v- West Norfolk AHA. 3 All Er 402, at 423-4.
unwise to rely on parental consent in such circumstances. If the child is insufficiently mature to consent, then valid parental consent must be obtained.

The physical integrity of children, as of all other people, is protected by law. Unless they, or their parents or guardians acting on their behalf, agree to it, nothing can be done lawfully that involves touching them. Research with children must normally be carried out only with the consent of parent, guardian or child. Some research based on observation, collating information from notes and tests already performed for therapeutic purposes may, however, be permissible without consent because it does not involve touching the child.

A general exception to the requirement for consent is the provision of medical care in an emergency. If emergency medical, surgical, and neonatal care are to be improved, research is necessary. On many, but not all, such occasions, it may be impracticable, or meaningless, to attempt immediately to obtain informed consent for the proposed research procedures from parents or guardians. To require such an attempt always to be made could also inhibit much potentially valuable research.

Provided, therefore, that the specific approval of a research ethics committee has been obtained for the project overall, it would be ethical to carry out research on children on such occasions of extreme urgency without obtaining consent. It is possible, however, that it would still be unlawful if the research were not expected to benefit the child in question, although legal action would be unlikely. The parents or guardians and, where appropriate, the child must be informed about the research as soon as possible afterwards: a requirement in ethics as in courtesy.

Parental consent will probably not be valid if it is given against the child’s interests. This means that parents can consent to research procedures that are intended directly to benefit the child, but that research that does not come into this category can only be validly consented to if the risks are sufficiently small to mean that the research can be reasonably said not to go against the child’s interests. Even when it is not legally required, researchers should obtain the assent or agreement of school age children to their involvement in the research, and should always ensure that the child does not object.

Legally valid consent is both freely given and informed. For consent to be freely given researchers must:

- offer families no financial inducement, although expenses should be paid
- exert no pressure on families
- give them as much time as possible (some days for a major study) to consider whether to take part in the project
- encourage families to discuss the project with—for example, their relatives, or primary health carers
- tell them that they may refuse to take part, or may withdraw at any time, even if they have signed a consent form
- say that they need not give a reason for withdrawing, although their reason may help the researchers and other children in the study
- assure them that the child patient’s treatment will not be prejudiced by withdrawal from the research

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108 S-v-S. 3 All ER 107, at 111.
• encourage parents to stay with their child during procedures
• respond to families’ questions, anxiety or distress throughout the study.

Consent is not a single response; it involves willing commitment that may falter during a long, difficult project. Families may need to be supported and informed frequently. Children’s ability to consent develops as they learn to make increasingly complex and serious decisions. Ability may relate to experience rather than to age, and even very young children appear to understand complex issues. They should therefore be informed as fully as possible about the research in terms they can understand.

For consent to be informed, researchers must discuss with families:

• the purpose of the research
• whether the child stands to benefit directly and, if so, how; the difference between research and treatment
• the meaning of relevant research terms (such as placebos)
• the nature of each procedure, how often or for how long each may occur
• the potential benefits and harms (both immediate and long term)
• the name of a researcher whom they can contact with inquiries
• the name of the doctor directly responsible for the child
• how children can withdraw from the project.

Researchers will also:

• willingly explain and answer questions throughout the project
• ensure that other staff caring for child subjects know about the research, and can also explain it if necessary
• give clearly written leaflets for families to keep
• should report the results of research to the families involved.

When explaining relevant terms, researchers need to discuss with families the consent implications. For example, consenting to a double blind randomised trial means not minding which of a choice of treatments the child will have, and that neither the family nor their doctor will know which treatment has been given until the trial has been completed.

These guidelines are designed to benefit children who take part in research, children who may be helped by the research findings, and medical research itself. Researchers who observe high standards will continue to enjoy public support and co-operation.

*These guidelines were produced initially by the Ethics Advisory Committee of the British Paediatric Association in 1992* and have been modified and updated by the Royal College of Paediatrics and Child Health Ethics Advisory Committee in 1999.

*Chairman, Professor C Normand; Members, Dr P Alderson, Miss G Brykczyńska, Professor R Cooke, Professor The Rev G Dunstan CBE, Professor Dame J Lloyd DBE, Mr J Montgomery, Dr R Nicholson, Professor M Pembrey.

Chairman, Professor N McIntosh; Members, Mr P Bates, Miss G Brykczyńska, Professor The Rev G Dunstan CBE, Dr A Goldman, Professor D Harvey, Dr V Larcher, Dr D McCrae, Dr A McKinnon, Dr M Patton, Dr J Saunders, Mrs P Shelley.
Commentary

The Ethics Committee of the British Paediatric Association (BPA), now the Royal College of Paediatrics and Child Health (RCPCH), has prepared guidelines on the planning, conduct, and review of research on children. Two of their basic principles are that “research involving children is important for the benefit of all children” and that “a research procedure not intended directly to benefit the child subject is not necessarily either unethical or illegal”. Research is necessary to ensure that children receive fully informed care.

Analysis of blood is an essential part of many research programmes—for example, the determination of nutritional status and the evaluation of therapeutic drugs. Taking blood is often painful, it sometimes leaves a worrying bruise, and the experience can be distressing. Debate both in and out of the Councils of the BPA/RCPCH has centred on whether taking blood from children poses a minimal or a low risk. Procedures that have a low risk are usually inappropriate if the child involved is unlikely to benefit from the experience.

Blood taken by a skilled person poses only a minimal risk of physical harm, except possibly the taking of a separate sample of blood from a very immature infant. It is the pain and distress and the memory of it that might cause more than minimal harm.

Taking blood from children can be a positive experience. Children, like adults, are capable of being generous and doing something worthwhile even if it means they experience discomfort. Parents when they are fully informed usually consent to their babies experiencing the brief pain of blood taking if the investigation might be to the benefit of other infants. It seems to me that for blood taking to be a minimal risk, it is important that all concerned know what is happening, that the moment when the blood is taken is appropriate, that the procedure is skilfully performed, and that all steps are taken to reduce the amount of pain the child experiences—for example, by using local anaesthetic creams.

Some children, however, like some adults are frightened of needles and the sight of blood. The guidance originally stated that “Many children fear needles and to them low rather than minimal risks are often incurred by injection and venepuncture”. It now says “Many children fear needles, but with careful explanation of the reason for the venepuncture and an understanding of the effectiveness of anaesthetic cream, they often show altruism, and allow a blood sample to be taken”. I welcome the move to a more positive position. It is in the common interest of children. But it makes it more, rather than less, necessary for research workers to be able to recognise when a child is very upset whether by the thought of the procedure or at the time of the procedure and to accept this distress as genuine dissent from being involved. The child’s feelings are not to be sacrificed.

I hope that the number of children who get very upset at the thought of needles or the sight of blood will fall as accident and emergency departments strive to ensure that when children attend for treatment, the experience enhances rather than undermines their confidence in modern clinical care.

PROFESSOR SIR DAVID HULL

Emeritus Professor
APPENDIX 4: RECENT REPORTS

Recent Reports from the Select Committee

Session 2005–06


Ensuring Effective Regulation in the EU (9th Report, Session 2005–06, HL Paper 33)

Evidence from the Minister for Europe—the European Council and the UK Presidency (10th Report, Session 2005–06, HL Paper 34)

Reports prepared by Sub-Committee G (Social Policy and Consumer Affairs)

Session 2003–2004


Session 2004–2005


Session 2005–2006

Minutes of Evidence
TAKEN BEFORE THE SELECT COMMITTEE ON THE EUROPEAN UNION
(SUB-COMMITTEE G)
THURSDAY 27 OCTOBER 2005

Present

Colwyn, L
Dundee, E
Gale, B
Greengross, B
Harrison, L (Chairman)

Howarth of Breckland, B
Massey of Darwen, B
Moser, L
Neuberger, B

Memorandum by Professor Sir Cyril Chantler

I have been asked by the EU Sub-Committee G (Social and Consumer Affairs) of the House of Lords to provide a brief view of the European Commission proposal on medicinal products for children.

The proposals are summarised in document MLX 323 of the Medicines and Healthcare Products Regulatory Agency (MHRA) dated 25 May 2005, Annex A.

A large proportion of medicines used in children in Europe are currently unlicensed for this purpose. A study in Liverpool in 1998 (Turner S et al, BMJ 316 343–345 1998: www.bmj.com) noted that 36 per cent of admissions of children involved the use of unlicensed or off-label treatments and the European Commission itself has noted that unlicensed use in newborn babies may reach 90 per cent.

There are basically two problems with the use of unlicensed medicine. First there are no studies of the pharmacokinetics or pharmacodynamics of the way the drug is handled by the child’s body. Pharmacokinetics refers to what the body does to the drug (how it is absorbed, distributed, metabolised and eliminated), whilst pharmacodynamics measures the effect the medicine has on the child. There is a study, currently being undertaken at the Hospital of Sick Children, Great Ormond Street, of the use of the analgesic medicine diclofenac to relieve acute pain in children having surgery (J Standing; Personal Communication). Post-operative pain for children is a major problem in hospitals throughout the country. Diclofenac is not licensed for use to relieve acute pain in children. It is nonetheless in widespread use. The study is measuring the pharmacokinetics; a dose of the medicine is given to the child after surgery and then the pattern of elimination from the body is measured over the next hours. This will allow the doctors to make sure that an adequate level of the drug is maintained to relieve post-operative pain. Pharmacokinetics are related to size and maturity and different in children and adults. Simply scaling an adult dose based on body size drastically oversimplifies drug clearance from the body, which involves systems which develop with age such as kidney function. Previous pharmacokinetic studies have, for example, led to lower dose recommendations of morphine related to body weight in infants and children and much higher doses of paracetamol per body weight during surgery.

There are numerous problems with the lack of pharmacokinetic or pharmacodynamic evidence in children. Obviously proper relief of pain is a problem. In the field of organ transplantation one cannot assume that either the dosage or the immunosuppressive effect of medicines given to prevent rejection of the transplanted organ will be the same in children as in adults, and indeed they are not. During my time as a children’s kidney specialist we certainly had problems in maintaining adequate immunosuppression following kidney transplant in children and these were documented. Other problems that have arisen in the past has been the effect of aminoglycoside antibiotics in causing deafness in children because of overdosage, the use of the diuretic furosemide also led to ototoxicity (deafness) in newborn babies, and chloramphenicol in children was associated with liver damage and collapse. When similar legislation was implemented in the USA, new, unpredicted dosing and safety information was found for 36 per cent of drugs studied between 1998 and 2001 (Roberts R, JAMA 2003, 290, 905–911).

Second, because the drugs are unlicensed the pharmaceutical companies do not produce preparations that are suitable for children, who obviously require smaller doses and who may not be able to swallow tablets. Some years ago isoniazid, which is a medicine used in tuberculosis, was found to be ineffective in some children with tuberculous meningitis because it had to be administered as crushed tablets and an inadequate therapeutic level of the medicine was achieved (Notterman, Pediatrics 1986, 77,850–852). A similar problem arose recently
in relation to a cancer drug, imatinib which was licensed for children but only made available as tablets. Much of the work of the Pharmacy at Great Ormond Street is spent in taking preparations dispensed for adults and turning them into preparations suitable for children. Such “extemporaneous” preparation is sometimes necessary on the high street, the danger of which was highlighted when a four day old baby died as a result of the wrong strength of chloroform water being used to make up his unlicensed medicine (Pharmaceutical Journal 200, 264 390–392: web link http://www.pjonline.com/Editorial/20000311/news/babymanslaughter.html). As well as producing formulations that the children can ingest, there is also the need to dilute dosages suitable for adults to those required for children. Serious errors can occur in diluting medicines in this way, and there have been examples of overdoses from opiates etc. Most paediatricians have encountered this problem at some time during their career, as have I. In view of the above I have no doubt that there is a significant mortality and morbidity to which children are exposed because of the lack of suitable and properly licensed medicines. A recent report to members of the European Parliament from the School of Pharmacy in the University of London in conjunction with the London School of Economics and Great Ormond Street Hospital and the European Forum for Good Clinical Practice carried the results of a survey of paediatricians throughout Europe where 90 per cent of them were in favour of increasing the number of clinical trials of medicines in children to ameliorate these difficulties.

In addition to adequate Phase 2 studies where the pharmacokinetics and dynamics of a new medicine will be studied in children, there is also the need for Phase 3 studies where the manufacturers are obliged to maintain surveillance of the introduction of new products in children to make sure there are no long-term ill effects. An example of such ill-effects in the past was the staining of teeth by tetracycline. In return for carrying out adequate studies in children the European Commission is proposing that manufacturers would be able to obtain a six-month extension of patent or supplementary protection as was recently introduced in the United States. They are also proposing that medicines that are currently on the market and out of protection could be re-examined for paediatric use and paediatric formulations produced. Such formulations would then enjoy a 10-year marketing exclusivity, the paediatric use marketing authorisation (PUMA). An example of this is to be found in the reformulation of diclofenac mentioned above. The medicine was initially introduced by Novartis, who do not wish to carry out the paediatric studies, and another firm, Rosemont Pharmaceuticals, have recently produced a paediatric oral suspension.

There would seem to be few arguments against adopting the European Commission’s proposal. I believe that most paediatricians would welcome them, as indeed was shown by the European Survey. Two arguments that have been raised are as follows: First, necessarily carrying out these studies in children requires the participation of children. There is a clear ethical basis for clinical trials in children and certainly in the United Kingdom no research study in children could take place unless it received permission from a properly-constituted ethical committee. In addition, proposals for paediatric investigations in children would have to be requested and agreed by the Paediatric Committee of the European Medicines Agency. In many cases the preparations being studied would be investigated in children who would be likely to benefit from their use.

The second argument against accepting the proposal relates to the cost. The Rand Organisation has estimated that the proposed regulation on better medicines for children would increase total medicine spending in the European Union by about €300 million a year. Currently European Health Services cost €1,000 billion annually of which 10 per cent or 100 billion goes on medicines. Thus the extra cost of providing a proper system to protect children will be 0.3 per cent of the medicines bill or 0.03 per cent of the total cost of health services. There will also be a similar one off cost to the generic industry, whose access to products would be postponed by six months. This would be spread over a number of years, and could perhaps be compensated for, in part or in whole, by the opportunities under the PUMA scheme. Bearing in mind the expected improvement in morbidity and mortality in children throughout the European Union, this would seem to be a reasonable expenditure, at least in my opinion. Morally it is difficult to sustain the argument that a process which is designed to protect adults should not be applied to children.

September 2005

Examination of Witness

WITNESS: PROFESSOR SIR CYRIL CHANTLER, Chairman, Great Ormond Street Hospital for Children NHS Trust, examined.

Q1 Chairman: Good morning to everybody. Good morning, Professor Sir Cyril Chantler. We are extremely grateful to you for coming to see us today and also for the essay which you have sent to us in which you express your views so clearly. We believe you are broadly in support, and we have written evidence from other appropriate professional bodies who also seem to be supportive, as of course does the Government as well. But, nevertheless, we are not quite sure that we fully understand everything and we
27 October 2005

Professor Sir Cyril Chantler

would be very grateful if you would enlighten us today, especially on some of the issues with ethical standards involved and implied by all of this, and also on whether the proposals are actually workable in the future. Just a few House points, if I may make them. This session is being recorded and may be broadcast in one form or another. If you later feel that there is anything that you have not amplified sufficiently, or if you have further thoughts you wish the Committee to have, please do contact us before we write up the report. The verbatim report will be on the parliamentary website, so, again, if there is any infelicity in what has been said, please reply, so that we can get that right and check the transcript that we send to you. I think you have had a note of the members’ interests, and you will see what a heterogeneous lot we are in Committee G. The acoustics in this room are dreadful, and we have already experienced some drilling noise, which comes on again as I speak. These rooms were for politicians of the 19th century, who stood up and declaimed, and those of us who are soft spoken are less effective in these rooms, so we would be grateful if you could speak up. Would you be kind enough to state for the record your name and your position and could you tell us if you would like to make an opening statement, just to set the scene.

Professor Sir Cyril Chantler: Thank you and thank you for asking me to do this. I am not an expert in this area, but I do know a lot more than I did as a result of being asked to do this. I was a practising paediatrician; I retired from clinical practice in the year 2000. During my time I have been the manager of a London teaching hospital and Dean of a medical school. Currently I am Chair of the Board of Governors of Great Ormond Street and of the King’s Fund, and I do one or two other things in addition to that. I should declare an interest. I was involved in a study which was carried out through the School of Pharmacy in 2004 to judge opinion regarding this Regulation across Europe. (I have referred to it in my paper and you may well have seen the results.) This was funded by the pharmaceutical industry. The money that was given to us, of course, went to Great Ormond Street and not to me. It was not a vast sum, but it is important that you should know that. I think that is really all I would wish to say to start with. I am sure the other matters will come out during the discussion.

Q2 Chairman: Thank you very much indeed. Perhaps you could say a little bit more about the present situation and what happens at the moment. Do the statistics we have seen and the examples you have given indicate a serious problem over medicines used in the treatment of children, in your opinion?

Professor Sir Cyril Chantler: Yes, I think it is a serious problem, for the reasons I go into in my paper. Since I sent you the paper, I have obviously been talking to other people who have specialised knowledge in this area. Tony Nunn, who is the Clinical Director of Pharmacy at Alder Hey and is a pharmacist professionally, sent me some information which is unpublished from Alder Hey that suggests that 40 per cent of new medicines have the potential to be used in children but have no market authorisation. The particular problem, as I mention in my paper, is in the formulation. It is not just a question of pharmacodynamics and -kinetics, though they are important, but a very particular problem is the formulation. It is very difficult sometimes to persuade children to take medicine. That will not come as a surprise, I imagine, to any of you. It does take a little bit more than a spoonful of sugar to help it go down, if you see what I mean. I was talking to a consultant at Great Ormond Street last week, and she is involved in a programme in South Africa to treat children with AIDS. The pharmacokinetics of the medicines that they use—which are very complicated and there are a lot of them—have been carried out, but there are huge difficulties in the formulations: children who could take tablets have to take syrup, and this means they have to cart vast containers of syrup around; the tablets themselves are not scored, so they cannot be cut; and then when they are crushed you are never quite sure when you dilute what has been crushed. She gave me a whole list of things which I am happy to pass over to you if you are interested. That was another particular example of the difficulty of formulation medicines for children.

Q3 Chairman: That partly answers my second question, which is that you have mentioned studies at Great Ormond Street, but clearly there are studies and research elsewhere which is bringing further light on to this issue of children’s medicines.

Professor Sir Cyril Chantler: Yes, but you asked me if I knew whether there was a database, and I do not. I know that people have carried out such studies. Some years ago, we carried some out in relation to immunosuppressive drugs for treating children following kidney transplantation (which is what I used to do). Those results are published, but there is no central database. But the good news is that there will be. Under the Government’s plans for the Children’s Medicine Network—which has been set up and has been funded and is masterminded from Liverpool—there will be a requirement to establish this database, and, of course, under the European Regulation there will also be a database, so this deficiency, as far as I can see, will be rectified.
Q4 Chairman: That is very helpful. Is Tony Nunn’s research in the public domain?

Professor Sir Cyril Chantler: No, he says it is unpublished. There are other papers. Great Ormond Street pharmacy has a paper that is not yet published looking at the difficulties that the families have when their children leave Great Ormond Street in obtaining medicines from the high street pharmacist. In a significant number of cases, when they go to the pharmacist they cannot get a medicine which is off-label because the pharmacist does not carry a suitable preparation. Great Ormond Street is a particular issue because of the complexity of the children who are in Great Ormond Street—we have the most wonderful pharmacists and pharmacy, so they do specialise in producing formulations which are suitable for children.

Q5 Baroness Greengross: Good morning, Sir Cyril. I wanted to ask you about the EU Clinical Trials Directive which I believe since last year has governed all the clinical testing in this country. Do you think this is a sound basis for that work? Does it work well?

Professor Sir Cyril Chantler: You probably know it is a little controversial because it did require a much more complex process to be carried out when studying medicines. I think university staff—people like I used to be—were not entirely sure that this level of bureaucracy was required. I think it is. I think there have been too many studies in the past where the data has finally proved inadequate for market authorisation. I believe that if you are going to study drugs then you need to do it to a good standard and one which the industry has been obliged to meet over many years. That is the view of my colleagues at Great Ormond Street. I was talking to the Director of Research and Development and his view was that we should meet these standards and we do. My personal view of the matter is that the Directive is sound.

Q6 Lord Moser: I am a statistician and I have long been interested in clinical trials and I am aware that even for adults there is a great deal of controversy these days. The talk is about evidence-based medicine and randomised trials are controversial. But the general feeling, I think, in the medical world is that they are necessary. I would like to wind up this particular issue. If the British Drugs Association meeting a couple of weeks ago is to be believed “more than two-thirds of children admitted to hospital are treated with drugs that have never been properly tested” and the pharmaceutical companies are hesitant because it is very expensive, etcetera. If my view were—my view is—that randomised clinical trials are absolutely essential, totally crucial, and the difficulties which you mentioned have to be overcome and it has to be a 100 per cent business—and we may not all share that view, but if that were my view—how far would that be from that being the future?

Professor Sir Cyril Chantler: I think for the future that will be normality if this Regulation is approved—as it is for adults as I have said in my paper. I simply do not understand how anybody can argue that we should have a lower standard for children than we apply to adults. It is bizarre. But it ever has been so, and it has been a problem to people like me throughout our careers. So I am with you entirely. I think there is a whole other conversation about the nature of the studies that are required to produce market authorisation. This is not an area that I could really debate with you because I do not know enough about it, but I was at the Institute of Medicine meeting in Washington over the weekend and they had a whole session related to medicines and how they are developed, and there is a big argument involved as to whether the pharmaceutical industry is given too many commercial advantages or whether they are not given enough—and you would not be surprised to find that there were strong proponents of both views—and there are questions about how long it takes to bring a medicine to the market, particularly in areas where people have mortal illnesses. There was a case study of a medicine for treating chronic myeloid-leukaemia in adults, where the doctor concerned with it—the academic who has no share in the intellectual property—had done some wonderful work but argued that the process could have been speeded up by using case studies leading into randomised trials. It is more complicated than just saying that every medicine should be studied only through the gold standard randomised trial. But, just with that sort of proviso, I am sure you are absolutely right.

Q7 Lord Moser: Most of your medical senior colleagues are with you even on the ethical issues.

Professor Sir Cyril Chantler: On the ethical issues, yes.

Q8 Baroness Howarth of Breckland: Clearly there is a question of children’s rights as against adult rights. It sounds as though you and your colleagues are quite firmly proposing that children’s rights have to come up the agenda to get some equality. Is there some danger, if there are some medicines/drugs available to treat children now that might in fact go on to a list, that, until they are proven, they could not be used? Is there any danger of there being any gap if this Directive arrives that puts children in danger.

Professor Sir Cyril Chantler: I do not see why there should be. As far as I understand the Directive, it applies to new medicines. It would be, I think, wrong to withdraw from the market all the off-label prescriptions which we have learned to use—and I do not think that is the intention. Indeed, about two weeks ago, the first edition of the British National...
Formulary for children was published. That is a major step forward. Through the Children’s Medicines Network more and more information is being obtained. Of course, over the years, even though the pharmaceutical companies have not done work, other work has been done by practitioners using these medicines, so we have learned a lot and that information is embodied within the Formulary. So, no, I do not think we should go back to the beginning and I do not think that is the intention. Assuming it is not the intention, then I do not see there is a risk.

Q9 Baroness Howarth of Breckland: Do you think that will be gathered into the database?
Professor Sir Cyril Chantler: Yes. I think more information will be gathered in. As I say, quite a lot is already available, which is how they produced the Formulary.

Q10 Baroness Howarth of Breckland: The Department of Health told us that the Clinical Trials Directive requires that a person with parental responsibility or a legal representative must give informed consent to any trial involving a minor. But it also provides that the explicit wish of a minor for participation to be withdrawn “must be considered” if that young person or child does not wish to take part. Do you think that is strong enough in terms of listening to the wishes and considering the needs of the child? That does not mean you always do as a child wishes, but are we listening well enough to those children? Is it an adequate safeguard?
Professor Sir Cyril Chantler: Baroness Neuberger knows more about this than I do, and I say that because she helped in drafting the guidance on seeking consent and the ethical considerations for the General Medical Council when I was Chairman of the Standards Committee. What is expressed in your question is common ground, that children should always be consulted. There is no age . . . Well, obviously there is some age, but one would be surprised how it is possible to find out what is in the child’s interests from the child’s point of view in very young children: you just have to find more imaginative ways of communicating with them. The notion that you would do something to a child that did not involve the child’s consent is not acceptable. Obviously there are occasions, I know, where doctors and nurses have to do things and the child does not want them done and the child may cry, but you pay a terrible price for that. I constantly as a paediatrician was upset by people saying to children, “This isn’t going to hurt.” Of course it is going to hurt. Once you say it is not going to hurt and then stick a needle in them and they cry, two things have happened: one is the child has suffered pain which you might have been able to find a way of avoiding—and we are better at that now—but, perhaps more importantly, you have lost that child’s trust forever. It is a very serious matter to do something to a child that does not have the child’s consent. Participation in a trial, I think, would require the child’s consent as well as the family’s. There is quite a lot of published guidance on this. I happen to have brought with me the MRC’s guidance on medical research involving children and the Department of Health’s recent advice: Seeking Consent: working with children.

Q11 Baroness Howarth of Breckland: Do you think they are strong enough?
Professor Sir Cyril Chantler: The European Clinical Trials Committee, I understand—and this is information from somebody who works in the European Agency—are drafting guidance, new guidance to go with the Clinical Trials Directive, on the ethics of study in children. That is underway, I am told.

Q12 Chairman: Just to go back one step, I am sure you are right to say that you can devise methods to define how the child feels, and you need to be as transparent as possible with the child to gain his or her confidence, but are there not times when there is just a simple rooted decision by the child not to accept any medicine and you as the doctor and the expert see that this will be of benefit. I am slightly worried by the phrase “must be considered”. It could be considered, but if someone has other reasons, including wanting to very keenly do the experiment, as it were, may the child’s lack of consent be overridden?
Professor Sir Cyril Chantler: The first thing is the parents have to be briefed. There are difficulties if the parents disagree with each other, and that can happen, but, putting that to one side—and it is very difficult to define every particular circumstance, one has to judge people’s judgment within a framework—the first thing is the parents would have to agree. We are talking here about the notion that the parents agree but the child does not. I think it would be important to consider very carefully the child’s view, and I can conceive that there may be circumstances where you would go ahead, but it would depend on their very particular circumstances. Of course, in terms of medical interventions, when you reach that point and it is clear that the child’s consent is not available—and the child is able to give valid consent in respect of the age—then you would go to court to seek advice about what to do.
Lord Colwyn: I like the word “informed” consent, because it is so different: some children of three or four are quite capable of consenting and others of 13 or 14 are not.
Q13 Baroness Neuberger: Sir Cyril, you and I have debated this on and off over many years, particularly at the GMC. I suppose I was concerned by the language—simply: “it must be considered”—like Lord Harrison. I think it is a different situation, if you are looking at medical intervention, compared with entry into a trial. The normal view is that anything done to a child must be for the benefit of that child. The question about trials is that it may not be for the benefit of that particular child, in which case the consideration given to the child’s wishes could be argued to need to be stronger. I wonder how you would deal with that ethically, whether there is not a stronger argument for listening to a child’s view, however irrational it may seem, in the circumstances where it may not necessarily be for the child’s own benefit.

Professor Sir Cyril Chantler: As you know, advice about the ethics of research in children distinguishes between research which is of no possible benefit to that particular child and research which is likely to benefit the child. Under the first case, where it is of no possible benefit to the child, the requirement is to do something which is minimally, absolutely minimally invasive, and if it does not meet that you do not do it. Here, I think, we are talking about the second case. I think you would wish to define it more than the simple statement here. I agree with that. I think it requires a proper document. I assume from what I have been told that such a document is in preparation and will go with the Clinical Trials Directive in the event of this Regulation being passed.

Q14 Baroness Neuberger: You would argue that that is necessary.

Professor Sir Cyril Chantler: Yes. Dr Peter Arlett from the European Commission says: “The European Committee overseeing the implementation of the Clinical Trials Directive is developing detailed guidelines on ethical aspects of clinical trials in children.” That seems to me entirely proper and correct. Given the force of the Clinical Trials Directive, that will be carried through because that determines how it is done. I am assuming that this guidance will deal with all these matters. It must do. You might want to see it.

Q15 Baroness Neuberger: I think we might want to see it. Equally, one of the things I would ask you is whether you think the standards concerning the ethics of the trials on children are really maintained to the same level across Europe. That is going to be a key question in all of this.

Professor Sir Cyril Chantler: I do not know the answer to that question. But any research that is carried out on the Clinical Trials Directive will be required to do that because it will be properly regulated and supervised. People argue that the Directive is too dirigiste. I do not think it is.

Q16 Baroness Massey of Darwen: Does this include vaccines?

Professor Sir Cyril Chantler: Yes, I believe so. Biological products are included. That was a problem, as I understand, in America: initially they were not, and then the FDA introduced a paediatric rule, but that was struck down in court and was, therefore, followed by another Act of Congress. This is my understanding. “Biologics” they are called.

Chairman: Our specialist whispers to me that the Commission’s Work Programme for 2006 intends to explore the question of the rights of the child. Whether it encompasses this particular narrow area, I do not know, but that is something we may be able to establish.

Baroness Howarth of Breckland: Bearing in mind the Framework for children, young people and maternity services and where this fits in, I think we have a responsibility to make sure that managing children’s medicines and pain, which is what all this is about, is clear. I know the Children’s Rights Commissioner Professor Al Aynsley-Green has that in his Framework, so hopefully there will be some support for some of these things.

Chairman: Our parent committee will of course be meeting with the Commission to discuss the Work Programme. Let us pass on to the European Medicines Agency.

Q17 Earl of Dundee: Sir Cyril, the draft Regulation proposes that the European Medicines Agency would supervise and coordinate the working of the Regulation. Do you believe that the EMEA is the right body for this, in the first place, and, even if it is, will it have the capacity to carry out these tasks properly?

Professor Sir Cyril Chantler: Yes, I think it is. I am advised that it has had a good record since it was set up. The Paediatric Committee that it will supervise, which was set up to look after this area, I think is an appropriate body. It will need to have appropriate professional skills on the committee itself. Tony Nunn—perhaps not surprisingly, given that he is a pharmacist, but I absolutely agree with him—says that pharmaceutical skills ought to be on that committee as well as paediatricians and clinical pharmacologists. I think they will need all those sorts of skills. It is dangerous to make things up as you go along, but it occurs to me that somebody with a background in clinical ethics might be an appropriate person to be on that committee as well.

Q18 Earl of Dundee: Could you give an example of the sort of action you expect the EMEA to have to take?
Professor Sir Cyril Chantler: The EMEA will set up a Paediatric Committee and it is the Paediatric Committee which will consider the plans that a pharmaceutical company produce to study the medicine in children. It will be, as I understand it, a requirement that all new medicines will be required to be passed to the Paediatric Committee. The Paediatric Committee can decide to agree with the pharmaceutical company concerned that its medicine has no particular use in children and therefore studies in children are not required, in which case they will issue a waiver. But in a very large number they will not, and they will say, “You must provide for us the information we require to licence this preparation in children,” or they may decide to issue a deferral which says, “We will authorise it for use in adults, and, in due course—when we have more information about its safety in adults, you can come back to us and we can decide whether or not to require you to do studies in children before we grant you the six months extra market exclusivity that goes with proper paediatric plans.” As I understand it, that is the way they are going to work. It is different from the initial American experience—and I think it is true to say that the people who drafted this Regulation, although I do not know this for sure, have paid attention to the American experience. Initially, it was a sort of voluntary system, after the 1997 Act in America, whereby a company could do studies in children and then apply for a six-month extension of exclusivity. They now require all medicines to be studied and also to be properly formulated. That was not a requirement initially. Whereas it was just pharmacokinetics and -dynamics, my understanding now is that the Paediatric Committee that the EMEA will set up will require paediatric studies in the way I have described for all new medicines. I understand that is how it is going to work.

Q20 Baroness Massey of Darwen: Could I pursue this idea of the Paediatric Committee and ask you if you are content with the structure and the way it is going to work? Are there terms of reference on which you would want to comment? Are there any further rules or guidelines which are envisaged?

Professor Sir Cyril Chantler: This is, again, a personal view: it seems to me that the plans are well-formed. I suppose there is one slight anxiety that I have, and that is the requirement to manage the process to completion. As I understand it, you cannot get a six-month extension until the studies in children have been properly completed to the satisfaction of the Paediatric Committee. If there were any risk of somebody seeking a deferral and saying they would do the studies in children and then not actually completing them, but the years go by and the six-month extension has disappeared and we still do not have the studies in children—and I understand, but it is only anecdotal, that that was a problem initially in America, and I cannot see how it can happen here but it is really just a question of proper management of the process—I imagine the Committee will properly manage that process and make sure that risk is ameliorated.

Q21 Baroness Massey of Darwen: When will they set up the Committee?

Professor Sir Cyril Chantler: I do not know. I would imagine as soon as you approve and others approve this Regulation. The sooner, the better. It must be clear to you that I believe this is long overdue and I am really excited—some of us have wanted this for years, not least Professor Al Aynsley-Green, whom I have spent hours talking to about this—so the sooner, the better.

Q22 Lord Colwyn: We are already talking about this six-month extension that is proposed as an incentive to industry to develop medicines for children. In your paper to us you mention this again and say that in fact it is recently introduced in the United States. Can you tell us whether you think this is likely to be effective and equitable. Would you also comment on the fact that the European Pharmaceutical Industry Organisation—I think it is very important that we do have an input from the pharmaceutical industry—that would like to see a 12-month period, which they feel would send out a stronger message in support of competitive European paediatric research and development, taking into account, they say, the particular circumstances of the European environment—which I gather actually offers a rather less attractive economic environment than the USA, with differences in market access and price controls. Are you able to enlighten us on that?
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Professor Sir Cyril Chantler: This is very dangerous territory. The price controls in Europe are a matter of great controversy within the pharmaceutical industry and a cause of tension between the United States and the rest of the world, so I would rather not go down that route. The generic pharmaceutical industry, of course, are very unhappy about a six-month extension, so they would be even more unhappy about a 12-month extension. All I can say is that, in my view, having spoken to others, the six months seems appropriate. The Government I think did suggest that there might be a variable extension, depending on the nature of the product and its use in children, but I understand that did not get a lot of support or enough support across Europe, so they went back to the six-month extension. I have no reason to believe that it will not be sufficient and it has been sufficient in the United States. The 10-years Directive for off-patent medicines through the Paediatric-Use Marketing Authorisation I think is very important. I made a mistake, which has been pointed out to me, in the paper I sent to you. On page 4, five lines from the bottom, I wrote, “Such formulations would then enjoy a 10-year marketing exclusivity.” That is not true. It is “data exclusivity”. In fact, it amounts to marketing exclusivity if they produce a new formulation; so that, in the example I give of a medicine where a manufacturer has taken the medicine and formulated it in a way that is acceptable to children, that would in effect be a market exclusivity on that particular preparation. But it is more correct to say, as you do in your question, that it is data protection not marketing protection.

Q23 Lord Colwyn: I do a certain amount of work with sedation in dentistry and I am very aware that the drugs I use have different effects in children of three, five, nine, 12—totally different right the way through the line. It is difficult to work out where they have evolved from children into adults. Professor Sir Cyril Chantler: Yes, it is. Of course, the younger you are, the more difficult this whole area is. When you are dealing with premature babies, there are huge difficulties. There is the capacity to treat even younger babies, premature babies of 24 or 25 weeks gestation, and the use of medicines there is very difficult. When you get to the age of 12, physiologically it is not that different from dealing with adults, although there obviously are emotional considerations and psychological considerations, but, when you are dealing with very young children, their metabolism is entirely different. They actually metabolise medicines much faster than adults do because they have a much higher metabolic rate in relation to their body volume, so you have to work out dosing schedules which are entirely different from those for adults. The loading dose you do in relation to the bodyweight of the child, but the frequency has to be in relation to the metabolic rate, which is, as I say, much higher and it varies from child to child. So it is a hugely difficult area. There is a problem, when you ask the question about labelling. If you put a label saying “Suitable for children” what do you actually mean? You really will have to define what age of child, and you cannot do that on a label. It gets just too complicated. I do not know the answer to the question you pose, other than you cannot put a “P” on it because that is used for something else, and I gather they have come up with another way of dealing with that. But is there a risk, if you write “Child authorised” across it, that people would then think it is suitable for children of all ages? I do not know. Mr Nunn’s view is that it would be better that you do not label it; that you make sure it is in the instructions as to how you use it in children. He says, “I see no practical value to professionals or patients in having these medicines distinguished. Would the distinction be for all medicines with a paediatric indication or just those that have been through the new process? Industry costs will rise with no benefit to the public. If a symbol must be used, it should embrace the family and not just the child.” I do not have a view about it, other than that I can see the argument on both sides.

Chairman: Lady Neuberger, I wonder whether you would deal with any residual points arising from the orphan medicinal products and the Clinical Trials Directive and then we will come back to Lady Gale about classification and labelling.

Q24 Baroness Neuberger: Thank you. Sir Cyril, I may have to leave slightly early because I am asking a question about a subject dear to your heart, graduate medical students and top-up fees. I am sorry about that. On orphan drugs, I think there is a bit of a dispute going on. Some of those whom we have consulted have questioned the need for the 12-year extended market exclusivity for orphan drugs. Particularly the Royal College of Paediatrics says that it should be six months, like everything else. I wonder what your view is and whether you have talked to others about this.

Professor Sir Cyril Chantler: I could not understand the 12 years. Where does the 12 year come in? It says two years for orphan drugs. Are you adding 10 years to that, which makes the 12?

Q25 Baroness Neuberger: Yes. That is what the people who are disputing it seem to think it will be. Professor Sir Cyril Chantler: Yes. I always hesitate to contradict my colleagues, but why do they not want 12 years? I would have thought they might want more rather than less.
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Professor Sir Cyril Chantler

**Q26 Baroness Neuberger:** They feel they would like them to come under the Regulation more quickly. They are worried about the market exclusivity going on that long. That is their argument. I do not understand it either, but I thought you might.

**Professor Sir Cyril Chantler:** I would have thought we want to encourage people to produce orphan drugs. It is a big problem. In my own area of practice it was a problem. There is a condition called cystinosis which can only be treated with a drug called phosphocysteamine, and persuading industry to produce that... I mean, they did, but it is an orphan drug and it is very, very valuable.

**Q27 Baroness Neuberger:** It is very hard to persuade people to do it.

**Professor Sir Cyril Chantler:** Yes. So the more incentive you can provide, the better. I would have thought 12 years in this way was a better incentive than going through the ordinary six months, because you do not have that much time: by the time you get a drug to market, the clock has been running for a long time from the first patent application. I may be wrong about this, but I would have thought 12 years was more protection. But, if I am wrong about that, the more, the merrier, as far as I am concerned.

**Baroness Neuberger:** I am equally confused. I kept trying to read it and re-read it and I could not work it out, so I am rather glad that you as an expert are puzzled. Maybe as a committee we should look at that a bit more closely, because it does seem a rather odd decision.

**Chairman:** I think we are in a cloud of unknowing.

**Professor Sir Cyril Chantler:** Dr Arlett from the European... says that the debate has moved on on the issue of “P”. They understand the “P” symbol is... that says you should... I think restrictions are necessary for commercial confidentiality. Perhaps I could ask you to elaborate the argument slightly and then say where you stand.

**Professor Sir Cyril Chantler:** There must be a register. The results of every trial must be reported, whether they are positive or negative. There should be no possibility at all of commercial confidentiality stopping the public availability of information that comes out of that trial. I know that you would agree with that. If you need more information, the man to consult is Professor Hertzheimer, who knows far more about this than I do. It seems to me that would be common ground amongst all of us. There is a real anxiety about a medicine where there are problems that have arisen and those problems are not in the public domain. I would err on the side of saying that the register should be publicly available. It has been put to me by somebody who is very experienced in the pharmaceutical industry that there are circumstances where it is perfectly reasonable that some information should be anonymised within that register for commercial concerns, otherwise a competitor will obtain quite unrealistic advantage— and, given the difficulty they have now in bringing medicines to market and how expensive it is (people talk about $800 million to bring a medicine to market) I think one has to pay attention to that. I think the principle ought to be that it is available, but it should be possible to consider how commercial confidentiality can be protected by anonymisation of certain information within the database for a period. But others would have to work out the detailed regulation of that. I am afraid that is beyond my pay grade.

**Q29 Baroness Gale:** I would like to ask you about identification and labelling of products suitable for children. The Department of Health say that the proposed use of the letter “P” to identify products authorised for children is unsuitable for use in the UK as that is already being used for over-the-counter sales rather than those on prescription. Some have suggested that could be replaced by a pictorial symbol of a child. This is something you have already touched on: Should there be more specific information, because of the age ranges of the children? I know Dr Peter Arlett has proposed a label “suitable to children under the age of 12”. Would that be suitable for you?

**Professor Sir Cyril Chantler:** Dr Arlett from the European office says that the debate has moved on on the issue of “P”. They understand the “P” symbol is to be dropped because it is confusing in relation to over-the-counter preparations and it will be replaced with something that will not be confused with over-the-counter medicines. But I think it still begs the question: Why put it there in the first place? To the point you raise: When is a child not a child? and it differs in children of different ages. I think that is a matter for others to debate a bit further. But I think one has to be very clear that it is the information with the medicine that should be clear about dosages for children of different ages. That is vital. If there is a symbol that says you should read the information in relation to children, maybe that is a way forward. I do not know.

**Q30 Earl of Dundee:** Sir Cyril, you say “when a child is not a child,” but, when a child is a child how many categories are we talking about? Three to five year olds, are very different children compared with five to seven year olds and so on. Taking Lady Gale’s point on labelling, if it could all be done in a simple way, how many groupings of children would you differentiate on the label?
Professor Sir Cyril Chantler: I do not think you can differentiate more than one on the label, otherwise it
would cease to be useful.

Q31 Earl of Dundee: If some medicine is right for children from three to five but it is not right for children from seven to 10, you would probably want to make that point on the label, would you not?
Professor Sir Cyril Chantler: I think this is the difficulty. It is a particular difficulty about newborn babies. If you have a symbol that says, “Suitable for children” by putting a symbol on it of a child, there is a big change in the physiology of a child between birth and two years, not least in their kidney function, so you could quite easily think of a circumstance where it would be safe to use in a two-year old but in a newborn baby you would have to be very, very careful. If you write, “Suitable for children” on it, would there be a risk that it might be used? This is the difficulty. I do not know the solution to it. People have talked about six possible stages of childhood, so I was told—though of course they are not; you do not move overnight from one to the other. This is the difficulty. To every complicated problem there is a simple and obvious solution that turns out to be wrong, and I think this is an example of it. I think the most you could expect of a label is that it would direct you to read the product information which is given with it. That is all it should do. It should not be taken as suitable for children, it should direct you to looking at the product information. It is how you do that, and whether it is better to have nothing on at all and just say to everyone, “Before use in children, check the information,” I do not know.

Q32 Baroness Massey of Darwen: Does it depend on the weight of the child?
Professor Sir Cyril Chantler: Yes, partly. But it is not just the weight; the maturity matters too. There are two groups of small babies at birth: those who are small because they have been inadequately nourished in utero but are mature and those who are small because they are born early. Their metabolism is the difference between the prescribed preparations that are bought over the counter. There will be medicines which are currently being used for which there will not be any stimulus/incentive to the manufacturers—be they generic or research based—to do the studies. It is not an easy area.

Q33 Baroness Howarth of Breckland: Is there a difference between the prescribed preparations that the GP or the paediatrician have worked out in relation to the individual child—and would they then be able to get the preparations that they are looking for?—as against those things in the chemist that a parent goes for and says, “Yes, this is a children’s aspirin” and worries about how much? I am concerned about not having things on the label. I should explain I work for the Food Standards Agency, so I know quite a lot about people’s behaviour in relation to labels and we know that they do not read a lot on the packet and they certainly do not read anything inside the packet—the middle-classes may do, but certainly the most vulnerable groups do not. I wonder if these are key differences and whether we should be looking to ensure that the doctors get their prescriptions right and the pharmaceuticals deliver those things the doctors require and have enough thought about those preparations that are bought over the counter.
Professor Sir Cyril Chantler: Obviously there is a difference between different medicines and the risk benefit. You would not be able to buy a preparation over the counter that needed to be prescribed because of the complexity of the medicine and the potential risk attached to it. However, there are medicines you can buy over the counter which are not suitable for children—and aspirin is one of them, because of particular problems of aspirin in young children. Lady Howarth, you know far more about labels than I do and this is why I do not think I can add to what I have said. Your view on this is probably going to be superior to mine. I can only point out the problems; I am not sure I can provide the solution.
Chairman: Nevertheless, that was a particularly useful set of replies there.

Q34 Baroness Greengross: Of course you will know about the proposal the Commission has made to set up a Community-wide network to link national networks and clinical trials centres through the EMEA and of this idea of introducing a Medicines Investigation for the Children of Europe (MICE) programme. What do you think of those proposals? Are they adequate? Do we need this sort of coordinating body? Is it going to help to stimulate research?
Professor Sir Cyril Chantler: I am getting into politics which I am not really qualified to do. Before you do anything in a European context, you should ask yourself whether it would be superior to doing it within the national context. That was my first thought. I think in this instance it is worth doing it in the European context. There will be medicines which are currently being used for which there will not be any stimulus/incentive to the manufacturers—be they generic or research based—to do the studies. It just will not be financially viable for them. In due course you will not need this fund, because the medicines will all have been studied and the new medicines will have gone through the process, but for the next few years I think the availability of such funds on a European scale would be very useful—not least because there is a lot of cooperation amongst paediatricians across Europe and there are paediatric societies that cover Europe in all areas. I was for many years very much involved in the European Society for Paediatric Nephrology. Doing studies
across Europe would be necessary for some of these conditions which are relatively rare. I have come to the conclusion that the MICE programme is a good idea and I hope that they will fund it adequately. There is, I am told as of yesterday, something called TEDDY, the Taskforce European Drug Development for the Young. That is a network of excellence from the European Commission Framework 6 programme and it has 4.4 million euros in total. It is to cover 2005–10 and the UK coordinator, Dr Ian Wong, who is at the Centre for Paediatric Pharmacy Research at the School of Pharmacy, the Great Ormond Hospital and the Institute of Child Health, has funds to set up this programme. There are some funds already available but I think this is a good idea.

Q35 Lord Moser: Do you think such a body could undertake clinical trials if the pharmaceutical industry was unwilling to?
Professor Sir Cyril Chantler: Yes. I do not think the pharmaceutical industry would oppose such studies; it just would not wish to finance them if it is not commercially beneficial for them to do so.

Q36 Chairman: The Commission’s proposals are based on current arrangements in the United States. Do you know how well these arrangements are working and is there anything we can glean from the experience of Canada and Australia that might again help us?
Professor Sir Cyril Chantler: I understand they are working very satisfactorily in America. The reason I know that is that I met Professor John Lewy over the weekend and he used to be the chairman of paediatrics at Tulane but now works in Washington in Congress on behalf of the American Academy of Paediatrics. He told me that the present arrangements are a great advance and they are very pleased with them. They have worked through a process since 1997 to improve it and the last Act that brought in the biologicals and the vaccines was in 2003. They now think it is working very satisfactorily. The proposed regulation from the European Union has built on that experience. You asked me about Canada and Australia and I do not know the answer to that.
Chairman: At the beginning of your evidence, you said that you had learned a lot more about this process than once you knew in terms of your knowledge and experience. The Committee now finds itself in that position because of the benefit of the evidence you have given today so helpfully and clearly. I would like to thank you for that and I think the Committee also would like to convey in its report your excitement at the prospect that these proposals may come to fruition and ultimately be of huge benefit to the kinds of children and young people that you have been dealing with in the past. We are most grateful to you.
THURSDAY 10 NOVEMBER 2005

Present
Colwyn, L
Dundee, E
Gale, B
Greengross, B
Harrison, L

Moser, L
Neuberger, B
Thomas of Walliswood, B (Chairman)
Trefgarne, L

Memorandum by the Department of Health

EXPLANATORY MEMORANDUM ON EUROPEAN COMMUNITY LEGISLATION

REFERENCE 13880/04 AND 13880/04 ADD1


SUBJECT MATTER

On 29 September 2004, the European Commission adopted a proposal for a Regulation on medicines for paediatric use. The proposal will make necessary changes to the regulatory structure for pharmaceuticals to stimulate appropriate development and studies of medicines for paediatric use. The overall aim of the proposal is to improve the health of the European paediatric population by increasing the research, development and authorisation of medicines for use in children. The proposal aims to improve availability of medicines for paediatric use and provide the necessary stimulus for the pharmaceutical industry to conduct the necessary research.

MINISTERIAL RESPONSIBILITY

The Secretary of State for Health. HM Treasury, the Department for Trade and Industry and the Patent Office also have an interest.

LEGAL BASIS

The proposed Treaty base for the measure is Article 95. The UK’s position, however, is that Article 95, which is subject to qualified majority voting, is not appropriate for measures which establish a centralised EC procedure or body, other Articles should be used, in particular Article 308, which is subject to unanimous voting. The UK position on the use of Article 95 is currently being tested in two cases in the European Court of Justice (ECJ) which we have brought regarding the use of a centralised authorisation procedure. Law Officers have taken a view on the line which the UK should take in future on proposals which the UK supports for policy reasons, even though we consider they use the wrong legal base. The Department of Health (DH) will follow this agreed line for this proposal.

VOTING PROCEDURE

Article 95 is subject to qualified majority voting. Article 308 is subject to unanimous voting.

IMPACT ON UK LAW

The Commission has indicated that the proposal is likely to become law in late 2006, at the earliest. A Regulation is directly applicable in all Member States.

Supplementary national legislation may be necessary to make the Regulation workable.
10 November 2005

APPLICATION TO THE EUROPEAN ECONOMIC AREA
This regulation will be applicable to the EEA.

APPLICATION TO GIBRALTAR
The proposal is not applicable to Gibraltar.

SUBSIDIARITY
The proposal builds on the existing European regulatory framework which exists for medicines.

POLICY IMPLICATIONS
A Council Resolution of 14 December 2000 called on the Commission to make proposals in the form of incentives, regulatory measures and other supporting measures in respect of clinical research and development to ensure that new medicines for children and medicines already on the market are fully adapted to meet the specific needs of children. The UK was supportive of the Council Resolution.

The key measures proposed are:

— a new expert committee within the European Medicines Agency to assess and agree paediatric investigation plans submitted by industry;
— a requirement to include data on the use of the medicine in children when a marketing authorisation application is submitted to the regulatory authority; (this will not delay the authorisation of medicines for adults);
— a provision to increase the information available on the paediatric use of medicines, whether or not such use is authorised;
— a system of waivers for medicines unlikely to benefit children and a system of deferrals to ensure that medicines are tested in children only when it is safe to do so;
— a reward for studying medicines for use in children of six months extension to the supplementary protection certificate—in effect, extending the patent holders monopoly on the product by six months;
— for off-patent medicines, 10 years of data protection for new paediatric studies awarded via a paediatric use marketing authorisation (PUMA);
— increased safety monitoring for children’s medicines and compulsory submission by industry of existing completed studies in children;
— a European inventory of the therapeutic needs of children and a network of investigators and trial centres to conduct the studies required; and
— a system of free scientific advice for industry to be provided by the European Medicines Agency.

The Commission has undertaken an extended impact assessment to support the proposal.

BACKGROUND AND UK POSITION
The Commission consulted on proposals in February 2002 and in March 2004. The UK has been supportive of the Commission’s efforts and has indicated that a regulation is key to addressing the lack of suitably labelled, suitably formulated medicines for use in children. It is estimated that over 50 per cent of medicines currently used to treat children are not authorised for use in children. Traditionally there has been widespread resistance to conducting clinical trials in children on ethical grounds. However, this has to be balanced by the ethical issues related to giving medicines to a population in which they have not been tested.

The UK Government welcomes the Commission’s proposal. However, we want to ensure that the provisions meet the following criteria:

— that the measures strike the right balance of costs and benefits for the UK’s National Health Service (NHS). We are currently exploring the costs for the UK; and
— that the provisions of the Regulation are practical and workable and will not create problems for existing arrangements in the UK.

At this stage, it is not clear whether the proposal will fully meet these criteria. Departmental economists are currently working to clarify what the balance is between costs and benefits.

**Timetable**

The proposal will be discussed in Council working groups during the current Dutch Presidency. The proposal will also be discussed at the Health Council in December 2004. The proposal is expected to be at an advanced stage during the UK Presidency in 2005. The Commission has indicated that the proposal is likely to come into force in 2006.

*Norman Warner*
Parliamentary Under Secretary of State (Lords)

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### Examination of Witnesses

**Witnesses:** Rt Hon Jane Kennedy, a Member of the House of Commons, Minister of State, Department of Health, Dr Julia Dunne, Department of Health and Mr Richard Carter, Department of Health, examined.

**Q37 Chairman:** Good morning and welcome, Minister. Thank you very much for sparing the time to come and speak with us today. We are aware that you have an appointment at 11, so we will try to be as business-like as we can. But there are a number of remarks I need to make now. We note the strong endorsement of the proposals in your recent letter to us and meanwhile you may know that we have taken soundings from a selection of professional bodies, all of which are broadly supportive of the proposals, and those views are generally in line with the responses on the consultation made by the MRHA, which the Department has also sent to us. Nevertheless, we do feel that this is a very important and far-reaching proposal. That is why we want to make sure that it is right when it goes into effect, and we want to make sure that we fully understand it as well; after all, this Committee is not made up of health professionals, although there is one amongst us. We also need to be completely satisfied that it fully meets acceptable ethical standards, especially where the health and welfare and the rights of children are concerned. We are interested also in striking the right balance between the incentives to industry and the need to avoid giving rise to excessive profits or unduly penalising EU health services, a matter which your letter also addressed. There are obviously some concerns about the very wide range of the costs and benefits which appear to be associated with this and we have a question which will try to tease out a little more about that. The legal basis for the proposals is something to which you, I know, have given some attention, but in view of the fact that we have a short time ahead of us for this discussion, maybe that is a matter which we could deal with in correspondence rather than across the table? As to the conditions under which the session is being held, you are probably aware—but I had better run through them for the record—that the session is open to the public and it will be recorded for possible broadcasting or web-casting. A verbatim transcript will also be taken and that will be published on the Parliamentary website and annexed to our Inquiry Report. But prior to that you will be sent a copy of the transcript so that you can make sure that it is correct in terms of what you said, and so forth, and if you do want to make any corrections perhaps you could send those back as soon as possible? Obviously, if you want to submit supplementary evidence to us after the session to clarify or amplify any points that you have made which perhaps we did not take far enough that would also be extremely welcome. You have had a note of Members’ interests and a copy of it should be on your table. A last problem is that the acoustics in this room are difficult. I do not know how they manage with witnesses when it is the High Court, but we have trouble even if their legal Lordships do not. So if you could make sure that anybody who is speaking keeps their head well up and speaks to the room then that would be helpful. If you would like to begin your evidence by stating your name and the name of your officials who are accompanying you, again for the record, and perhaps you would like to make a brief opening statement before we get into the question and answer session. Welcome once again to this Committee.

*Jane Kennedy:* Thank you very much, Chair. It is a very welcome opportunity for me to rehearse with you the arguments and the reasoning behind taking this measure forward. Just in terms of the acoustics in the room, one of the first lessons I learnt in the Other Place is when my very good friend, Gwyneth Dunwoody, leaned over and, as only Gwyneth can, sotto voce, with the whole Committee hearing my first-ever speech in a Standing Committee, she whispered, “For goodness sake speak up, Jane!” So I
learnt that very early on and I will do my best to make sure that you can hear, and also obviously our friend in the centre can hear too. I am joined this morning by two officials who are leading on this regulation for the Department of Health and for the Medicines and Healthcare Products Regulatory Agency, the MHRA. Dr Julia Dunne is currently chairing the Council Working Group negotiating this Regulation, so she is actually chairing the group. She is also one of the UK representatives on the Committee on Human Medicines. With me also is Richard Carter, who is from the Department of Health Medicines and Pharmacy and Industry Group within the Department, who is also involved in the negotiations. So I am confident that I am supported by two very knowledgeable individuals who I hope will achieve your objective with me, which is to make sure that the proper scrutiny is given to this important measure. It is also worth noting that I am aware that there is interest in the Other Place, the other Scrutiny Committee also will be interested in our discussion today. I will say just a few brief words to set the background and then we can get into the detailed discussion. You will be aware that the lack of medicines authorised and formulated specifically for paediatric use has been a concern in the UK for a number of years, and it is our view that the proposed Regulation will be key to addressing the current situation. The proposal responds positively to concerns expressed by all Member States, which resulted in the Council resolution in December 2000. The wheels of Europe turn not particularly swiftly, but here we are now considering that. It recognises the need for a regulatory approach which includes both incentives and requirements to ensure that new medicines for children and medicines already on the market meet the specific needs of the paediatric population, whilst at the same time ensuring that children are not subjected to unnecessary clinical trials, or delay the authorisation of medicines for adults. I think it is important to take a minute or two to address an area that I know is of particular concern to the Committee, and that is the issue of the ethics of conducting trials in children, and the safeguards that need to be in place to ensure that their best interests are protected. The Government believes that the protection of those participating in clinical trials must be the overriding priority. The Paediatric Proposal contains a range of measures specifically to safeguard those participating in paediatric clinical trials. These are over and above the standards introduced by the Clinical Trials Directive. That Directive, the Clinical Trials Directive, already provides additional protection for minors by setting specific ethical and procedural criteria for entering children into trials. The rules that govern recruitment and retention in clinical trials are both detailed and specific. I can reassure the Committee unequivocally that the Government would not support a proposal with implications for conducting clinical trials in children if we were not absolutely convinced from all of the expert advice that we have received that this is the right thing to do. As is the case with all clinical trials, conducting trials in children will make an important contribution to public health. They will contribute to improving public health because they provide the basis for identifying new medicines for children and new uses of existing medicines, particularly for inadequately treated diseases, as well as demonstrating the safety and efficacy of medicines so that they can be placed on the market. In addition, they help us to develop optimum treatment regimens with resulting improvements in disease associated morbidity and mortality. The Committee will be aware that the Commission consulted on informal draft proposals in 2002 and again in 2004. In addition, the Department of Health and the MHRA consulted with a range of stakeholders including the medical profession, the Royal Colleges, patient organisations and the pharmaceutical industry. The Committee will have seen from the summary of the consultation responses that we have provided that there is strong support for the regulation. Just to give you a brief update on negotiations, you will be aware that negotiations on the proposals have been conducted during the UK Presidency. The European Parliament voted on the proposals on 7 September and voted to adopt the proposals by a significant majority. The Commission has indicated that a revised proposal will be available, we believe this week—I think it is in circulation—and we do not expect any surprises in the revised text. I will undertake now to write to you should there be any detailed changes arising from that text. So the key issues that we expect them to bring forward are, very briefly: first of all, making parts of the proposed Regulation key to addressing the detailed changes arising from that text. So the key issues that we expect them to bring forward are, very briefly: first of all, making parts of the proposed Regulation key to addressing the detailed changes arising from that text. So the key issues that we expect them to bring forward are, very briefly: first of all, making parts of the proposed Regulation key to addressing the detailed changes arising from that text. 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opening remarks, I believe that the proposal strikes the right balance between protecting public health through the development of properly tested and formulated medicines for children, and at the same time assuring high quality paediatric clinical trials here in the UK. The proposal has been long awaited and we hope to contribute to its progress by reaching political agreement under the UK Presidency at the December Health Council. I am going to rely heavily on my two colleagues to answer the detail of your questions, particularly as my focus has been certainly on other things in the last 24 hours!

**Q38 Chairman:** You have cleared almost all of the detail and the questions about political clearance and agreement and so on, and it is clear that there have been some quite important changes, and the government supports those changes. Are there any other outstanding matters available and do you think that the go-ahead, as it were, will still be achieved at the Health Council meeting on 9 December? I think that is what “political agreement” means, does it not? It means that the Council has agreed and now it can go on to its next stage; am I right in thinking that?

**Jane Kennedy:** That is what I understand it means. I am not aware of any other issues that may arise and I believe that we are quietly confident that we will reach the agreement we seek in December.

**Q39 Chairman:** Are there still other Member States who have particular concerns that only refer to their problems? Are you aware of that?

**Dr Dunne:** There are not any major outstanding concerns. There are still some issues that have to be discussed at the last important meeting with Member States at the Working Group level, the Working Group that I chair, but I expect that most of those issues will be resolved at that meeting and then it would go on to one other meeting of officials before it goes to the Health Council.

**Chairman:** To the Health Council, yes. Thank you very much for saying that you will in fact inform us if there are any unexpected changes; that is a very helpful offer from you to us.

**Q40 Lord Colwyn:** My Lord Chairman, just at this early stage could we try to clarify what is meant by “children” because drugs affect different ages totally differently. So what is effective in a neo-natal child is different to a one year old, different to a two-year old, a four-year old; it changes right through that whole spectrum. I wondered whether the word “children” is too broad a description?

**Jane Kennedy:** It is 18.

**Q41 Lord Colwyn:** I know that 18 is the maximum age but because the drugs act so differently on different ages it is very difficult to say that these medicines are going to be effective for “children”.

**Jane Kennedy:** I am going to ask Dr Dunne to answer on some of the detail that you are asking. But one of the things that I have learnt in coming into this post, to my surprise I had not realised that the vast majority of medicines used on children have never been tested on children, and indeed are not licensed. So they are used on children outside the terms of their licence, which is the reason why there has been a concern about the lack of guidance to paediatric specialists.

**Q42 Lord Colwyn:** I am envisaging the pharmaceutical companies having to do tests on the whole range of different age groups, which is going to take years and years and years and they will not want to do it.

**Dr Dunne:** The definition is under the age of 18 and normally we refer to the “paediatric population”, but that is a bit of a mouthful so for short we refer to “children”. But acknowledging that within the paediatric population, which goes from nought to 18, there are different sub-groups, different ages of populations which have different needs, and there are differences between them. But with this Regulation what it will target within a particular medicinal product are the age populations within the paediatric population which are relevant, and you would not necessarily need—to answer one of your remarks—to do the same extensive testing in each age population, because it may not be appropriate to use the product in neonates, for example, but you would work from the oldest population down, mostly, and you would be able to from one group perhaps extrapolate some information to the next group, but you would not necessarily need to do a full programme in each age population within the range from nought to 18.

**Q43 Baroness Neuberger:** That is very interesting and I think everybody who has been involved in this at all is absolutely delighted that these proposed regulations are coming up, for precisely the reasons you gave us. But is not the biggest issue actually about the drugs to be used on very small children rather than, as you describe it, going from the top of the range down? From the evidence that we heard from Sir Cyril Chantler it seemed as if the worst issues were about drugs being used on neonates and on very small children because their organs are so poorly developed. So is it not the logic going to go the other way around?
Dr Dunne: It depends very much on what the medicinal product was, but you are right that it is a particular problem, and although we say generally that over 50 per cent of medicines have not been tested for use on the paediatric population, if you actually break them down into their sub-populations for neonates it is 90 per cent, so it is a particular problem and they are a particularly vulnerable population. And for the medicines which are to be used in that population then there will need to be extremely careful studies. But not all of the medicines that are relevant to the older age groups would be relevant to that particular population.

Q44 Lord Trefgarne: Is it not the case that it is not a question of which medicines can be used for the youngest children, but what we need to know is those that cannot be used for the youngest of children? We had evidence, as Baroness Neuberger said, from Sir Cyril Chantler, that up to now the formula has been that anything approved for children is generally approved for children and the dose relates to their body weight, but the Professor suggested that that was not a sufficiently sophisticated testing arrangement and I think other witnesses acknowledged the point that maybe there are categories of medicines which can be used perhaps for older children and not for younger children, and the arrangements to provide for that do not seem to be coming forward in what we are reading.

Dr Dunne: I am not sure why you have that impression.

Q45 Lord Trefgarne: Professor Chantler, is the answer to that.

Dr Dunne: I cannot remember exactly what he said but it may not have been sufficiently clear. When a product is authorised for use in the paediatric population there is usually a lower age limit. So it would not necessarily be authorised in the whole of the population, so it would say, for example, “Not to be used in children under the age of one year”, but it still may have an authorisation for children above one year. So it would be quite exceptional for a blanket statement using children and not to have a clear lower limit, if one is appropriate; and within the dosing information if there is an authorisation for use in children then the different age ranges would have clear dosing information.

Q46 Lord Trefgarne: Generally based on their body weight.

Dr Dunne: Not necessarily. If the product has been studied so that it has an authorisation in neonates, for example, then the dosing would not necessarily be based on the body weight, it may be based on something like body surface area. It depends very much on the particularities of the medicine and the data that has been collected to support the authorisation.

Q47 Lord Trefgarne: But the testing is bound to be a bit limited in those cases.

Dr Dunne: It depends on the product. In some cases, for example the surfactants, which are really used primarily in newborn babies with lung and breathing difficulties, they were initially studied entirely in babies, they were not studied in adults at all because that was a paediatric indication.

Q48 Chairman: I just want to draw something out. This detail that we are talking about now is of course the essence of the matter. I am not trying to deny that. But is it not the kind of thing that is more likely to come out in guidelines rather than the actual piece of paper which is the Proposal? I am not saying that we have to take it on trust but we have to be reassured that these are the sorts of matters, these extremely detailed instructions as to how clinical trials should be conducted, and all that sort of thing, which are likely to come out in the guidelines; is that right?

Jane Kennedy: The guidelines will be extensive. It is not unusual for proceedings of this type to be taken forward using guidelines, and they will provide the kind of detail that I think the Committee is concerned to see. Unfortunately that is yet to be developed.

Q49 Baroness Greengross: My question is a very brief one, but I think there is a huge difference between the guidelines which apply to prescription medicines and the ones for over-the-counter sale because you are not relying on the medical profession or even a pharmacist always to be absolutely clear as to what is going to happen; you are relying on the general public to interpret what they read or what they have heard or from an advertisement or something. Will we be certain that that will be properly covered in the action plan?

Jane Kennedy: Certainly I would want to be reassured of that, that is our objective. When the guidelines come out they will cover a whole range of products and it might be helpful if I give you an idea of what some of those areas will be, and I do not know if they have already been supplied to the Committee? The guidance would cover coordination between the Paediatric Committee, which would be established as a result of this resolution, which would have the role of oversight of the clinical trials and coordination between that and other working groups. It will cover the rules of procedure for the Committee; it will cover the content and format of data, which is to be collected for the survey of medicines used in children, all of which is what will feed into the kind of guidelines that would be issued on the use of the medicines. Guidance on the format and content of applications for the agreement of the Paediatric
Investigation Plan, and the Paediatric Investigation Plan is a new concept. They will cover guidance on additional post-marketing requirements to ensure the safe use in children, which I think addresses Baroness Greengross’ concern. They will cover guidance on paediatric Clinical Trials Database, how the data is to be entered and what parts of the data would be able to be made public. And they will cover implanting the strategy for paediatric clinical trials networks. So we do accept that there will be a lot of this work that will be taken forward using guidelines, but, as I have said, I do not think that that is an unusual procedure and those working in this field will be used to managing it.

Q50 Lord Harrison: Chairman, I would like to pursue Lord Trefgarne’s point. Minister, we were made very aware by Professor Cyril Chantler that there was concern about these paediatric populations as they derive, but also that there are other sets of variables including the weight of a child and also the effect of the drug advice as to the child’s body. If I have heard Dr Dunne right she, in answer to Lord Trefgarne, implied that there would not be extensive research done in each of the paediatric populations and that perhaps you would start at the top with the 18-year olds because they were the most mature. But if that is the case and you then extrapolate from that research thoughts about the smaller, the lower age paediatric population, that then gives me cause to worry because whilst it may show that it is sufficient for a 14 to 18 year old, to then extrapolate and go on that basis for younger children down to the neonates—despite what you have said about there being a cut-off point where it would be inadvisable to lower it beyond seven, or whatever that particular paediatric population is—it does seem to me, in a sense, the wrong way around because you are testing that part of the paediatric population that perhaps would be best resistant to any adverse effects of the drug.

Dr Dunne: I have probably over-simplified because what we are talking about now is not really part of this Regulation. The Regulation sets the framework for doing the clinical trials and it makes clear that the appropriate age populations within the paediatric population should be studied, so that no age group, for example neonates, are excluded. But all the detail of how trials will be conducted in the paediatric population and the timing of trials in different populations will all be handled through guidelines, and it would not be possible through a regulation to set out all that information, nor would it be desirable because the guidance is constantly revised to take account of technical advances. But the framework that the Regulation sets out enables or tries to ensure that all of the appropriate paediatric populations will be studied.

Chairman: Thank you for that answer. I think we must move on. Lady Neuberger.

Q51 Baroness Neuberger: Thank you, and I think very largely you have answered in your opening statement, Minister, the third question about ethical safeguards; you clearly are content that the system will actually give the full necessary protection for the health welfare and rights of any children involved in paediatric medicine testing. I think we do await the guidelines to be completely clear, but broadly that is what you are saying. But I do want to pick up with you the concern that I think we all have, and we teased out a little with Sir Cyril Chantler and with others, which is that in your letter—and indeed having read all of this material—the Clinical Trials Directive says that a person with parental responsibility or a legal representative has to give informed consent for any trial on a minor. Then the bit that worries us is that the explicit wish of a minor to refuse to take part in or withdraw from a clinical trial must be considered. Not necessarily taken on board, but “must be considered”. We are worried that that may be an inconsistency and not clear that it is necessarily an adequate safeguard and wondered whether there was a chance of strengthening it within the Regulation?

Jane Kennedy: I do not believe that there is an inconsistency. When I saw your question we did discuss this when we were preparing for today’s hearing. Obtaining informed consent from a parent or a person with parental responsibility is going to be a pre-condition; the child cannot go into the trial without that informed consent. It does not determine inclusion in a trial; it does not even guarantee the child is included in the trial; that will depend on a number of other factors. But in discussing this issue it is clearly necessary to balance what may be the opportunity for the child to benefit from medicines that will bring clear benefits to that particular child in their particular medical condition. It is a judgment, is it not, between their objection perhaps on a particular day, perhaps the medicine itself is making them feel unwell, making them less inclined to cooperate, and balancing that with the overall best interests of that child, which is why we did not feel that the child’s view should be a veto on participation in the trial. I am informed that this will be dealt with in detail again in the guidance. It is not an issue I want to duck and I accept that there is concern about this; but, as I say, we felt that it was important that while the view of the child is important there are only certain age groups actually of children who will be able to express an opinion anyway. So there has to be a balance between, is this child making that decision from a properly informed position of saying, “This is not in my interests to do it,” or is it something, perhaps a whim on the day?
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Q52 Baroness Neuberger: Can I tease this out because actually I think this is terribly important, and I do not know what the answer is. You have a 14-year old who has a long history, say, of cardiac problems, and there is a drug which may or may not be for the child’s own benefit because of course you cannot tell when you are doing a trial whether it is necessarily going to be for the child’s own benefit, but you assume that it will be. But you do not know, it may turn out that the trial shows that the drugs should not be used; so you cannot say definitely that it is for the child’s own benefit. This is a 14-year old, getting on towards an age where we would allow them to make their own decisions about consent, and the child says, “I have been through goodness knows how many trials, I have had enough, I do not actually want to do this.” The parent gives consent but the child, him or herself, says, “No, I do not want to do that.” It seems to me that if you just say it has to be considered but not necessarily taken seriously that really is not good enough. That is a particular example because that is the sort of age obviously when this is a key issue, and you push it younger and you might say that you cannot take the child’s view seriously; you push it older and you have the age of consent. So it is that sort of area where it does seem as if there is an inconsistency here.

Jane Kennedy: I do not know if Dr Dunne wants to say anything on this, or indeed Richard, but my view is that these are some of the detailed ethical decisions. The guidance will be very clear and that kind of decision is probably going to have to be taken on a case-by-case basis. A child in those circumstances, I do not know how rare that would be, if the child had very, very strong views. You can imagine a child maybe as young as 12 being very ill with cancer, having undergone some very difficult treatments that have made the child feel very ill, and resisting further trials. That child actually might be very well informed, and therefore I think a different weight would be given to that child’s opinion, and I think the guidance will allow for that.

Q53 Baroness Neuberger: I think the difficulty here is that we have this actually, if you like, within the Clinical Trials Directive itself and that is why I suspect we picked it up because presumably the guidance can try and tease it out, but it does seem to us, as stated, that there is an inconsistency here and that is why I wanted to raise it, and I think others of my colleagues want to get in here.

Q54 Lord Trefgarne: I have a slightly different concern, my Lord Chairman. What about the circumstances where there is a child, say, of five years of age, close to the point of death, the mother is at the extremities of grief and the doctor says, “I have this pill here. We have not tried it on anyone, shall we try it on your child?” She will say, “Yes, of course you can.” That is not informed consent. What on earth are we to do in those circumstances?

Jane Kennedy: Can I ask Dr Dunne, who is experienced in this area?

Dr Dunne: We are really rather now moving over to discuss the Clinical Trials Directive rather than the Regulation for Medicines for Paediatric Use, and the situation that you have just outlined is as applicable to adults as it is to children, but in this particular case the paediatric regulation refers to the Clinical Trials Directive and that is the piece of legislation which deals with all these sorts of things, and we know that it cannot open up the Clinical Trials Directive, it cannot be used for that. But as one of the implementing texts of the Clinical Trials Directive the Commission has already produced quite a bit of guidance to help those implementing the Clinical Trials Directive and they are currently drafting specific guidance on the ethics of conducting clinical trials with children, and they are hoping to release that for consultation by around April of next year, so that it will be in place by the time that we get the regulations adopted. It aims to discuss and to provide guidance on all of these questions which are difficult and which relate to the ethics of conducting these trials.

Chairman: Lord Moser, and I think this has to be the last question on this matter.

Q55 Lord Moser: Chairman, thank you. My question follows directly on Lord Trefgarne’s comment. There is an insoluble problem here, which is this. That we are all in favour of clinical trials, obviously, and the Minister made that very clear in her opening, so there is no problem there. We are all very concerned about the ethical issues which you have answered. As you will know, these have been around in relation to clinical trials—and I am a statistician—with adults, which is why clinical trials are in trouble worldwide. With children the ethical issues are even more concerning to us. Supposing we follow the ethical issues—and I am with Baroness Neuberger on this—to the hilt, that would actually undermine the clinical trials; this is the problem. Because the one word which has not been used in this discussion is the word “random”, and the whole point of clinical trials is randomness, that is the only point, and I worry that the pharmaceutical industry in particular would get away with clinical trials which are not randomised clinical trials. So if you believe in randomised clinical trials as the essence of experimentation that means that the more children that have the option—and we are talking about children—and have more good reasons for opting out because they do not want to be in them, that undermines randomness which undermines the
strength of the clinical trials, and I think this is an insoluble problem.

Jane Kennedy: Which is what we are seeking to resolve!

Lord Moser: If you allow a lot of kids not to take part for the best possible reason, then that undermines the randomness; it is as simple as that.

Q56 Chairman: I understand entirely the point, and I am sure that the Minister does too, the point that Lord Moser is making, but I think when we are stating that things are insoluble we have got to the stage where we should move on. I can see that whoever is going to draft these guidelines is going to be in considerable difficulty in satisfying the practitioners and onlookers and so on that things are right, but I think they will probably have to be left to that stage. You would like to have a final word?

Jane Kennedy: Just a final point on this because it is such an important issue. I would seek to give you the strongest reassurance that we in the government share the concern—we want to get the balance right. We want to create an environment within which clinical trials can be conducted for all of the reasons that we all agree, whilst at the same time being done in a very strong and robust ethical framework, and that is the objective. I do think that perhaps some of the detail of this will become clear in the guidelines.

Chairman: We will probably, in any final document we write, I am sure, express whatever opinion the Committee has come to on this issue, and I daresay they will be quite familiar to you and that is all we shall be able to say on the matter. I do not think we will be able to solve the problem around this table any more easily than others will be able to. We should move on and have a series now of more technical questions. Lord Dundee, I think you are going to ask about the EMEA.

Q57 Earl of Dundee: Minister, do you think that the European Medicines Agency is really the right body to oversee and coordinate the working of the regulation? And if so, will it necessarily have enough capacity to do so properly?

Jane Kennedy: We think that the EMEA has a proven track record with 10 years’ experience in overseeing and coordinating pharmaceutical legislation. It operates in close cooperation with all of the competent authorities in the Member States, and with their networks and experts. The role that the Member States will play is set out clearly in the Regulation and this has been the way that it has been done for about 40 years, so we do not believe that there should be a problem. The EMEA is funded by a mixture of state funding and fees and this work has been taken into account; this new work has been taken into account in this current budget, so as things stand at the moment I am confident.

Q58 Earl of Dundee: That appears to be satisfactory. Yet interaction between the two processes should be considered. Firstly the work of the Member States’ health services and agencies. Secondly the function of the EMEA. Are you confident that overlap and contradiction between those two processes can be avoided?

Jane Kennedy: I believe so. Member States are used to working in a harmonised way in medicines regulations across Europe; it is not a new field. The consistency of practice that we are seeking to ensure across Europe is something that we have been developing for some time. I believe that we are okay on this.

Q59 Earl of Dundee: Although, as you said, there has been good experience for 40 years nevertheless we do have a new agenda here. From this are there not some aspects arising which would threaten a competent and consistent direction between these two processes, and thus challenge them too much. Should we not guard against this?

Jane Kennedy: Not at this stage but I would want to keep it under review, as I have been interested to follow the implementation of the Clinical Trials Directive that was negotiated by predecessors. I have been very interested to follow the impact of it and I would be equally interested as this regulation goes forward to keep under review how it is working and to listen to feedback from practitioners as they work under the terms of this new directive. So I would be very interested to see how it is carried forward. So while at this moment I am satisfied that we are getting it about right I want to keep that under review and if problems develop then it is appropriate that we return to them. That is one of the reasons why you do it through guidelines so that you can go back and revisit if you find that there is a particular area that is not working as you envisaged when you originally set up the framework.

Q60 Lord Trefgarne: The Paediatrics Committee, which I think is being brought into existence specifically for the purposes of these new arrangements, needs—or at least it has been suggested it needs—a rather wider range of expertise. I wonder whether you agree with that and whether you think that any of these proposals are likely to be taken forward and do there need to be any revised arrangements to ensure that the Committee can function effectively?

Jane Kennedy: As it stands at the moment I am satisfied that we have the broadest range that we need for the Committee to conduct its work. It is going to comprise at least 31 members, of which 15 will also be members of the EMEA’s Committee on Human Medicines, the CHMP. The Committee members may be accompanied by experts in
particular areas from time to time, and as it stands—and I do not know if Dr Dunne wants to add anything to that—I think we have got it right. I accept that the Royal Pharmaceutical Society has suggested that expertise in pharmacy should be represented, but there is a broad range; you have scientific expertise that will be represented that will include the range including pharmaceutical development, paediatric medicine, general practitioners, paediatric pharmacy, paediatric pharmacology. There is quite a lot of representation there already.

Q61 Lord Trefgarne: Here am I maybe asking for more members and I now hear that it has 31 members already. A committee with 31 members tends to move slightly more slowly than others, I think. Jane Kennedy: I am sure that that will not be the case. Chairman: Clinical Trials Database, Baroness Greengross.

Q62 Baroness Greengross: I think, Minister, that you have already said that you are making this more accessible and my question is really the wording of "certain aspects". I do not know if you can qualify that at all? Jane Kennedy: Only slightly in the sense that we think there may be some parts of the data that should not be disclosed at all, and there may be other parts that should not be disclosed immediately following the trial and these will be largely for commercial confidentiality reasons. Again, the Commission will draw up guidelines on which elements of the database should be made public. Chairman: Then there is the whole question of the Supplementary Protection Certification and the market authorisation, Lord Colwyn.

Q63 Lord Colwyn: I fear it gets a little more technical now and we probably need a lot longer than an hour with you. The European Pharmaceutical Industry Organisation welcomes extension of the duration of intellectual property protection, and in fact it was called for in the 2002 G10 high level group on medicines meeting as a way of encouraging innovation. Article 36 provides for an extension limited to the Supplementary Protection Certificate. Do you not think that to be fully effective this extension should consist of an extension on all existing protection of a given product? That is, patent, SPC and regulatory data protection, which might address the circumstances where, for example, SPC protection is not available or it might expire before RDP, thus neutralising the effect. How confident are you that the Commission's proposals for a six-month extension of SPC and a ten-year data protection for off-patent medicines will give the desired incentives to the pharmaceutical registry?

That is what really worries me. Would there not be a better alternative? Would perhaps not a 12-month period send out a stronger message to the pharmaceutical industry to encourage that? Jane Kennedy: I am going to ask that Richard Carter to reply in detail to that, although I would say to Lord Trefgarne, I was horrified, I spent three years in Northern Ireland where I got used to the Army acronyms and I could not believe that the Department of Health was worse!

Q64 Chairman: Much worse! Mr Carter: I think the first thing to say about the incentives and rewards is to remind the Committee on this that this is an area which has created as much heat as it has light in the discussions both in the Council and outside it. So it is an area where any measures which are brought forward or discussed will need ultimately be such as to command the right kind of support. In that context the government’s view is that these are the right kind of measures in the sense that they are reasonable and that they are implementable and that they will command support of the Council. The idea that a longer or shorter SPC extension might be more or less of an incentive has been much debated, and I do not think I would want to comment on the more technical points about the possible conflict or overlap of intellectual property protections because I am not a patent lawyer and I am not well qualified to comment on it. I note that the written question also refers to an issue of excess profiteering and I think that profiteering was a word that my Lord Chairman used a little earlier. Again, I do not believe that we would want to comment on a judgmental word like that, but the arguments and discussions about this have taken that into account.

Q65 Lord Colwyn: I left that out of my question. Mr Carter: I noted that! We believe that they will work. There are two separate things here, obviously. The SPC extension is meant to compensate for the imposition of a requirement on the industry and that needs to be measured and proportionate. The view taken in the Council, after much discussion, which the government supports, is that a six-month extension to the SPC is measured and proportionate. The industry in its responses to public consultation has largely supported that view. The experience in the United States was that six months was an adequate reward or compensation. In relation to the Paediatric Use Marketing Authorisation, the point I make about that is that it is meant to, as it were, pull on medicines which are no longer in patent. New medicines will have to go through this gateway and therefore there is some compensation needed for the imposition of that requirement. A medicine that is out of patent does not have to have any kind of testing; there is no incentive for the people
manufacturing it to test it in this way. So you have to create the kind of incentive which is going to present an adequate reward.

Q66 Lord Colwyn: I suppose as an adult patient I would want assurances that the need for paediatric testing was not going to delay the filing of the adult trials on any drug.

Mr Carter: I think we are persuaded that that is not going to be the case. The timing of applications should make that not a problem and, in any event, there are provisions for deferrals where there might be an issue. So it ought not be a problem.

Chairman: Lord Harrison is now going to ask two questions about generic products and orphan medicinal products.

Q67 Lord Harrison: Minister, the government has a good record in helping the specialist small businesses enter into the generic product market. Can you say are satisfied as a government with the current proposals? And how do you react to the question of whether there are some Member States who perhaps want to accelerate their entry into the market, and what do you think the Council’s decision will be in on that? And in a related area of the orphan medicinal products, perhaps you can explain how the market exclusivity provisions for orphan medicinal products are supposed to work and why the government, unlike, we understand, some other Member States, apparently believes that the plan is justified, the 10 plus two making 12 units. So it is apparent that it is consistent with the Commission’s proposals but there seem to be rival positions taken up by others and I wondered if you could explain why we can justify our view and resist others?

Jane Kennedy: Again, with your permission, I am going to ask Richard to respond to that because he will know, certainly better than I do, the detail of particularly what other States are saying and what positions they are taking.

Mr Carter: I will do my best to help the Committee. On the issue around generics it is true to say that not all Member States have taken the view that the timings of the exclusivities are the best from the point of view of the entry of generics into the market, and in many ways the balance that needs to be struck is between the obvious beneficial effect of competition arriving and therefore the downward pressure on overall medicines expenditure, and the need to incentivise properly and to compensate properly the people who are carrying out the tests in the innovative sphere. The Council has by a very significant majority accepted the Commission’s view that a six-month SPC extension—and the rest of the architecture—is the right way to go. There is a minority of countries, and I believe it is Poland, Hungary, Latvia and Slovakia—and Dr Dunne is Chair of the working group and is probably more up-to-date on that than I—who have expressed reservations and who formally still maintain those reservations. The arithmetic under the Qualified Majority Voting system would not enable that block of countries to block the proposal as it is currently.

Q68 Lord Harrison: What is the kernel of their objection?

Mr Carter: It depends on which country we are talking about, but it is broadly around the speed of generics’ entry.

Q69 Lord Harrison: But you are happy with the Council Commission’s proposals?

Mr Carter: The Government has taken the view that this is the most realistic and reasonable way, which is deliverable through the European decision making-process of achieving the objective.

Q70 Lord Harrison: And on the orphan drugs?

Mr Carter: If I may, I will pass that to Dr Dunne.

Dr Dunne: There are only two Member States who have an issue with the additional period of exclusivity and those are both Member States who are concerned about rapid entry of generics into the market. The reason why it is two years and not six months—I know you have not raised that now but it has been raised before—is because orphan medicinal products, when they are granted a marketing authorisation, get 10 years of market exclusivity. Some of these are off-patent medicines so they do not always have a Supplementary Protection Certificate. So it was felt that the simplest and most workable way of giving them their incentive was to extend the period of market exclusivity. Because these are by definition small market products it was felt that extending it by six months would not be enough, so it has been extended by two years.

Q71 Lord Harrison: Who are the two Member States?

Dr Dunne: Poland and another Member State, but I cannot remember off the top of my head Latvia, I think.

Chairman: I am concerned that it is now very nearly 11 o’clock. I am going to suggest that the identification, research and experience elsewhere questions you might care to respond to by post, but if you have time the cost estimate one is one that has taxed quite a lot of us. I do not know which minute you need to leave the room, so perhaps Lord Moser could raise that matter because we are concerned about the very wide range of cost estimates that have been placed before us.
**10 November 2005**  
Rt Hon Jane Kennedy MP, Dr Julia Dunne and Mr Richard Carter

**Q72 Lord Moser:** It is simply that we are obviously very interested in the cost estimates and costs should not be that difficult. These stem from the Rand Europe operation—and all I know about them is that they are very expensive. Their ranges are between £30 and £120. My instinct is that it is probably too early to get a sensible estimate. These are not sensible estimates. Do you think we should press further or forget it for the moment?

*Jane Kennedy:* Again, I am going to ask Richard to respond to that.

*Mr Carter:* I cannot respond to the question about Rand’s fee levels because that is for the Commission, but I think the point I would like to make is that the estimates in the Regulatory Impact Assessment, which the Department supplied, are those which our own economists have made; they did not simply lift all of the Rand figures. We made some estimates of our own in relation to possible levels of expected costs. I think the only thing one can say about the uncertainty in this area is that because this is an area where we simply do not know that much about what numbers of medicines may actually come through this particular gateway and how quickly, and what their sales levels are and therefore the prices that health services will have to pay, we do not actually know anything about that at the moment. The only thing that we can do is to provide an indicative range and inevitably that must be quite a wide one.

**Chairman:** Is it something that you will be keeping on as the process itself begins to get underway?

*Mr Carter:* I think there is an important point that I perhaps should have made slightly earlier under the issue of the architecture of the incentive and reward scheme. The Council has taken the view and certainly originally it was our initiative but it has commanded almost universal support, that there should be a robust review of the economic and health impacts of the regulation as it operates, at a point whose timing has not been finally fixed but will be somewhere between six and 10 years after the start of operation of the legislation. So, yes, we will be keeping it under review and there are provisions for that review to effect changes if that becomes necessary.

*Chairman:* Colleagues we must let the Minister go now; 11 o’clock was her deadline and it is now one minute to 11 and how far she has to get in that minute and I am not quite certain.

**Q74 Lord Harrison:** In the replies that you give to the final answers, I know Baroness Gale was particularly anxious to raise the question about labelling and related to our anxieties about some of the discussion we had earlier about the appropriateness of these drugs for children, even to the point that we were worried about whether there should be some indication of children on the drug. If you are able to encompass that in your reply we would be most grateful.

*Jane Kennedy:* I would be more than happy to do that, and the other questions that we did not get time to cover. May I just say for the record that I am grateful to you for the freedoms which I have been able to involve my two closest advisers on this subject, which I felt was probably for the benefit of the Committee, as well as being informative to me too.

*Chairman:* Thank you, Minister, on behalf of the Committee. It was very good of you to come, and thank you so much for your time.

**Supplementary memorandum by the Department of Health**

**LEGISLATION IN THE UNITED STATES**

In the United States, specific legislation to encourage the performance of clinical trials in children was introduced by the “paediatric rule” and the “paediatric exclusivity” provisions adopted in 1998 and 1997 respectively.

The paediatric rule requires companies to perform paediatric studies and/or to develop paediatric formulations for new and already marketed medicinal products if the product is likely to be used in a substantial number of paediatric patients or if it would provide a meaningful therapeutic benefit to patients over existing treatments.

The paediatric exclusivity provision introduces an incentive (six months added to market exclusivity or patent protection) for companies who undertake clinical studies in the paediatric population. The incentive is granted when the studies, conducted according to a written request from the Food and Drug Administration (FDA) based on public health needs, are submitted to the FDA. The incentive is granted irrespective of whether the studies have demonstrated safety and efficacy. In addition the Act required the FDA to draw up guidelines and a list of medicines for which additional paediatric information is expected to be beneficial.
The provision was reviewed by the US Congress after three years of operation and was enshrined in the Best Pharmaceuticals for Children Act (BPCA) which became law on 4 January 2002. Under the BPCA, the FDA determines required studies and issues written requests for “on patent” products. According to the FDA it has resulted in new studies, new prescribing information and new labelling for paediatrics. The Act also:

- mandates that the FDA and the National Institutes of Health (NIH) collaborate in the study of “off-patent” and “on-patent” drugs that industry does not want to study;
- mandates public dissemination of studies conducted as result of exclusivity; and
- mandates public review of safety reporting on products granted exclusivity.

The Paediatric Research Equity Act (PREA) became law on 3 December 2003 and replicates the paediatric rule of 1998 which requires paediatric studies for certain applications. The PREA also established a paediatric advisory committee.

AUSTRALIA AND CANADA

Both Australia and Canada face the same problem of a lack of medicines licensed for use in children. Neither have an existing legislative framework despite calls from their national professional and regulatory bodies.

CANADA

In Canada no legislative action has been taken so far although the Canadian Paediatric Society issued a position statement in 2003 calling on the Canadian Government to create a comprehensive regulatory framework for medicines for children.

AUSTRALIA

The Australian Drug Evaluation Committee Report of the Working Party on the Registration of Drugs for Use in Children (1997) and the Australian Association of Paediatric Teaching Centres policy document: pharmaceuticals for children both called on the Government to bring forward legislation to create a suitable regulatory framework to ensure that medicines were developed for use in children. No legislative action has been taken so far.
Written Evidence

Memorandum by the Association of the British Pharmaceutical Industry (ABPI)

The Association of the British Pharmaceutical Industry (ABPI) represents the research-based pharmaceutical industry in the UK. It has over 70 member companies who research, develop, manufacture and supply medicines for prescription within the NHS. It also has over 20 research affiliate members who provide clinical research support to the full members.

The ABPI fully supports the overall objective of the Regulation to improve the health of European children by increasing the research, development and authorisation of medicines for use in children. In our view, there is no doubt that the regulation will lead to more licensed medicines being available for children in Europe and, as long as the six month extension to the supplementary protection certificate (Article 36) is maintained, then this will attract clinical research on children to Europe and particularly the UK. However, there are still some Member States that would like to see that period reduced but this would make Europe less competitive than the United States and certainly would not attract research. The pharmaceutical industry is a vital component of a healthy UK economy and any loss of competitiveness would be detrimental to that position. The Government in March 2004 provided an extra £100 million over 2004–08 to enhance medical research in the UK and one of the outcomes of that new money has been the development of the Medicines for Children Research Network (MCRN) as one of the specific networks of the UK Clinical Research Collaboration (UKCRC) announced by Lord Warner in June 2004. One of the key roles of the MCRN will be to provide a research network for clinical trials in children which will be required once the Regulation comes into law as part of the proposed European Research Network. The UK is at the forefront of the Research Network along with a few other Member States but will only thrive if conditions for pharmaceutical company sponsors are attractive.

Specific Comments on the Regulation

A Paediatric Investigation Plan (PIP) will be required as part of an application for a marketing authorisation of a medicine. It is the view of the ABPI that development of a medicine for use in children must not delay the development of that medicine for adults unless, of course, it has a major potential use in children. We believe that in the majority of situations, research in children should not begin until some adult data on the efficacy and safety of the medicine is available and therefore adult development will generally lead the paediatric development.

We fully support the incentivisation of research into off-patent medicines by the development of the Paediatric Use Marketing Authorisation (PUMA) and believe that this will provide opportunities for a number of companies to develop niche markets for children to the benefit of children in Europe.

Undoubtedly, long-term safety studies will be required for some medicines licensed for use in children and we believe that the UK is extremely well placed to do many of those studies because it has a comprehensive health service and is developing an electronic patient record for all of the population of England which will provide an opportunity to monitor the potential long-term effects of medicines in children.

One area of concern we do have with the Regulation is the identification of medicines with a licence for use in children. The labelling of the medicine must not be confusing and the current proposal that a “P” be used would be particularly confusing in the UK as that currently means the medicine is a pharmacy medicine ie is available over the counter rather than on prescription. Any labelling must be clear and unambiguous to enable medicines to be given to children safely.

One further concern is that the Regulation does not allow for research taking place prior to the Regulation coming into force to count for the incentives. The ABPI has consistently called for a line to be drawn in the sand to allow companies to begin their research now in the knowledge that if a PIP is completed, it will attract one of the incentives. This would provide benefit to children sooner than waiting for the Regulation to go through its full Parliamentary process.

Conclusion

There is no doubt that the Regulation will lead to more licensed medicines for children and the ABPI fully supports that. However, we believe that the increased research that will be required to provide more licensed
medicines should be attracted to Europe and particularly the UK and therefore the incentives outlined in Article 36 are essential to the whole process and must be supported. The UK Government supports that position and we hope that, whilst it holds the EU Presidency, the Regulation will move forward rapidly without major or significant changes to the ultimate benefit of children in Europe.

Supplementary written evidence by The Association of the British Pharmaceutical Industry (ABPI)

The Association of the British Pharmaceutical Industry (ABPI) welcomes the opportunity to comment on the MHRA’s consultation on the European Commission’s proposal for a regulation on medicinal products for paediatric use. The ABPI has recognised the need for legislation in this area for some time and indeed jointly published a report on “Licensing Medicines for Children” with the then British Paediatric Association in 1996. We are disappointed that by the time the legislation is in place that it will have taken six years from the time of the original Council Resolution on 14 December 2000 under the French Presidency. Nevertheless we believe that the current proposal will benefit the children of Europe by providing more licensed medicines and hopefully more paediatric research in Europe and particularly in the UK.

Our detailed comments are as follows:

Paragraph 7—there is no doubt that the proposal will improve the availability of medicines for paediatric use and we firmly believe that it will provide the necessary stimulus for the pharmaceutical industry to conduct the necessary research in Europe. However, the latter is conditional on the articles relating to rewards not being adversely amended. If Europe is seen to be less competitive than the US and soon Canada, the ABPI will find it very difficult to encourage its members to bring paediatric research to Europe and particularly the UK.

Paragraph 8—The ABPI strongly supports the proposal of an extension to the Supplementary Protection Certificate (SPC) as a minimum reward for investigating the use of a medicine in children.

Annex A

Paediatric Committee—We believe that the membership of the Committee should include someone with expertise in paediatric medicine development and that that person may work or may have worked within the pharmaceutical industry.

Paediatric Investigation Plan (PIP)—We believe that medicines are developed for children on the basis of therapeutic need.

Waivers—The ABPI supports this provision.

Deferrals—We support this provision and believe that it is highly likely to become the default position with the majority of new medicines so that some adult data will be available before testing in children begins.

Marketing Authorisation Procedures—We support this provision.

Extension of the duration of the SPC—We regret that the MHRA has reintroduced the concept of a variable incentive in this section. The ABPI has consistently pressed for a fixed incentive period of at least six months extension to the SPC in order to provide clarity to the research-based industry which will take all the risk in developing new indications for children. Furthermore, we have consistently believed that six months was the minimum time period required to attract research to Europe. We support a robust review of the incentives after 10 years.

Extended market exclusivity for orphan medicinal products—We welcome this provision.

PUMA—The ABPI supports this provision.

Identification—We support the need for identification of products that are authorised for paediatric use but the current proposal would cause great confusion in the UK and would be dangerous. One possible identifier would be a smiling face child.

Maintaining availability of paediatric medicines on the market—The ABPI supports the maintenance of the availability of paediatric medicines on the market as proposed in this new article. However it must be made clear that withdrawal could be appropriate where there is an efficacy or safety issue.

Information on the use of medicines for children—The ABPI supports the proposal to make part of the paediatric clinical trials database accessible to the public to avoid unnecessary trials in children. Furthermore we would hope that the Paediatric Committee or competent authority would search the database for previous trials as part of the review of a PIP. The industry is committed to registering new trials designed to investigate therapeutic benefit at inception on a public website already.

Inventory of Therapeutic Needs—We support this provision.
European Paediatric Clinical Trials Network—The ABPI is very supportive of the development of a European Paediatric Clinical Trials Network and indeed has publicly welcomed the development of the Medicines for Children Research Network here in the UK. However we do have reservations about whether the EMEA is the right organisation to co-ordinate the network and wonder if it would be better placed in one of the European Paediatric Societies.

Obligatory submission of completed paediatric clinical trials—The ABPI recognises that completed trials in children should be submitted to the regulatory authorities. Indeed we have encouraged our members to voluntarily provide such information to the MHRA and latterly the EMEA. However we do believe that a transitional period could have been introduced to encourage paediatric research in Europe rather than wait for the legislation to be finally put in place. There are precedents for transitional arrangements we believe that this could have and still could benefit children.

Exclusions from the current proposal—The ABPI was disappointed that the establishment of a European study programme, present in earlier drafts was excluded. We believe that this is an important area for the licensing of older medicines for paediatric use. Whilst recognising that this is likely to be included in the 7th Framework Programme, we do support those MEPs who have introduced amendments regarding these older products in the Parliamentary Committee processes.

Regulatory Impact Assessment

We would be interested in seeing the evidence for the ADR figures quoted on page 12. Certainly this does not comply with the yellow card reports for under 18s by a factor of 10.

On costs, we disagree with the estimate of £1–7 million for carrying out the necessary research. A few of our members have estimated the cost of a Paediatric Investigation Plan and estimate a figure of £20–30 million. Formulation development for children is particularly expensive. With regard to the cost of individual clinical trials in children, two of our members have provided us with data. One had a multi-national paediatric trial costing over £1 million with the UK arm costing £250k and the other provided total costs on these trials for patients ranging from 31–111 with total costs ranging from $3.1–5.6 million.

On competition assessment in paragraph 8, the figures in paragraph 1 do not make sense to us. If no company has more than 10 per cent market share, how could two have more than 20 per cent and three 50 per cent?

We hope that you find our comments helpful and constructive and we look forward to the regulation gathering pace under the UK Presidency.

October 2005

Memorandum by British Medical Association

The BMA very much welcomes the proposed legislation and, in particular welcomes the proposal for MICE—Medicines Investigation for the Children of Europe—which will support and fund research into off-license drugs.

Between 50 and 90 per cent of medicines used in paediatrics are not specifically licensed for use in children. The market for paediatric drugs is relatively small and it is notoriously difficult to recruit to studies. These disincentives to invest may necessitate an extension of patent cover.

Recent studies in the US show that in about two-thirds of labels containing paediatric information for established medicines, the information contained important new dosing/pharmacokinetic (drug absorption, elimination and distribution within and from the body), and/or safety information. Without specific studies in the paediatric population, this important information would not be available and children would continue to be more vulnerable than they need to be.

At present, doctors have little choice but to administer to children reduced dosages of adult medicines, without always knowing whether they are really effective or what the side effects may be.

It is important to make the point that this is not to say that current prescribing practices are unsafe. However, the provisions contained in this Regulation would undeniably make prescription for children much more accurate and safer. Currently, paediatricians refer to Medicines for Children—a UK paediatric formulary produced jointly by the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group, in conjunction with issued guidance. The guidance allows for prescribing to be standardised across the country and draws on a combination of experience and studies to determine the most appropriate treatment.
The British National Formulary contains some prescribing information for paediatric patients. In addition, the BMA (in partnership with the Royal Pharmaceutical Society of Great Britain, the Royal College of Paediatrics and Child Health and the Neo-natal and Paediatric Pharmacists Group) in September 2005 published the first BNF for Children, which replaces Medicines for Children and will be widely distributed to healthcare professionals across Europe. The BNFC will play a key part in the progress of the Commission’s initiative to develop more treatments for children and expand research and information in the field. For your information, attached is our press release on the publication of the BNF for Children.

The objectives of the draft EC Regulation should be met without subjecting children to unnecessary clinical trials and in full compliance with the EU Directive on clinical trials. We are encouraged that there is recognition of this in the text.

In conclusion, the BMA believes that the Commission’s proposal strikes the right balance between targeted investment in children’s health and commercial reward. We welcome the outcome of the First Reading vote on the Grosstete Report on the Commission’s proposal on 7 September 2005.

URL for the press release referred to in this letter:

11 October 2005

Memorandum by the Royal College of Nursing

With a membership of over 370,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. RCN members work in a variety of hospital and community settings in the NHS and the independent sector, including educational settings. The RCN promotes patient and nursing interests on a wide range of issues by working closely with the Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations.

We fully support the proposals aimed at improving the health of children by increasing the research, development and authorisation of medicines for use in children. In particular we are particularly pleased to see the proposed establishment of a paediatric clinical trials database and network, as well as an inventory of the therapeutic needs of children. We acknowledge and support the identification measures suggested by the UK—authorised for paediatric use rather than just the use of “P” on labels, particularly as P denotes pharmacy sales in the UK. In addition we support access to clinical trial information as denoted in Annex A.

29 September 2005

Memorandum by the Royal College of Paediatrics and Child Health

The Royal College of Paediatrics and Child Health welcomes the opportunity to submit comments on the above consultation document. The College’s response was developed following consultation with the Joint RCPCH/NPPG Medicines Committee, chaired by Mr James Wallace.

We fully support the European Commission’s proposals for a regulation on medicinal products for paediatric use.

Our detailed comments are set out below:

1. Extended Market Exclusivity for Orphan Medicinal products (chapter 5, article 37). We are unclear why orphan products should be treated differently from other products with respect to extended market exclusivity. We believe that if there is no flexibility in periods of extended exclusivity for other medicinal products then orphan products should also have a six month extension.

2. Identification (chapter 3, article 33). We agree with the UK stance on identification of paediatric products.

3. We particularly welcome the UK proposal for the addition of a new article to maintain the availability of paediatric medicines on the market.

4. Information on the use of medicines for children (chapter 6, article 40). We are disappointed that the clinical trials data base will not be accessible to the public. We support the UK view that parts (if not all) of the data base should be accessible to the public and would urge the MHRA and Government to press for as much as possible to be available for public access to prevent any unnecessary duplication of clinical trials in children.
5. European study Programme. We are very disappointed that this has been excluded from the regulation and would urge the UK to ensure that the Commission does set up such a programme through the 7th Framework programme as indicated.

12 October 2005

Memorandum by the Royal College of Physicians of Edinburgh

The Royal College of Physicians of Edinburgh is pleased to respond to the Medicines and Healthcare Products Regulatory Agency on Consultation Letter MLX 323.

Currently, a high proportion of medicines are used in paediatric practice either off-licence or in unlicensed indications. Proposals for incentives and regulatory and other measures for research which would determine the safety and efficacy of the use of many more medicines in paediatric practice must therefore be strongly welcomed, and are long overdue. The intention that medicines are developed for children based on therapeutic need rather than market forces is obviously to be supported strongly, and the proposals set out in principle and in some detail processes by which these aims can be achieved. From the industry point of view, this involves a mixture of “sticks and carrots” and how effective these would be is speculative, although some modelling and consultation has taken place. Certainly, current incentives alone have proved ineffective.

Current UK-wide initiatives are starting to address some of these issues with funding from the DoH to Liverpool and Hammersmith/Imperial, and CSO support for a Scottish CRC with nursing and administrative support in Aberdeen, Dundee, Edinburgh and Glasgow and co-ordination from Aberdeen, but this needs addressing at a European level as well, and these proposals are to be welcomed in that context.

The proposed European legislation appears to have learned some of the lessons from the paediatric rule introduced in the United States in 1997, and is framed in order to avoid some of the distortions of clinical trials that have occurred in that country as a result of the legislation. The proposed EU legislation seeks to obtain benefits from the increased interest and support from industry in extending the information on the safe and effective use of medicines relevant to children, while reducing the likelihood of trials of therapeutic agents that have large adult but limited child application. The clinical trials directive (2001/20/EC) with its encouragement and drive to increase treatment of rare conditions, particularly within phase III clinical trials, but also the current proposal to try to avoid unnecessary trials for children if possible (phase I/II) is also welcomed. The introduction of the multinational Paediatric Committee should help ensure that these principles are followed.

Specific comments on some of the proposals follow.

Paediatric Committee (Chapter 1)

Establishment of a relevant new expert committee within the EMEA is supported, and also that Article 18 should be revised to clarify that the Paediatric Committee should give its opinion on whether measures taken to adapt a formulation for paediatric use are adequate. Paediatric learned societies are to be approached to propose members of this Committee, bearing in mind that there will need to be a mix of skills, including those paediatricians with current hands-on experience of clinical trials. It must be remembered that many paediatric sub-specialists now only meet in the context of larger speciality organisations in Europe in which they have very strong and well-established paediatric assemblies. For example, this includes large European societies such as the European Respiratory Society and the European Academy of Allergy and Clinical Immunology.

Paediatric Investigation Plan (PIP) (Chapter 2)

The requirement for paediatric investigation plans to be agreed by the Paediatric Committee is to be welcomed and is of central importance to the success of legislation and need to avoid duplication of effort and unnecessary studies in children. This seeks to avoid some of the distortions that have occurred as a consequence of the legislation in the United States, where a number of expensive and time-consuming studies have been performed for therapeutic agents that have very limited application in child populations, but where there is a large adult market and where pharmaceutical companies have benefited from the six months exclusivity extension. It is important that industry includes data on the use of medicines in children when applying for marketing authorisation.
In order to ensure no unnecessary delays in initiation of important trials in children, attention will have to be given to the meeting frequency of the Committee and how to seek advice on particular specialist applications. One way of dealing with this might be for the Committee to consider formal links with relevant specialist professional societies and patient organisations in Europe, so that the Committee will have rapid access to expert opinions when trials are being considered in specialist and sub-specialist areas.

**Waivers from the Requirements/Procedures to Defer Studies in Children (Chapter 2)**

It is essential that the Paediatric Committee sees and approves, or not, applications for waivers; at the time of marketing, value for the childhood population is not always initially recognised. The role of the Paediatric Committee is also crucial in decisions about deferment of studies.

**Extension of the Duration of Supplementary Protection Certificate/Extended Market Exclusivity for Orphan Medicinal Products (Chapter 5)**

Both these proposals are supported. A balance of rewards in terms of monopoly extension, for instance, to encourage pharmaceutical companies to investigate drug use in children is supported but, in practice, how much of an incentive would a six month SPC extension be for industry? Increased safety monitoring should also be continued during these extensions. It is noted that “proportional” incentives were discussed but rejected.

**Maintaining Availability of Paediatric Medicines on the Market (Title IV, New Article)**

This is specifically welcomed, as there are significant instances of withdrawal of certain drugs or formulations where there is no alternative for children.

**Information on Use of Medicines for Children (Chapter 6)**

It would be helpful to identify what parts of paediatric clinical trials base would be accessible to the public. As a minimum, the medicines and/or formulation to be used, the age range to be studied, the indication and the main outcomes being assessed should be available.

**Inventory of Therapeutic Needs (Chapter 6)**

How are the surveys of existing users of medicines in Europe to be performed? Would this be by sales, in which case companies would be expected to provide these, or by dispensed prescriptions, information that may be available in many Member States, or other means? Would this be left up to Member States to decide? There are significant costs involved in any of these methods of ascertaining current uses of medicines for children of different ages.

**European Paediatric Clinical Trials Network/Obligatory Submission of Completed Paediatric Clinical Trials (Chapter 6)**

Although the EMEA would have a co-ordinating role and supporting budget, the establishment of a truly functional network across Europe would require significant investment along the lines of that recently agreed in the UK as part of the clinical research consortium. This would clearly be up to Member States to identify how this would be achieved. Could the example of the UK be provided as a model? This is also relevant to Article 44 and the apparent exclusion of a requirement to fund studies of off-patent medicines in children from earlier drafts of the legislation. In this latter context, mention of the seventh framework programme without explicit provision for such trial support is no guarantee that paediatric networks would be established, and that trials of off-patent medicines where there is no industry interest would be forthcoming. Why was the proposed programme to fund studies into off-patent medicines removed? It would certainly be highly desirable to establish a European paediatric study programme to fund studies into the paediatric use of generic/offset patent medicines which are, of course, widely used in paediatric practice and it is unfortunate that this is not included in the current proposals.

It seems as though public accessibility to parts of the paediatric clinical trials database has also been excluded. Accessibility to information which is not commercially or scientifically confidential should be supported.
SUMMARY

The proposals appear to be highly advantageous to children in the long term, ensuring that medicines in children in the future will be evaluated to the highest level for safety, quality and efficacy. However, where drugs have an established use off-licence, and where that use has been shown to be effective and safe, availability for children should continue. Establishment of a European paediatric study programme to fund studies into the paediatric use of generic/ off-patent medicines should be supported.

17 August 2005

Memorandum by the Royal Pharmaceutical Society of Great Britain (RPSGB)

The Royal Pharmaceutical Society of Great Britain (RPSGB) is the professional and regulatory body for pharmacists in England, Scotland and Wales. It also regulates pharmacy technicians on a voluntary basis, which is expected to become statutory regulation under anticipated legislation.

The primary objectives of the Society are to lead, regulate, develop and represent the profession of pharmacy.

The Society leads and supports the development of the profession within the context of the public benefit. This includes the advancement of science, practice, education and knowledge in pharmacy. In addition, it promotes the profession’s policies and views to a range of external stakeholders in a number of different forums.

The Society has responsibility for a wide range of functions that combine to assure competence and fitness to practise. These include controlled entry into the profession, education, registration, setting and enforcing professional standards, promoting good practice, providing support for improvement, dealing with poor performance, dealing with misconduct and removal from the register.

For some time now the RPSGB has been concerned about the position on medicinal products for paediatric use. We have recently, in conjunction with the BMA, published the British National Formulary for Children.

I understand that a decision has not been taken at this stage about whether a full inquiry will be held. A full inquiry would be supported by the RPSGB and should it proceed we would be happy to compile detailed evidence to assist this important work. The Society has access to a broad range of specialist expertise within its membership and would welcome the opportunity to undertake this work in the public interest.

The involvement of a number of stakeholders in pharmacy will be essential. This work could have important implications for the safety of children and the development of medicines for use with children across Europe.

Thank you for the opportunity of commenting, at this stage, on this proposal.

12 October 2005

Correspondence between the Chairman of the Select Committee on the European Union and the Department of Health

Letter from Lord Grenfell to Rt Hon Lord Warner dated 9 December 2004


Your Explanatory Memorandum dated 8 November was considered by Sub-Committee G on 8 December.

We are grateful to you for giving us an early opportunity of examining these important and complex proposals, which clearly require much more work before a considered view can be formed of their merits.

We acknowledge the purpose and potential benefits of these proposals. But, bearing in mind the traditional resistance on ethical grounds to conducting clinical trials in children acknowledged in your Explanatory Memorandum, we will want to be sure that the right balance will be struck between ethical considerations and practical advantages.

We note that the Commission’s Extended Impact Assessment admits the difficulty of making a balanced estimate of costs and benefits, while your own initial Regulatory Impact Assessment has only been able to produce some very broad estimates, which your Departmental economists are currently endeavouring to refine.
We assume that the results of that further consideration, and of the consultations with the pharmaceutical industry which the Department propose to carry out in the New Year, will be incorporated in a final Regulatory Impact Assessment. We would be glad to know when we might expect to see that Assessment, and whether your consultations will take account not only of the views of the industry but also those of the medical profession and other interested parties.

We also note that the Government consider that Article 95 is an inappropriate legal base for the proposed regulation and that Article 308 would be more appropriate. But it is not clear to us what is meant by your statement that Law Officers have taken a view on the line which the UK should take in future on proposals which the UK supports for policy reasons, even though the Government consider that they have the wrong legal base.

You should know that this Committee has been very concerned about other instances where the Government has supported proposals which it regards as otherwise worthwhile despite having reservations about the legal base proposed. Our 2004 Annual Report records our view that the Government should stand firm in pursuing examples of an inappropriate legal base.

We would therefore be grateful if you would explain precisely what is meant by the description of the Law Advisers' view in your Explanatory Memorandum, and what action the Government proposes to take to assert their position on the inappropriateness of the legal base with the Commission and other Member States. We would also be glad to know whether the Commission have given any explanation for their reasons for proposing to use Article 95, rather than what the Government would consider a more appropriate Article.

We also consider that more could have been done to consult the medical profession; and query whether this apparent lack of consultation is in anyway linked to the reliance on Article 95.

We would also welcome a report on the general policy discussion on these proposals which we understand from your officials is expected at the December meeting of the Employment, Social Policy, Health, and Consumer Affairs Council and to know how negotiations on these proposals are planned to proceed.

In the meantime, we will retain this document under scrutiny.

I am copying this letter to Jimmy Hood, MP, Chairman of the House of Commons European Scrutiny Committee, Dorian Gerhold, Clerk to the Commons Committee, Michael Carpenter, Legal Adviser to the Committee, Les Saunders (Cabinet Office), Mark Grey (DoH) and Caroline Brennan (Medicines and Healthcare Products Regulatory Agency).

Letter from Rt Hon Jane Kennedy to Lord Grenfell dated 11 July 2005

I am writing to update you on developments in negotiations on the European Commission’s proposals for a Regulation on medicines for paediatric use and also to respond to the points you raised in your letter of 9 December 2004 to Lord Warner.

As you know, the UK has been supportive of the European Commission’s efforts to develop a legislative framework to address the current lack of medicines available specifically for use in children and considers that the Commission’s proposal for a Regulation will be key to addressing this situation.

Considerable progress has been made in negotiations on the dossier during the Luxembourg Presidency. The proposal was discussed at the Health Council on 3 June 2005. The European Parliament will be voting on the dossier in plenary in September 2005. The Commission has indicated that the Regulation is likely to come into force in late 2006, at the earliest.

The proposed provision (Article 36 of the draft Regulation) to grant an extension of six months to the supplementary protection certificate (SPC) for investigating the use of a medicine in children—in effect, extending the patent holders’ monopoly on the product by six months—has been the most contentious aspect of the proposal as it impacts on the health budgets of Member States. At the Health Council on 3 June, most Member States including the UK, Germany and France indicated their support for the Commission’s proposal for a fixed six months extension of SPC. Slovenia, Poland, Latvia, Hungary and Slovakia indicated that they favoured a shorter period of SPC extension given the strength of the generics market in their countries. In earlier discussions, the UK put forward an alternative proposal which linked SPC extension to sales as we believed this would be fairer to products with a low volume of sales and avoid excessive profits for “blockbuster” products. There was, however, little support from other Member States for this proposal and we were unable to find a workable way of implementing such a mechanism given that it would have to be implemented in 25 Member States. We did, however, press for a review of the economic impact of the Regulation at 10 years and this has been agreed. The dossier will be given priority during the UK Presidency and our aim is to make significant progress in negotiations in the Council.

I would like to respond in turn to the points you raised in your letter to Lord Warner of 9 December 2004.
**Ethical Concerns**

In your letter, you mentioned that there has traditionally been resistance to conducting clinical trials in children on ethical grounds and that you would want to be sure that the proposal strikes the right balance between ethical considerations and practical advantages. Ethical concerns about conducting clinical trials in children have to be balanced by the ethical issues related to giving medicines to a population in which they have not been tested (estimates suggest that more than half of all medicines currently used to treat children have not been tested or authorised for use in children). It is our view that the proposal effectively takes account of ethical concerns. A key objective of the proposal is to increase the information available on the use of medicines for children. To achieve this objective, it is proposed to build on the database established under the Clinical Trials Directive (2001/20/EC) to include all ongoing and completed paediatric studies conducted in the Community and in third countries. In addition, we have argued that in the interests of transparency, parts of the clinical trials database should be accessible to the public. This was discussed at the Health Council on 3 June where the Commission argued against making parts of the database publicly accessible on grounds of commercial confidentiality. The Luxembourg Presidency subsequently called on the Commission and the Council Legal Service to clarify the legal and technical requirements for amending Article 40 in order to increase public access to data concerning paediatric studies. This is an issue that we will need to take forward during the Presidency.

The proposal also contains a provision to allow for studies to be deferred when it is considered that studies in children would be more appropriate after initial experience on the use of a product in adults has been obtained. These provisions will help to avoid unnecessary clinical trials in children. Further ethical safeguards are provided in the existing European Clinical Trials Directive (2001/20/EC).

**Legal Base**

It is the UK’s view that Article 95 EC is not appropriate for measures which establish a centralised EC procedure or body and we have raised our objections with the European Commission and in negotiations. Article 95 EC is concerned with the harmonisation of national law. Setting up bodies or procedures at the Community level does not in itself amount to the harmonisation of national law because it is outside the scope of national law. It is not something that any national legislator can do. The European Commission’s view is that Article 95 EC is the appropriate legal basis for achieving the aims set out in Article 14 of the Treaty, which includes the free movement of goods, in this case medicinal products.

This issue has arisen before and the UK has mounted a legal challenge to two Regulations based on Article 95 EC. The measures in question are Regulation (EC) No. 2065/2003 of the European Parliament and of the Council of 10 November 2003 on smoke flavourings used or intended for use in or on foods (Case C-66/04 UK v Council and Parliament) and Regulation (EC) No. 460/2004 of the European Parliament and of the Council of 10 March 2004 establishing the European Network and Information Security Agency (Case C-217/04 UK v Council and Parliament). Until these cases are resolved, the UK will continue to register concerns about the inappropriate use of Article 95 EC. In this situation, we would enter a minute statement recording our disagreement with the legal base. This would not prejudice the UK’s approach to future challenges under Article 95 EC. More broadly, the UK Presidency will work with partners to help ensure that measures are adopted using legitimate and appropriate legal bases.

**Consultation**

The European Commission consulted extensively, including with health professionals, patient representatives and the pharmaceutical industry on informal draft proposals in February 2002 and in March 2004. In addition, in 2002, the Medicines Control Agency, now the Medicines and Healthcare products Regulatory Agency (MHRA), co-ordinated a UK response to the consultation involving a wide range of stakeholders, including the medical profession, in the process. In the UK, meetings have taken place with a range of stakeholder groups, including patient representatives, the Royal Colleges, medical charities and the pharmaceutical industries to discuss the Commission proposal. On 25 May 2005, the MHRA issued a consultation document on the Commission proposal. The document was circulated to a range of interested organisations and is also available on the MHRA’s website at www.mhra.gov.uk/inforesources/publications/mix323.doc. Responses were invited by 17 August 2005. Once the consultation is concluded, we will finalise the regulatory impact assessment for the proposal. A copy of the consultation document is attached for information.
To ensure the Committee is kept abreast of progress with this dossier, I will write again after the recess. In the meantime, if there are any further queries related to the proposal, please do not hesitate to contact my officials at the MHRA or the DH.

I am writing in similar terms to the Chairman of the Commons European Scrutiny Committee, and copying my letter to the clerks of both committees, Les Saunders at the Cabinet Office and Mark Grey, DH Scrutiny Co-ordinator.

Letter from Lord Grenfell to Rt Hon Jane Kennedy dated 21 July 2005

Thank you for your letter dated 11 July which was considered by Sub-Committee G on 20 July. We are grateful to you for reporting on the progress made thus far in consideration of the Commission’s proposal.

Before dealing with details, I must reiterate the importance we attach to the ethical aspects of this proposal. We will want to weigh up the ethical considerations fully in the round before final Council decisions are needed.

As we see it, three of the key ethical considerations raised by this proposal involve the retention of patent rights, the use of drugs on children and, related to that, clinical trials in children.

In my letter dated 9 December 2004 to Lord Warner I said we would want to be sure that the right balance will be struck between ethical considerations and practical advantages. I should perhaps have made clear in saying so that the over-riding priority in our view must be the health and welfare of the children concerned. With that in mind, we think it is important to understand what you mean when you say that the proposal “effectively” takes account of ethical concerns and would welcome clarification.

We note from your letter that the consideration of ethical concerns will depend to some extent on the clarification requested by the Luxembourg Presidency from the Commission and the Council Legal Service regarding public access to data concerning paediatric studies. We look forward to learning the outcome.

Your letter also mentions the provision to allow for studies on children to be deferred until initial experience of using the product concerned on adults has been evaluated. Your letter says that this will help to avoid unnecessary clinical trials on children. But your EM stated that this procedure would “ensure that medicines are tested in children only when it is safe to do so”. These two definitions do not seem to us to be entirely consistent. The former depends critically on what is meant by “unnecessary” and how it would be interpreted.

It is not clear from your letter whether other Member States have supported this aspect of the proposal or whether more work needs to be done on it during the UK Presidency. In any case, we would want to ensure that satisfactory safeguards governed this procedure and would be grateful if you could explain how it is intended to work in practice.

Your letter adds that further ethical safeguards are provided in the existing European Clinical Trials Directive. We would be grateful if you would explain more fully what is meant by that statement.

We have tried to follow your description of the Government’s attempts to find a workable solution to the contentious proposal to grant a six-month extension to the Supplementary Protection Certificate for investigating the use of medicines in children. You say that the UK alternative proposal failed to gain acceptance, although a review of the economic impact after 10 years was agreed. We would not regard that as an adequate fallback.

On the other hand, you say that this will be given priority during the UK Presidency when you aim to make significant progress in negotiations, which would imply that the UK might still be able to resolve the impasse between the views of Member States. Here again your clarification would be appreciated.

We also note what you say about the UK view that Article 95 is not an appropriate legal base for this proposal. We recall that your EM stated that Article 308, which requires unanimity, would be more appropriate. We note that parallel legal challenges have already been mounted by the Government on two other proposals to base regulations on Article 95 and that the Government will continue to register concerns about the inappropriate use of Article 95, including in this particular case, in the meantime.

We reiterate our view that the Government should take a firm line in opposing any proposals to adopt an inappropriate legal base, whatever the other merits of the proposal might be. We trust that the Government will continue to press the Commission on this point, as well as striving to persuade other Member States to
support that line in this particular case. We look forward to your further report on progress made on this important aspect.

We are glad to note the extent to which consultation has already been undertaken by the Commission and look forward to seeing the results of the MHRA consultation incorporated in the promised Regulatory Impact Assessment (RIA) as soon as it is available. We trust that this will include consultation with the medical profession, as recommended in my letter dated 9 December 2004.

We look forward to receiving the progress report which you have promised to let us have after the Summer Recess and hope that will cover the above points as well as developments in Working Group negotiations and in the European Parliament. We will continue to retain the document under scrutiny in the meantime, pending that report and your RIA.

I am copying this letter to Jimmy Hood, MP, Chairman of the House of Commons European Scrutiny Committee, Dorian Gerhold, Clerk to the Commons Committee, Michael Carpenter, Legal Adviser to the Committee, Les Saunders (Cabinet Office), Mark Grey (DoH) and Caroline Brennan (Medicines and Healthcare Products Regulatory Agency).

Letter from Rt Hon Jane Kennedy to Lord Grenfell dated 24 September 2005

Thank you for your response to my letter of 11 July about the European Commission’s proposal for a regulation on medicines for paediatric use. I am writing to respond to the specific points that the committee raised, and to update you on progress in negotiations.

Firstly, given the specific concerns outlined in your letter, I thought it would be helpful to provide further background information and reassurance on the ethical framework that now applies to the conduct of clinical trials in the UK and the rest of the EU, and how this will apply to the conduct of trials involving children. The committee will be aware that the Commission’s proposal was developed to address the current situation whereby more than 50 per cent of the medicines used to treat children in Europe have not been tested or authorised for specific use in children. The proposal builds on and is consistent with the existing European regulatory framework which exists for medicines.

The Clinical Trials Directive (2001/20/EC) and ethical considerations

The Clinical Trials Directive (implemented in the UK from 1 May 2004) requires all clinical trials to be designed, conducted and reported in accordance with good clinical practice (GCP). This ensures that the rights, safety and well-being of participants are protected and that the results of the trials are credible. The Directive also requires that all medicines used in trials must comply with good manufacturing practice. MHRA inspects against these standards and has powers to enforce them.

The Clinical Trials Directive also, most importantly, sets out the requirements for obtaining agreement from an ethics committee for every trial that is conducted in a Member State. This requirement will therefore also apply to UK trials conducted in compliance with the paediatric Regulation. In the recitals to the paediatric Regulation, there is a specific cross reference to the Clinical Trials Directive, making it clear that the controls and monitoring of studies in children conducted in the EU must comply with that Directive. Article 1 of the paediatric Regulation also states that the development of medicinal products to meet the needs of the paediatric population must be conducted in compliance with the Clinical Trials Directive. This is what was meant in my earlier letter, when saying that the proposal “effectively” takes account of ethical concerns. The Clinical Trial Directive also provides, in the body of the provisions, additional protection for minors (persons under 16 years). In particular (Article 4) it sets out specific restrictions that require:

- the ethics committee considering the trial must either have relevant paediatric expertise or take advice on questions relating to the protocol from persons involved in the relevant field of paediatric care;
- a person with parental responsibility or a legal representative must give informed consent and may withdraw the minor from the trial at any time;
- the explicit wish of the minor to refuse participation or to be withdrawn from a clinical trial at any time must be considered; and
— there must be no incentives or financial inducements to take part in the trial, except compensation.

In relation to the minor:
— staff with experience with young persons must inform him/her of the risks and benefits of the trial according to his capacity to understand;
— the investigator must consider his/her explicit wish to participate or to be withdrawn from the trial at any time;
— the clinical trial must relate directly to an illness from which he/she suffers or that can only be carried out on minors;
— the trial must aim to provide some direct benefit for the group of patients involved; and
— the interests of the patient must always prevail over those of science and society.

In relation to the trial itself:
— the clinical trial must be designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the developmental stage of the child.

These points are particularly relevant to the concerns raised by the committee—with which the Government strongly agrees—that the health and welfare of children must be the over-riding priority in conducting paediatric trials, and to provide reassurance that unnecessary trials would not be accepted by an ethics committee. In response to your question about the position of other Member States in relation to this specific point, I can confirm that all Member States share our view that it is important that the legislative provisions are tightly drawn in this respect.

The committee will also recall that the paediatric Regulation provides additional safeguards; the paediatric committee, which will include EU health professionals from relevant paediatric disciplines, is required, in reviewing paediatric investigation plans, to waive the requirement to conduct trials if there is evidence showing any of the following:
— the specific medicinal product or class of medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population;
— the disease or condition for which the specific medicinal product or class of product is intended occurs only in adult populations (Alzheimer’s disease, for example); and
— the specific product does not represent a significant therapeutic benefit over existing treatments for paediatric patients (in this situation the paediatric committee may decide that as an appropriate product already exists there would be no significant therapeutic benefit to be gained from undertaking clinical trials to test product).

If the paediatric committee comes to a judgement that a waiver should be granted such that clinical trials/studies on a specific product should not take place on any one of the grounds specified above, there will be no financial or other incentive to conduct paediatric development work on that product.

In addition, sometimes studies in children will be more appropriate when there exists some initial experience on the use of a product in adults or studies in children might take longer than studies in adults. To deal with these situations, a system of deferrals is proposed along with a procedure for agreeing them with the paediatric committee.

The paediatric committee will also carefully consider the timing of any trials in children. For example, if there was uncertainty based on trials in adults as to whether a product is safe or effective in children or if a product looks likely not to complete development in trials in adults. There are also agreed international guidelines which cover the timing of the conduct of trials in the paediatric population in relation to trials conducted in the adult population. In July 2000, a guideline (ICH El 1) was developed and agreed by the International Conference on Harmonisation (ICH). ICH develops harmonised guidelines on regulatory requirements for medicines which apply in the EU, Japan and the United States. In the United States, specific legislation to encourage clinical trials in children was introduced from 1997. The Commission’s proposal draws on experience gained in the United States. Under the Commission’s proposal, there would be a requirement for studies undertaken under the US regime to be submitted to the European regulatory authorities; thereby reducing participation of children in further trials.

Both the waiver and deferral aspects of the proposal have the full support of the Member States and no modifications have been suggested during the EU discussions so far. As is the practice with European pharmaceutical legislation, the details of how the procedure will operate, will be set out in implementing texts drawn up by the Commission in consultation with the Member States. These will include the scientific and other criteria to be considered when agreeing the conditions of a deferral.
On the proposal that data included in the paediatric clinical trials database should be accessible to the public, we continue to press our view that certain aspects of the database should be publicly accessible and there is significant support from other Member States. In their proposal, the Commission had proposed that the database would not be accessible to the general public. Currently the database established under the Clinical Trials Directive is not publicly accessible (it is proposed to build on this database to include paediatric clinical trials). However, the Commission has now changed its policy on this following the support from the Member States and a European Parliament amendment on transparency of the database. It may, therefore, be possible to include in the paediatric Regulation a requirement to make data on paediatric clinical trials publicly accessible. This has yet to be clarified with the Commission. We will also want to ensure that the proposal for public accessibility is consistent with current personal data protection legislation and there may also be technical issues to address, in relation to the level of transparency of some data but not of others.

In addition, in order to provide healthcare professionals and patients with information about the use of a medicine in children and as a transparency measure, it is proposed that information regarding the results of studies in children (whether positive or negative) would be included in product information. Information on the status of paediatric investigation plans, waivers and deferrals would also be included in product information. It is also proposed that when all of the measures in the paediatric investigation plan have been complied with, this would be recorded in the product’s marketing authorisation.

The committee also raised a concern about the retention of patent rights. The Regulation as drafted preserves all current patent rights, and aims to provide an appropriate extension of such rights (an extension to the supplementary protection certificate—SPC—which protects the product from generic competition for an additional six months) when the required trials have taken place. Further explanation of the SPC/patent provision is at Annex A.

**UK Position on the Proposal for SPC Extension**

The committee has noted that we have revised our original position on the SPC extension and commented that our current position (to support the six month extension but to seek a review of the economic impact of the rewards and incentives within 10 years) does not provide an adequate fallback. As the committee was previously advised, there was no support for the UK’s proposal for a variable SPC extension based on volume of sales of product. We needed therefore to re-examine our position with a view to finding an alternative mechanism to limit the possibility of the industry generating unreasonable profits that the NHS could ill afford. Other Member States shared the UK’s concerns over the Commission’s proposal but it did not prove possible to find an alternative regime that these Member States could support (see section which provides an update on negotiations). One of the major stumbling blocks to our alternative model is the lack of real information about the possible impact on the health budgets of Member States. Our own calculations produced wide-ranging estimates of the possible cost to the NHS in England of between £30 million and £120 million.

**Review**

The proposal to require a review of the effect of the six months SPC extension and the scope to take action if profits are excessive, has received strong support from the Member States, and we feel that this represents a real opportunity to revisit the incentives offered in this Regulation. The review is timed for “within 10 years” after introduction of the Regulation because we calculate that it will be some years before products that are eligible for the incentives will be available on the market. Until a fair number have been marketed for a reasonable time, we can not make a realistic assessment of their economic impact. In many cases the paediatric plan will not be completed until after the initial marketing authorisation has been granted. An average programme of paediatric clinical trials on a product might be expected to take 3–6 years (excluding a deferral period) from beginning to end, followed by time to complete the regulatory process (currently around a year). Unlike in the UK, there is a delay in a number of Member States in new medicines entering the market following receipt of a marketing authorisation as Governments and companies negotiate pricing and reimbursement agreements. The delay in each country varies but in some Member States this can take up to three years. In addition, the economic effect of the SPC extension will not be measurable until the end of the patent life of the product. In short, it is unlikely that there will be a significant number of products on the market, for which sufficient volume of sales data will be available until a number of years have passed following entry into force of the Regulation.

We have therefore taken the view, based on this knowledge, that to undertake the planned full review of the economic impact of the new Regulation within a maximum of 10 years would provide us with the information to accurately forecast the impact of a six month SPC extension on health budgets. The impact of the SPC
extension will be staggered as medicines will have started their patent life at different times so there should not be excessive burdens placed on health budgets during this period. That said, the committee will be aware that the original review clause in the draft Regulation remains. This requires the Commission to “publish a general report on experience acquired as a result of its (the Regulation’s) application, including, in particular a detailed inventory of all medicinal products authorised for paediatric use since its entry into force”. It therefore remains possible for Member States, on review of this report, and if the volume of products eligible for the incentives at that time appears to be more significant than we currently expect, to call for the full economic review earlier than at the end of the 10 year period. We will carefully consider this report.

Legal base

On the issue of the legal base for this proposal, I can unequivocally reassure you that the Government intends to maintain a firm line with respect to any Commission text that proposes adoption under an inappropriate legal base. As you point out, the Government has mounted parallel legal challenges on two other proposals to base legislation on Article 95 rather than Article 308 of the Treaty. The cases concerned relate to the use of a centralised authorisation procedure for smoke flavourings and the foundation of the European Network and Information Security Agency (ENISA). As Presidency we are working to achieve agreement on this dossier, while continuing to register our concerns about the proposed legal base. In negotiations we continue to register our objection to use of Article 95 for this Regulation, and Denmark and Portugal have also registered a reservation on the use of this legal base. It is still possible that other Member States will register an objection in relation to this proposal, but it is highly unlikely that there will be sufficient opposition to affect the outcome of any vote.

Update on the UK’s consultation exercise and progress in negotiations

The committee has already seen our consultation document on the proposed Regulation and the consultation closed on 17 August 2005. The document was circulated to a range of stakeholders including the medical profession and was also posted on the MHRA website. 21 responses were received, two of which made no comments on the proposals. Responses were received from a range of organisations including the Royal College of Paediatrics and Child Health, Royal College of General Practitioners, Royal College of Physicians, Royal College of Nursing, the National Patient Safety Agency, the Association of Paediatric Anaesthetists, the Royal Pharmaceutical Society, the Guild of Healthcare Pharmacists, Epilepsy Action, the Consumer Association and industry trade associations.

You will see from the summary of responses (attached at Annex B) that those respondents who provided comments welcomed the aims of the draft Regulation and some were strongly supportive of certain proposed provisions. A number of respondents indicated support for the proposed system of waivers, deferrals and the inventory of therapeutic needs. Some respondents asked for clarification of some of the proposed provisions. I attach an updated regulatory impact assessment (RIA) that reflects the feedback received from the consultation exercise.

As I mentioned in my last letter, the dossier was discussed at the Health Council in June 2005. The majority of Member States, including the UK, signalled their support for the Commission’s proposal on Article 36. Poland and Hungary subsequently circulated alternative proposals for consideration by Member States but at present there remains overwhelming majority support in the Council for the Commission’s proposal for a fixed six-month extension to the SPC. As the Regulation will be agreed by a qualified majority vote, the six-month extension to the SPC is already secure in the Council. Two Council working groups have taken place under the UK Presidency. The European Parliament (EP) voted in plenary on the proposals on 7 September 2005. The EP voted to adopt the proposals (by a significant majority), including the proposal for six-months extension to SPC. The Commission has indicated that their response to the EP’s vote will be available by late October 2005. The proposals will be discussed at the Health Council on 9 December 2005, when it is hoped that political agreement will be reached. As I have outlined previously the Government attaches significant importance to this Regulation and is committed to making progress in negotiations. I hope that the information I have provided in this letter will enable the committee to grant scrutiny clearance at this time.

I am writing in similar terms to Jimmy Hood MP, Chairman of the Commons European Scrutiny Committee, and copying my letter to the clerks of both committees, Les Saunders at the Cabinet Office and Mark Grey, DH Scrutiny Co-ordinator.
EXTENSION OF THE DURATION OF THE SUPPLEMENTARY PROTECTION CERTIFICATE (SPC)—CHAPTER 5, ARTICLE 36

Under current legislation, a supplementary protection certificate (SPC) may be granted for the patent-protected active ingredient (“product”) of a medicine. This extends protection of the product to a maximum of 15 years from the date on which the first marketing authorisation (MA) for a medicine containing the product was granted in the Community. Under the paediatrics Regulation, it is proposed that a six-month extension to the SPC would be granted for products which comply with all of the conditions included in the proposal, including submitting all of the studies conducted according to an agreed PIP. The six-month extension would take effect at the end of the original SPC period and would in effect further extend the patent protection on the product by six months. It is proposed that a statement will be included in the marketing authorisation of the product to indicate that all of the conditions have been met. Companies will be required to present the MA to the appropriate patent office who will award the SPC extension.

This is the same period of extension that applies under the US paediatric exclusivity provision.

PARTIAL REGULATORY IMPACT ASSESSMENT

Title of Proposal


1. PURPOSE AND INTENDED EFFECT OF MEASURE

(i) The objective

The overall aims of the proposal are to improve the health of the children living in Europe, by increasing high quality research into medicines to be used in children, promoting the development and authorisation of such medicines and improving the information on medicines developed for children while avoiding unnecessary studies in children and not delaying the authorisation of medicines for adults. The proposals were developed by the European Commission following extensive consultation with a range of stakeholder groups and following calls for a European regulatory solution to address the current situation.

(ii) The background

More than 50 per cent of the medicines used to treat the children of Europe have not been tested and are not authorised for use in children. In order to address this, on 29 September 2004, the European Commission adopted a proposal for a Regulation of the Council and the European Parliament on medicinal products for paediatric use. An extended impact assessment was produced by Rand Europe to support the proposal. The proposal was developed in response to a Council Resolution of December 2000 which called on the Commission to develop proposals in the form of requirements and incentives to ensure that new medicines for children and medicines already on the market are fully adapted to the specific needs of the paediatric population. The Commission consulted on informal drafts of the proposals in 2002 and in Spring 2004. The proposal will be adopted through the co-decision procedure and is expected to come into force in 2006, at the earliest.

(iii) Current situation in the UK

Increasing access to paediatric medicines which have been evaluated to the same standards of safety, quality and efficacy as those available to adults has been a concern in the UK (and the rest of Europe) for a number of years. Medicines regulation in the UK derives largely from Europe. In the UK, steps have been taken at a national level within the existing regulatory framework to produce, in the short to medium term, a measurable increase in appropriately labelled and formulated medicines for children, to increase information on paediatric use of medicines for prescribers, carers and patients and to facilitate the conduct of paediatric clinical trials. The UK has always considered that a pan-European solution is required to address the current situation and has been supportive of the Commission’s efforts to develop a legislative proposal.
(iv) The proposal

The proposal contains provisions both to require and to encourage the pharmaceutical industry to carry out the necessary research and development. The proposal aims to strike a balance between improving the availability of medicines licensed specifically for paediatric use and providing the stimulus for the pharmaceutical industry to undertake the necessary research. Some of the provisions will carry a cost for industry, for the regulatory authorities in Member States, for the European Medicines Agency (EMEA) and for the National Health Service (NHS). The proposals are wide-ranging. They take account of experience gained in the United States where legislation introduced from 1997 has aimed to address the same problem.

The key provisions contained in the proposal are:

Paediatric Committee

The proposal includes a recommendation to establish a paediatric committee within the European Medicines Agency (EMEA). The committee would be responsible primarily for the assessment and agreement of paediatric investigation plans. The committee would comprise five members of the EMEA’s Committee for Medicinal Products for Human Use (CHMP), one paediatric expert representative to be nominated by each Member State who is not represented by a CHMP member and six members to be appointed by the Commission following a public call for expressions of interest from European patient associations and paediatric learned societies.

Paediatric investigation plan (PIP)

Under the proposal, the results from a PIP would have to be submitted with all marketing authorisation applications for new medicines. The PIP would set out the studies required in all relevant paediatric age groups and would have to be agreed by the paediatric committee. The requirement would also apply to products covered by a patent or supplementary protection certificate when applications are submitted for new indications, new pharmaceutical forms and new routes of administration. This requirement will ensure that medicines are developed for children based on therapeutic need rather than market forces. There is a similar requirement in US legislation.

Waivers from the requirements

The proposal includes a provision to grant a waiver for medicines which are likely to be ineffective or unsafe in the paediatric population, for products being developed for conditions which occur only in the adult population or for products for which there is no paediatric therapeutic need. The paediatric committee would be responsible for agreeing waivers.

Procedures to defer studies in children

It is proposed that the paediatric committee would agree that the initiation of studies should be deferred when it is considered that it would be more appropriate to first obtain initial or more experience on the use of a product in adults. Again, the deferrals would be agreed by the paediatric committee.

Marketing authorisation procedures

Under the proposal, regulatory authorities would be required to check for compliance with the paediatric investigation plan, taking into account waivers and deferrals, when validating marketing authorisation applications.

Extension of the duration of the supplementary protection certificate (SPC)

It is proposed that a six-month SPC extension would be granted for products covered by a patent or SPC which comply with all of the conditions included in the proposal, including submitting all of the studies conducted according to an agreed PIP. This would effectively give the patent/SPC holder an additional six-month monopoly on sale of the product.

Extended market exclusivity for orphan medicinal product

Under the EU Orphan Regulation, medicinal products designated as orphan medicinal products (products that have been developed for the treatment of rare diseases) gain 10 years of market exclusivity when a marketing authorisation is granted in an orphan indication. It is proposed to extend the 10 year period to twelve years if the requirements for data on use in children are fully met.

Paediatric use marketing authorisation (PUMA)

In order to provide an incentive for the paediatric development of off-patent medicines, a new type of marketing authorisation is proposed- the paediatric use marketing authorisation (PUMA). This is the only incentive in the proposal for off-patent products. PUMAs would apply to paediatric use only and would attract the same data and market protection as marketing authorisations of new products. An application for a PUMA would require the submission of necessary data to establish
paediatric medicines: proposed eu regulation: evidence

safety, quality and efficacy specifically in children. In some cases a company may apply for a PUMA for a paediatric use associated with a new paediatric formulation. However, in other cases a PUMA may also be licensed for use generically in adults and used off-label for children.

Information on the use of medicines for children
A key objective of the proposal is to increase the information available on the use of medicines for children. It is proposed to build on the database established under the Clinical Trials Directive to include all ongoing and terminated paediatric studies conducted in the Community and in third countries.

Inventory of therapeutic needs
An inventory of therapeutic needs of children would be established by the paediatric committee. This would be based on a survey of existing use of medicines in Europe.

European Paediatric Clinical Trials Network
The proposal includes the establishment of a European paediatric clinical trials network. This would be managed by the EMEA, who would have a co-ordinating role. The EMEA would act as a focal point to facilitate communication and collaboration between existing networks and to act as an information point for companies looking to conduct multinational trials. There is no funding foreseen for a network infrastructure, although the EMEA will receive funds to carry out its co-ordinating role.

(v) Risk assessment
Before a medicine is authorised for use in adults it must have undergone extensive testing including pre-clinical tests and clinical trials to ensure that it is safe, of high quality and effective. In contrast, it is estimated that more than half of all medicines currently used to treat children have not been tested or authorised for use in children. The table below shows estimates of the number of children that are likely to be receiving off-label prescriptions (medicines that have not been tested or authorised for paediatric use) in England in 2002-03.

<table>
<thead>
<tr>
<th>Extent of Off-Label/Unlicensed Prescribing¹</th>
<th>Number (Annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Hospital Ward² (36 per cent—67 per cent)</td>
<td>394,000–733,000</td>
</tr>
<tr>
<td>Intensive Care (75 per cent)</td>
<td>6,000</td>
</tr>
<tr>
<td>Neonatal Intensive Care (90 per cent)</td>
<td>2,000</td>
</tr>
<tr>
<td>Outpatients³ (22 per cent—56 per cent)</td>
<td>1,374,000–3,496,000</td>
</tr>
</tbody>
</table>

Off-label prescribing in the community
In their response to our recent consultation exercise, the British Pharmacological Society indicated that most studies suggest that 20–30 per cent of all children throughout Europe receive an off-label prescription each year.

Off-label/unlicensed prescribing potentially poses significant risks such as adverse drug reactions (ADRs), ineffective treatments through under dosing and restricted access to therapeutic advances.

Currently there is little incentive for the pharmaceutical industry to conduct paediatric trials on medicines aimed primarily at the adult market. The number of children suffering specific diseases is generally lower than the number of adults, and, in terms of research, children (ie from 0-18) can not be considered a single population so studies may be more complex. Industry has also been concerned about liability, malpractice and, to a lesser extent, ethical issues. However, concerns about conducting clinical trials in children must be balanced with the ethical issues related to giving medicines to a population in which they have not been tested The current situation suggests that current incentives alone are insufficient to stimulate adequate research into and authorisation of medicines specifically for children.

Because of the current shortage of medicines licensed for use in children, healthcare professionals have been left with no alternative other than to use products off-label or use unlicensed products with the associated risks of ineffectacy and/or adverse reactions. The table below shows estimates of the number of adverse reactions by

² The number of paediatric inpatient admissions for England was obtained from the Department of Health’s Hospital Episode Statistics.
³ The number of paediatric outpatient attendances for England was obtained from the Department of Health’s Hospital Activity Statistics.
setting in England. The evidence available is limited because generally clinicians are less likely to report adverse reactions for products which have been prescribed off-label.

### Annual adverse drug reactions (ADRs) 2002–03

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric inpatients</td>
<td>11,000</td>
</tr>
<tr>
<td>Paediatric outpatients</td>
<td>20,000</td>
</tr>
</tbody>
</table>

2. **Options**

(i) *Continue to rely on existing arrangements*

The current situation demonstrates that current incentives are insufficient to stimulate the necessary research and development to increase the availability of appropriately tested medicines for use in children. In the event that this regulation is passed, UK legislation in this area derives from European law. To do nothing would risk incurring infraction proceedings from the European Commission.

(ii) *Introduce a voluntary or self-regulatory scheme*

Such a system would rely entirely on the goodwill of industry. So far, industry has been unwilling to make the investment required to authorise medicines for children in the European Union even when the data to support authorisation have already been generated as a result of the laws that currently exist in the United States. Industry is free to decide what medicines to develop. Decisions are based on potential revenue from sales balanced against the costs of research and development, manufacturing and marketing. The number of children with specific diseases is generally lower compared to adults and clinical studies in children can be complex.

(iii) *Introduce the Commission’s proposal*

Currently medicines legislation derives from Europe. It would, therefore, seem sensible to improve the availability of medicines for paediatric use across the Community via the existing pharmaceutical legislation. We have looked carefully at the proposed provisions to ensure the measures strike the right balance of costs and benefits for the National Health Service (NHS) and that the reward for industry is adequate to provide an incentive to carry out the necessary research.

(iv) *Introduce requirements for industry to undertake paediatric trials and provide no incentives*

This approach would not respond to the Council Resolution of 2000 which invited the Commission to make appropriate proposals in the form of incentives, regulatory measures or other supporting measures. In addition, requirements without incentives would risk inhibiting innovation.

4. **Benefits**

Under Options (i) and (ii) the current situation is highly unlikely to change and experience to date shows that this will not result in any significant health benefits.

Option (iv) would introduce new costs for industry and provide no incentives which could ultimately discourage industry from conducting the necessary research. There would be fewer health benefits.

**Health Benefits**

(i) The proposals should lead to significantly less off-label prescribing, and a consequential reduction in ADRs. The evidence base relates to off-label prescribing for hospital in-patient and out-patients. There is evidence of a significant amount of off-label prescribing in a community setting, but there has been no assessment that we could find, of the associated adverse reactions—this has therefore been excluded (see reference to off-label prescribing in the community under risk assessment on page 4). The proposals should also lead to a more effective use of medicines, with use of the correct dosage. Currently it is possible that there is significant underdosing in some situations leading to lack of efficacy, but there is no systematic evidence that allows us to quantify this.

(ii) The main assumptions in the assessment of the health benefits are that;
— all of the branded products identified as important for children currently on the market will be appropriately tested and have appropriate labelling changes;
— the incidence of ADRs will fall to levels associated with on-label prescribing more generally.

(iii) These are clearly somewhat optimistic assumptions, so some sensitivities are also provided. These assume an impact of less than 100 per cent—ie that the reductions in ADRs would be 50 per cent, 25 per cent or 10 per cent of the full potential impact.

(iv) In addition, we have made some assumptions about the monetary valuation of the health benefits in order to allow comparisons with costs of the proposal. We have taken Department of Transport monetary valuations of the value of mild and serious road casualties as a rough proxy for the value of reductions in ADRs that, in the literature, were similarly classified.

(v) The table below shows the estimated impact under the assumptions (with the sensitivities set out above) as they relate to England in 2002–03.

### Annual Estimated Monetary Benefit (£m)—Different Levels of severity

<table>
<thead>
<tr>
<th>Success Rate</th>
<th>100 per cent</th>
<th>50 per cent</th>
<th>25 per cent</th>
<th>10 per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients</td>
<td>274</td>
<td>137</td>
<td>68</td>
<td>27</td>
</tr>
<tr>
<td>Outpatients</td>
<td>217</td>
<td>108</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>491</strong></td>
<td><strong>245</strong></td>
<td><strong>122</strong></td>
<td><strong>49</strong></td>
</tr>
</tbody>
</table>

(vi) Grossed up to EU levels this would amount to

<table>
<thead>
<tr>
<th>Success Rate</th>
<th>100 per cent</th>
<th>50 per cent</th>
<th>25 per cent</th>
<th>10 per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients</td>
<td>3.2 (£2.2)</td>
<td>1.6 (£1.1)</td>
<td>0.8 (£0.5)</td>
<td>0.3 (£0.2)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>2.5 (£1.7)</td>
<td>1.3 (£0.9)</td>
<td>0.6 (£0.4)</td>
<td>0.3 (£0.2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5.7 (£3.9)</strong></td>
<td><strong>2.9 (£2.0)</strong></td>
<td><strong>1.4 (£1.0)</strong></td>
<td><strong>0.6 (£0.4)</strong></td>
</tr>
</tbody>
</table>

(vii) There is a considerable difference between the valuation of a serious and mild health impact. If we were to assume that all the avoided ADRs were mild. Then the likely impact would be as shown below.

### Annual Estimated Monetary Benefit (£m)—All Mild Success Rate

<table>
<thead>
<tr>
<th>Success Rate</th>
<th>100 per cent</th>
<th>50 per cent</th>
<th>25 per cent</th>
<th>10 per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients</td>
<td>119</td>
<td>60</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Outpatients</td>
<td>217</td>
<td>108</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>336</strong></td>
<td><strong>168</strong></td>
<td><strong>84</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Success Rate</th>
<th>100 per cent</th>
<th>50 per cent</th>
<th>25 per cent</th>
<th>10 per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients</td>
<td>1.4 (£1.0)</td>
<td>0.7 (£0.5)</td>
<td>0.3 (£0.2)</td>
<td>0.1 (£0.1)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>2.5 (£1.7)</td>
<td>1.3 (£0.9)</td>
<td>0.6 (£0.4)</td>
<td>0.3 (£0.2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3.9 (£2.7)</strong></td>
<td><strong>2.0 (£1.3)</strong></td>
<td><strong>1.0 (£0.7)</strong></td>
<td><strong>0.4 (£0.3)</strong></td>
</tr>
</tbody>
</table>

### Savings to hospital costs

(viii) Rand Europe\(^4\) has provided estimates of cost savings to the hospital sector if ADRs amongst children from off-label / unlicensed prescribing were eradicated. We have adjusted these estimates for various factors. The estimates below (loosely based on the Rand figures) show the estimated savings in hospital costs (at the EU level) of reducing hospital admissions to levels that might be expected if ADR rates were reduced to those

\(^4\) The company employed by the European Commission to conduct the Impact Assessment.
of on-label prescribing. Again sensitivities are shown assuming various levels of “success” of the policy—at 50 per cent, 25 per cent and 10 per cent.

### Annual estimated savings to the hospital sector—EU (m euros)

<table>
<thead>
<tr>
<th>Impact Level</th>
<th>Savings Range</th>
<th>Cost Range (£m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 per cent</td>
<td>77–277</td>
<td>(£53–£191)</td>
</tr>
<tr>
<td>50 per cent</td>
<td>39–139</td>
<td>(£27–£96)</td>
</tr>
<tr>
<td>25 per cent</td>
<td>19–69</td>
<td>(£13–£48)</td>
</tr>
<tr>
<td>10 per cent</td>
<td>8–28</td>
<td>(£6–£19)</td>
</tr>
</tbody>
</table>

(ix) Adjusting for child populations, this gives estimates for England as shown in the table below.

### Annual estimated savings to the hospital sector—England (£m)

<table>
<thead>
<tr>
<th>Impact Level</th>
<th>Savings Range</th>
<th>Costs Range (£m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 per cent</td>
<td>7–24</td>
<td>£97–£369</td>
</tr>
<tr>
<td>50 per cent</td>
<td>3–12</td>
<td>£49–£184</td>
</tr>
<tr>
<td>25 per cent</td>
<td>2–6</td>
<td>£28–£100</td>
</tr>
<tr>
<td>10 per cent</td>
<td>1–2</td>
<td>£16–£56</td>
</tr>
</tbody>
</table>

**Benefits for industry**

(x) The proposal includes a provision for a six-month extension to the SPC for products which comply with a number of conditions set out in the proposal. The Rand study estimates that this incentive would allow the innovative industry to recover the costs of testing and make a profit of between 0.8 and 9.1 m euros per product and between 63 and 205 m euros over the entire sector. The Rand study suggests that the proposed incentives, including the proposal to offer an SPC extension, would stimulate innovation and provide opportunities for both multinational companies and small and medium sized companies.

5. **Business Sectors Affected**

All sectors of the pharmaceutical industry will be affected, including the innovative and generics sectors. The pharmaceutical industry is broadly split into two sectors, the innovative industry and the generics industry. The industry employs around 73,000 in the UK and generates another 250,000 jobs in related industries. These figures have been taken from the website of the Association of the British Pharmaceutical Industry (ABPI). The ABPI estimates that the pharmaceutical industry invested £3.2 billion in UK research and development in 2003.

6. **Costs**

**Costs to the EMEA**

(i) Rand has estimated that the proposed measures will add 182 m euros (£126 million) to the EMEA’s costs for processing applications in the initial catch up period (the period when drugs currently on the market will be assessed). Thereafter, Rand estimates additional costs would be in the region of 52–17 million euros (£36–£12 million) per year.

**Costs to the research-based pharmaceutical industry**

(ii) Based on the same assumptions, on the number of new applications that would be required, and assuming costs of carrying out the necessary research of between 1 million—7 million euros, it is estimated that the costs in the catch up period would be 140 million–980 million euros (£97–£676 million), and 40 million–630 million euros (£28–£434 million) per year thereafter. We understand the Rand estimate was based on the cost of one study. For some medicines, more than one study may be required. It is, therefore, possible that these costs may be under-estimates. In our recent consultation exercise (closed on 17 August 2005), we invited the industry trade associations in the UK to provide information about the costs of conducting paediatric clinical trials. The Association of the British Pharmaceutical Industry (ABPI) estimated that the cost of a paediatric investigation plan (PIP) would be in the region of £20–30 million. In addition, the ABPI provided estimated costs for conducting individual clinical trials in children. Figures provided for a multi-national paediatric trial were over £1 million with the UK part of the trial costing £250K.
Costs to the generics sector

(iii) Generics companies will have delayed access to markets resulting from the proposal to grant six-months SPC extension for products which comply with a number of conditions set out in the proposal. Departmental economists estimate that this could cost the generics sector 34 million—410 million euros (£23–£283 million) per year in lost sales. We would not expect the SPC extension to result in fewer generic medicines. Where generic entry would be expected to occur, the SPC extension will result in a delay of six months. The British Generics Manufacturers Association did not respond to our recent consultation exercise but when we met with their representatives, they expressed a wish for a shorter SPC extension. The European Generic Medicines Association has also indicated that it does not favour the proposal to grant six-months SPC extension and argues that an extension period of three or four months would cover the costs of conducting paediatric clinical trials.

(iv) Costs to the drugs bill

The proposed six-month SPC extension would have implications for the drugs bill. Economists have estimated the drugs bill cost for England to be in the range of £30 million to £120 million per year, with a central estimate of £75 million assuming the regulations were currently in force and in steady state. It is not possible to know which products will qualify for the SPC extension, nor how much the (delayed) generic alternative would have cost.

7. Equity and Fairness

The proposal will provide reassurance that medicines used in children are safe, effective and of high quality by laying down specific requirements to:

— ensure that medicines used to treat children are subject to high quality research;
— ensure that medicines used to treat children are appropriately authorised for use in children;
— improve the information available on the use of medicines in children; and
— achieve these objectives without subjecting children to unnecessary clinical trials.

This will address an imbalance between the availability of limited medicines for children compared to adults. In addition, introducing a new regulatory framework within the European Community will ensure fairness for companies by ensuring that the standards and procedures applied in the UK are the same as in the rest of the Community.

8. Competition Assessment

Simple Competition Assessment

The UK pharmaceutical industry is broadly split into two sectors: the innovative (research and development, including biotechnology) industry and the generics industry. Around 3,000 organisations and companies exist in the pharmaceutical sector in the UK. Although there are some major players in the UK pharmaceutical industry, we consider that no single company has more than 10 per cent of the market share, no two companies have more than 20 per cent, and no three have more than 50 per cent market share. Other elements of the supply chain (ie wholesalers and pharmacies) should not be affected.

The innovative sector can be characterised by significant technological change, however, the proposed Regulation should not have any material impact on this. The pricing of products in the innovative sector will continue to be governed by the Pharmaceutical Price Regulation Scheme (PPRS) in the UK. The prices of branded prescription medicines and the profits that companies are allowed to make on their sales to the NHS are controlled by the PPRS. Under the scheme, the profits made by pharmaceutical companies from their sales to the NHS are regulated. If a company’s profits exceed its target profit, it is required to reduce its prices or make a repayment to the Department of Health. There is no guarantee that the target profit will be achieved. It is a voluntary agreement but the Health Act 1999 gives powers to impose statutory price and profit controls on those companies, which elect not to sign up to the scheme. A new five-year scheme, negotiated with the ABPI, commenced on 1 January 2005.
The proposed Regulation contains a raft of measures which includes both requirements and incentives. Generic companies will have delayed access to markets resulting from the proposal to grant six-months SPC extension for products which comply with a number of conditions set out in the proposal (an estimate of the costs to the generic sector is at 6 (iii)).

The direct costs of carrying out the necessary studies will be borne, in the main, by the innovative sector. Existing firms and new and potential firms will have to comply with the new requirements. Therefore, the setting up and on-going running costs associated with the proposed Regulation would not discriminate against new firms wishing to join the market. Both large and small firms will receive the SPC extension, contingent on compliance with the provisions laid down in the Regulation. The Commission’s proposal was developed with the principles of the European Single Market in mind.

9. Consultation with Small Business: the Small Firms’ Impact Test

Most marketing authorisations (MAs) are held by large pharmaceutical companies, although there are a number of smaller operators in the market. We have met with the industry trade associations, including the Bio Industry Association (BIA) whose members include small and medium sized enterprises operating in the bioscience sector. We invited comments from small businesses in our recent consultation exercise. We specifically invited information from small businesses on the costs associated with the proposals. One of the industry trade associations which represents small biotechnology businesses welcomed the Commission’s proposals and suggested that the proposed incentives for industry strike a balance between the obligation to conduct complex and lengthy paediatric trials and the need to stimulate innovation.

10. Enforcement and Sanctions

Certain aspects of the Regulation will be operated primarily by the EMEA and others by the regulatory authorities in the Member States.

11. Monitoring and Review

There is a commitment to review the Regulation after a specified period of time. In addition, we have made the case for a further review to take account of the economic impact of the proposals. There is strong support from Member States for a specific review of the economic impact of the proposed incentives (see 13 (viii)).

12. Consultation

(i) Within government

The Department of Health (DH) and the Medicines and Healthcare products Regulatory Agency (MHRA) are leading in negotiations on the proposal. HM Treasury, the Department of Trade and Industry and the Patent Office all have an interest in the proposal and are working together to ensure the UK’s interests are represented.

(ii) Public consultation

The European Commission consulted extensively on proposals in 2002 and in 2004. In 2002, the Medicines Control Agency (now the MHRA) co-ordinated a UK government response to the consultation. Overall, there was support for a legislative proposal.

The DH and the MHRA have organised meetings with key stakeholders, including industry, representatives of the Royal Colleges, patient organisations and charities to discuss the Commission proposal.

MHRA/DH launched a public consultation exercise on the Commission’s proposals in May 2005. The consultation period closed on 17 August 2005. The consultation document was sent to a wide range of stakeholders, including the Royal Colleges, professional associations, consumer/patient groups and the pharmaceutical industry trade associations. The document was also posted on the MHRA website. 21 responses were received. Responses were received from a range of organisations including the Royal College of Nursing, Royal College of General Practitioners, National Patient Safety Agency, the Royal Pharmaceutical Society and industry trade associations. All of those respondents who provided comments welcomed the aim of the Commission’s proposals.
13. Summary and Recommendation

Summary of costs and benefits

(i) In order to compare costs and benefits we compare the up-front costs with the benefits that would occur after all in patent drugs currently on the market have been tested and have completed the relevant processes. The assumption is that the up-front costs relate to the catch up period, after which only new products are required to go through this process. After this catch up period has been completed, we assume that the current stock of in patent drugs that are of clinical significance for children will have been tested and appropriate labelling changes will have been made, and the health benefits associated with this will then flow.

(ii) The table below shows a summary of the costs and benefits identified above.

<table>
<thead>
<tr>
<th>Costs and benefits EU (million euros)</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Benefits</td>
<td>391</td>
<td>5,708</td>
</tr>
<tr>
<td>Savings in hospital Costs</td>
<td>8</td>
<td>277</td>
</tr>
<tr>
<td>Total Annual Benefit</td>
<td>399</td>
<td>5,985</td>
</tr>
<tr>
<td>Up Front Costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMEA</td>
<td>182</td>
<td>182</td>
</tr>
<tr>
<td>Originator Industry</td>
<td>140</td>
<td>980</td>
</tr>
<tr>
<td>Total Up Front Costs</td>
<td>322</td>
<td>1,162</td>
</tr>
</tbody>
</table>

In some cases the costs and the benefits cannot be attributed to individual Member States. For example, the EMEA costs will be borne by the European Commission and, though ultimately may impact on the UK, the UK share cannot be readily estimated. Also, costs and benefits to the industry are also difficult to attribute to Member States as these will be borne by multi-national companies, and we have little idea of what the UK share would be. For this reason, the table above focuses on costs and benefits at the EU level. However, estimates for England are shown in the text where we have been able to calculate these.

(iii) The results show that, even if we take the worst case scenarios where only 10 per cent of the potential benefit is achieved and all avoided ADRs are valued as mild (a benefit of 399 million euros), and taking the upper range of the costs (at £1,162), it would take only three years of benefit in order for the benefits to outweigh the upfront costs. We would normally assess the benefits over a much longer period (say 10 to 20 years) so; on this basis we can conclude that the proposal is likely to be cost effective.

(iv) Strictly speaking, as the benefits occur later than the costs these should be discounted (to take account of the fact that future benefits are worth less than present benefits) and net present values calculated. Assuming the benefits will occur three years after the costs have been incurred and that the benefits will flow for a further 7 years (a 10 year period overall), the net present value of the lowest estimate of annual benefit is in the region of 4.3bn euros—three times as high as the up-front costs.

(v) It should be remembered that the assessment of the benefits is based on the evidence found in the literature. We could not find evidence on the extent of ADRs resulting from off-label prescribing in the community, and though this is thought to be much lower (in proportional terms) than in a hospital setting, they are nevertheless likely to be significant. Hence, the assessment of the benefits is likely to be on the cautious side.

(vi) The method adopted above does not examine the steady state situation—ie where all drugs currently on the market that need to be tested have been tested, and only new drugs will have to go through this process. However, the broad assumption is that, if the proposal is expected to be cost-effective in the “catch up” period, it is likely to be cost effective in the steady state also.

5 Takes the scenarios of 10 per cent success and values all avoided ADRs at the Dept of Transport “mild” rate.
6 Assumes 100 per cent success and uses the split of mild and severe as documented in the literature.
7 A conservative assumption to take account of regulatory lag.
8 Using the standard discount rate applicable to health benefits of 1.5 per cent.
(vii) Finally, the assessment above has been carried out on the basis of resource costs. However, the analysis shows that the proposal has considerable public expenditure implications. Extension of effective patent life could result in extra costs to health service payers estimated to be in the region of 308 million to 1,231 million euros per year for the EU as a whole. In an England context, this could amount to £30–£120 million in extra drugs expenditure, depending on the price differential between brands and generics.

**Review**

(viii) Negotiations on the proposals are currently taking place in Europe in the Council working group. It has been proposed to build into the Regulation a review of the impact of the proposed incentives and the scope to take action if profits are excessive. The review would take place within 10 years after introduction of the Regulation. We believe 10 years would be required in order to make a robust assessment of the economic impact given it will take some time for new medicines to come on to the market.

**14. Declaration**

I have read the regulatory impact assessment and I am satisfied that the benefits justify the costs.

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<th>Organisation</th>
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<tbody>
<tr>
<td>1.</td>
<td>British Association of Dermatologists</td>
<td>2 June 2005</td>
<td>No comments to make on the proposals.</td>
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<tr>
<td>2.</td>
<td>Royal College of Surgeons, Faculty of Dental Surgery</td>
<td>2 June 2005</td>
<td>No comments to make on the proposals.</td>
</tr>
<tr>
<td>3.</td>
<td>Royal College of Physicians and Surgeons of Glasgow</td>
<td>3 June 2005</td>
<td>Is strongly supportive of the aims of the proposed Regulation to more closely regulate and investigate medicines used in children.</td>
</tr>
<tr>
<td>4.</td>
<td>Epilepsy Action</td>
<td>30 June 2005</td>
<td>Is supportive of the proposals. Believes the proposals are thorough, well balanced and can only be of benefit to children with epilepsy.</td>
</tr>
<tr>
<td>5.</td>
<td>Royal College of Nursing</td>
<td>25 July 2005</td>
<td>Is fully supportive of the proposals. In particular, welcomes the proposed paediatric clinical trials database and network, as well as the proposed inventory of therapeutic needs. Supports the UK’s position on identification (in that “P” would not be appropriate in the UK) and the UK’s position on public access to information about clinical trials.</td>
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<td>7.</td>
<td>The Association of Paediatric Anaesthetists</td>
<td>13 August 2005</td>
<td>Is strongly supportive of the Commission’s proposals. Believes the proposals strike the right balance of requirements and incentives. Welcomes the proposed European paediatric clinical trials network. Overall, considers the proposals seem likely to achieve the objective of improving paediatric health in Europe by increasing the availability of appropriately tested, authorised and labelled medicines.</td>
</tr>
<tr>
<td>8.</td>
<td>Pharmaceutical Society of Northern Ireland</td>
<td>17 August 2005</td>
<td>PSNI welcomes the proposals. Suggests the proposed European paediatric clinical trials network is timely given a national network is currently being developed in the UK but suggests care must be taken to avoid duplication of effort by both networks. Suggests that off-patent medicines are commonly used off-label and envisages that use of off-patent medicines will increase under the proposals for PUMAs. Careful co-ordination will be required to avoid unnecessary repetition of clinical trials in children. Supports the UK’s position on identification and use of the letter “P”. Suggests that “authorised for paediatric use” has the potential for confusion given some medicines may be suitable for use in older infants and children but may not be safe and effective for use in neonates. Suggests the use of abbreviation “SPC” is confusing given this is widely used to indicate summary of product characteristics. Is strongly supportive of the proposal to establish funding streams to facilitate research.</td>
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paediatric medicines:
proposed eu regulation: evidence

Annex B

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<td>9</td>
<td>Jane Lamprill Paediatric Research Consultant</td>
<td>17 August 2005</td>
<td>Suggests there is a critical need to bring the general public and patient groups on board. Most parents don’t realise that their children may be receiving medicines that are untested in the paediatric population. Suggests regulators sometimes request inappropriate tests and do not plan and prioritise for the needs of the individual trial participant. Communications between the Paediatric Committee and the regulatory authorities will need to be clear. Testing medicines in children must be conducted to the highest ethical standards or companies will run the risk of being accused of using children as “guinea pigs” to make money even though children will ultimately benefit from safer, more effective medicines. Those involved in conducting trials, including ethics committees, must be seen to be “squeaky clean” in terms of the processes employed for informed consent. As well as compliance with the Clinical Trials Directive, the provisions contained in the proposal should also comply with ICH E11 guidelines. Marketing authorisation procedures Suggests retrospective data should be allowed in order to prevent unnecessary testing of medicines in children. Identification Suggests a pictogram of a child would be better than the proposed “P”. SPC extension Suggests six-month SPC extension may not be enough to cover research costs except in the case of blockbusters, suggests nine months. Paediatric clinical trials network European funding must be provided for the establishment of the network. Labelling The proposed labelling changes must be made mandatory. Labelling changes are not mandatory under the US legislation; this is no help to healthcare professionals.</td>
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<td>10</td>
<td>Royal College of General Practitioners</td>
<td>15 August 2005</td>
<td>Welcomes the proposals. Suggests the proposals will result in benefits for children as well as clinicians (the increased availability of medicines authorised for paediatric use will reduce the current burden on clinicians currently using unlicensed medicines). Raised specific concerns/queries as follows: — there is a potential danger that increasing legislation may delay the release of beneficial medicines onto the market; — there is likely to be a considerable period of time between introduction of the legislation and introduction of new medicines authorised for specific use in children; — believes the proposed database should be accessible to the public in view of recent concerns about concealed trials and SSRIs in children; — believes the Paediatric Committee should receive regular reports on progress of the studies it approves; — studies that have not been approved should not be allowed to be pursued outside the European Community; — supports the proposal to require industry to include data on the use of medicines in children when submitting a marketing authorisation application; — suggests it would be useful to introduce a mechanism to encourage clinicians to submit data when using key medicines in children in order to build an information base; — questions whether companies would get the proposed rewards even if the medicine shows no benefits in children and suggests this could provide a perverse incentive for companies to test for paediatric effects even when the likelihood or benefit or need is low;</td>
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<td></td>
<td>Drug Safety Research Unit</td>
<td>17 August 2005</td>
<td>Response focuses on post-authorisation monitoring of medicines (Articles 34 &amp; 35). Suggests that even in the best clinical development programmes there is under representation of children so the information available about the use of the medicines in children when a marketing authorisation is granted will be limited. Suggests post-authorisation monitoring is important given the range of different age groups of children and because clinical trials are unlikely to cover all age ranges. Agrees with the proposals contained in Articles 34 &amp; 35. Acknowledges that there is limited information available on the use of medicines in children. Prescription Event Monitoring (PEM) studies the use of newly marketed medicines prescribed by GPs in England, suggests this information could usefully be added to the information obtained from paediatric clinical trials. Suggests it will be important to pool information and suggests PEM studies could inform the discussions in relation to the proposed system for waivers and deferrals under the proposed Regulation. The Drug Safety Research Unit conducts studies on behalf of PEM.</td>
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<tr>
<td></td>
<td>ABPI</td>
<td>17 August 2005</td>
<td>The ABPI is disappointed that it has taken so long for the Commission’s proposals to materialise but believes the proposals will benefit the children of Europe. Believes there is no doubt that the proposals will improve the availability of medicines for paediatric use and that the proposed incentives will provide the stimulus for industry to conduct the necessary research in Europe so long as the incentives (as currently drafted) remain. If Europe is seen to be less competitive than the US, it will be difficult to encourage industry to bring paediatric research to Europe. ABPI strongly supports the proposal to offer an SPC extension of six months and a robust review of the proposed incentives after 10 years. Paediatric Committee Suggests that the membership should include someone with expertise in paediatric medicine development and that should not exclude individuals who work in industry or may have done so in the past. Waivers and deferrals Supports the proposed provision for waivers. On deferrals, supports the proposal and believes this is likely to become the default position with the majority of new medicines so that some adult data will be available before testing in children begins. Marketing authorisation procedures Supports this provision. PUMA Supports this provision.</td>
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<td>13.</td>
<td>Guild of Healthcare Pharmacists</td>
<td>17 August 2005</td>
<td>Supports this provision, the voluntary approach has not worked to date.</td>
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<td><strong>Identification</strong></td>
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<td>Supports the need for identification of products authorised for paediatric use, agrees that the current proposal to use the letter “P” would cause confusion in the UK, suggests use of a pictorial identifier.</td>
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<td><strong>Maintaining availability of paediatric medicines on the market (Article 35A)</strong></td>
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<td>Supports this provision but it must be made clear that withdrawal could be appropriate if there is a safety or efficacy issue.</td>
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<td><strong>Information on the use of medicines</strong></td>
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<td>Supports the proposal to make parts of the clinical trials database publicly accessible (mentions that industry is already committed to registering new trials on a publicly available website) and would hope that the Paediatric Committee or regulatory authority would search the database for previous trials when considering PIPs.</td>
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<td><strong>Inventory of therapeutic needs</strong></td>
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<td>Supports this provision.</td>
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<td><strong>Paediatric clinical trials network</strong></td>
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<td>Is very supportive but has reservations as to whether the EMEA is the appropriate organisation to co-ordinate the network. Suggests one of the European paediatric societies may be better placed.</td>
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<td><strong>Obligatory submission of completed paediatric clinical trials</strong></td>
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<td>ABPI recognises that completed trials should be submitted to the regulatory authorities but believes a transitional period should have been introduced to encourage paediatric research in Europe as opposed to waiting for the legislation to come into force.</td>
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<td><strong>European study programme</strong></td>
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<td>ABPI is disappointed that the previous proposal to establish a European study programme has been dropped. Suggests this is an important area for the licensing of older medicines and is supportive of the related amendments voted by the EP’s ENVI Committee.</td>
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<td><strong>RIA and costs</strong></td>
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<td>ABPI would be interested in seeing the evidence for the ADR figures quoted in the RIA.</td>
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<td><strong>Estimated costs for a PIP are in the order of €20-30 million (as opposed to €1-7 million estimated by Rand Europe) according to figures provided by ABPI members.</strong> Formulation development is particularly expensive.</td>
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<td>On costs for conducting clinical trials, two companies provided data to ABPI. One of the trials was multi-national; the costs were in the region of just over £1 million with the UK constituent costing £250K. The second suggested total costs of $3.1—5.6 million.</td>
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<td>Welcomes the proposals, suggests the current situation is unsatisfactory and many parents find it difficult to understand why such a situation exists and do not understand the legal implications of the use of unlicensed medicines. The GHP considers that the proposals will result in substantial benefits in terms of safe medicines for children.</td>
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<td><strong>PIPs</strong></td>
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<td>Supports this provision.</td>
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<td><strong>Waivers and deferrals</strong></td>
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<td>Supports these provisions.</td>
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### Annex B

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| 14. | Royal College of Physicians of Edinburgh | 17 August 2005 | Paediatric Committee  
Supports this provision. Suggests regulatory authorities will need to check PIPs as well as applications for waivers and deferrals to ensure compliance.  
**Maintaining availability of paediatric medicines on the market (Article 35A)**  
Supports this proposal.  
**Incentives for industry**  
Supports these provisions including the proposed six-month extension to SPC but questions whether this will be sufficient in all cases. Supports the proposal for a full review of the proposed incentives.  
**Identification**  
Agrees with the UK position on identification.  
**Inventory of therapeutic needs**  
Supports this provision.  
**Paediatric clinical trials network**  
Supports this provision.  
**Obligatory submission of completed paediatric clinical trials**  
Supports this provision.  

The Royal College supports the proposals which are long overdue and believes legislation is necessary at European level. Suggests the proposals will avoid some of the distortions that occurred in the US under the paediatric rule. Believes the proposals will be advantageous in the long term. Also suggests that off-label use should be allowed to continue for medicines that have an established off-label use with proven safety and efficacy.  
**Paediatric Committee**  
Supports this provision and the UK’s position on Article 18. Suggests that many paediatric specialists generally meet only in the context of larger European organisations/societies.  
**PIPs**  
Supports this provision and believes this will be of central importance to the success of the legislation. In order to avoid unnecessary delays in initiating important trials, attention will have to be given to the frequency of meetings of the committee. Suggests it might be useful for the committee to consider formal links with relevant specialist professional societies and patient organisations.  
**Waivers and deferrals**  
Supports these provisions.  
**Incentives for industry**  
Supports these proposals and asks how much in practice the proposed six-months SPC extension would be. Suggests that increased safety monitoring should continue during the period of extension.  
**Maintaining availability of paediatric medicines on the market (Article 35A)**  
Specifically welcomes this provision, believes there have been a significant number of cases where medicines have been withdrawn where there is no alternative available.  
**Inventory of therapeutic needs**  
Asks how the inventory of therapeutic needs would be developed and suggests there will be significant costs involved. |
Paediatric medicines: proposed EU regulation: evidence

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<tr>
<td>15.</td>
<td>British Dental Association</td>
<td>17 August 2005</td>
<td>The BDA welcomes the proposals and believes they are long overdue. Suggests incentives for industry are necessary in order to stimulate the necessary research. Believes the proposed PIP will ensure that medicines are developed for therapeutic needs rather than market forces. Accepts that in the long term the benefits will outweigh the set up and development costs.</td>
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<tr>
<td>16.</td>
<td>The Bio Industry Association</td>
<td>17 August 2005</td>
<td>The BIA supports the proposals but believes that the objectives should be achieved in a way that neither discourages innovation nor delays access to medicines in the adult population.</td>
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<td>Incentives for industry</td>
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<td>Supports the proposed provisions. Believes the proposal for a fixed six-month extension to SPC is fair and considers a variable extension would constitute a significant barrier to innovative bioscience companies to undertake research. Believes transitional measures would further stimulate paediatric research and development in Europe and suggests that paediatric studies initiated before the Regulation comes into force should fall under the Regulation. The BIA has seen the ABPI response and endorses the comments made in that response.</td>
</tr>
<tr>
<td>17.</td>
<td>Which?</td>
<td>17 August 2005</td>
<td>Which? Welcomes the proposals to improve the health of children by increasing the availability of authorised medicines and the amount of information available to patients, carers and healthcare professionals and believes the Regulation provides the opportunity to identify where the therapeutic needs of children are not being met.</td>
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**Paediatric Committee**

Welcomes the proposal to include patient representatives on the PC, suggests the number of places to be allocated to patient and public interests should be fixed (perhaps three). Welcomes the proposed strict conflict of interests policy.

**PIPs**

Welcomes this provision and is reassured that the plan will take account of different paediatric age groups. Suggests the proposals do not address the question of the necessity and ethics of paediatric trials of medicines that perform an identical or similar therapeutic role as a medicine already on the market.

**Incentives for industry**

Believes incentives are appropriate but is concerned about the impact of the proposed incentives on the generics market. Suggests the proposed incentives will need to be reviewed.

**Identification**

Supports the UK position on the use of the letter “P”. However, Which? has concerns about the implications of the absence of such a statement on a product and believes clarity is required particularly for medicines where use in children is not supported by evidence collected by a PIP.
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| 18 | British Pharmacological Society       | 17 August 2005| Suggests the proposals are generally sound and laudable. Believes the proposals to defer studies in children are sensible and suggests it would be reasonable to extend this approach to currently used medicines where there is significant knowledge available about their use. Suggests the extent of off-label use of medicines in the community has not been considered in the RIA, states that most studies suggest 20–30% of all children in Europe receive off-label medicines in the community each year. Believes the proposed database should be publicly accessible. Raises reservations as follows:
  — asks whether all medicines currently used in children are to undergo trials in children. Suggests this would be unnecessary and would subject children to unnecessary risk. Suggests expert advisory committees should be established to produce consensus guidelines for medicines used in children;
  — asks for clarification as to what procedures will be established for medicines which have no apparent paediatric use when developed, but which later develop a use in children for a new indication;
  — suggests it would be preferable for European advisory committees to assess commonly used agents and to recommend which should be available for use in children. Suggests this approach would negate the need for expensive studies in children that might add little to current knowledge; and
  — asks what the outcome would be for healthcare professional who prescribe medicines not authorised specifically for use in children. |
| 19 | National Patient Safety Agency        | 16 August 2005| The NPSA welcomes the Commission’s proposals and specifically supports the proposed provisions which establish:
  — the paediatric committee;
  — a requirement for industry to include in marketing authorisation applications data on the use of the medicine in children;
  — a requirement to increase the information available on the paediatric use of medicines, including whether or not such use is authorised;
  — a system of waivers and deferrals;
  — identification requirements; |

Clinical trials database
Welcomes this provision but strongly believes the database should be publicly accessible.

Inventory of therapeutic needs
Welcomes this provision but with provisos. Suggests the emphasis should be on developing medicines that could offer genuine therapeutic advantages rather than competing with established authorised medicines. Believes the proposal to base the inventory on current use of medicines does not necessarily equate to an understanding of the current therapeutic needs of children. The inventory should not be based on industry’s perception of need.

Obligatory submission of completed paediatric clinical trials
Welcomes this provision and believes the trial details and data should be made publicly available in the interests of openness and in order to provide further information about the appropriate use of medicines in children. Which? would be interested to know more about the sanctions that would apply for companies who fail to comply.
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<td>— increased safety monitoring for medicines in children; and the requirement for industry to submit information about existing completed studies in children.</td>
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<td>Suggests that more information is required about the proposed inventory of therapeutic needs. Emphasises the importance of ensuring that formulation, labelling and packaging needs of children are addressed as part of this process.</td>
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<td>Is concerned that the proposed incentives will be insufficient to encourage the development of paediatric formulations of established medicines. Suggests MHRA should work pro-actively with the NHS to identify existing medicines of this type and seek to actively commission work to enable the development of standard strengths and formulations for these products.</td>
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<td>Suggests that a reduction in adverse drug reactions is a better measure of benefit than “a reduction in off-label prescribing” and is willing to share information held about paediatric adverse reactions. Is unclear what is being proposed for marketing authorisation applications made to the MHRA and would support similar measures being adopted by MHRA.</td>
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<td>20. The Royal Pharmaceutical Society</td>
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<td>Paediatric Committee</td>
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<td>Suggests expertise in pharmacy must be included and the Neonatal and Paediatric Pharmacists Group should be included as a paediatric learned society.</td>
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<td>Waivers and deferrals</td>
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<td>Supports these provisions.</td>
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<td>SPC extension</td>
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<td>Extensions should only be granted for studies that result in information for the treatment of children.</td>
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<td>PUMA</td>
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<td>Suggests this provision should be used to provide an incentive to develop suitable paediatric formulations for off-patent medicines.</td>
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<td>Supports the UK position on the use of “P”.</td>
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<td>Maintaining availability of paediatric medicines on the market (Article 35A)</td>
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<td>Is strongly supportive. Suggests the impact of discontinuation of products should not be underestimated.</td>
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<td>Agrees that parts of the proposed database should be publicly accessible.</td>
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<td>21. Royal College of Paediatrics and Child Health</td>
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<td>Is fully supportive of the Commission’s proposals. Raises specific points as follows:</td>
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<td>Orphan products</td>
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<td>Believes orphan products should not be treated differently to other products, the six months SPC extension should apply.</td>
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<td>Supports the UK position on identification.</td>
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<td>Maintaining availability of paediatric medicines on the market (Article 35A)</td>
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<td>Particularly welcomes this proposal.</td>
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Letter from Lord Grenfell to Rt Hon Jane Kennedy dated 20 October 2005

Thank you for your letter dated 24 September which was considered by Sub-Committee G on 13 October and again on 20 October.

We are grateful to you for such a thorough response and for letting us have your updated partial Regulatory Impact Assessment and the summary of the results of the MHRA Consultation. All these have been carefully considered.

As we have already explained to your officials, however, the Sub-Committee decided that this Proposal raised sufficiently important issues to warrant carrying out a short Inquiry by gathering a selection of views from interested parties. Having considered those views, the Sub-Committee have decided to invite Professor Sir Cyril Chantler, the President of the Great Ormond Street Hospital NHS Trust, to give oral evidence about the Proposal at a public session on Thursday 27 October at 10am in Committee Room 4. Your officials are, of course, welcome to attend that session if they wish.

We note from your letter that you hope to secure political agreement on the Proposal at the Health Council on 9 December and have asked for scrutiny to be lifted in time for that. Nevertheless, the Sub-Committee hope that you would be able to help them in completing their short Inquiry by giving oral evidence about the Proposal in the usual way. If a mutually convenient date and time can be found for this early enough in November it should still be possible to reach a decision on your request for scrutiny clearance in sufficient time for the Council meeting. We will be in touch with your officials in the hope that this can be arranged.

I am copying this letter to Jimmy Hood, MP, Chairman of the House of Commons European Scrutiny Committee, Dorian Gerhold, Clerk to the Commons Committee, Michael Carpenter, Legal Adviser to the Committee, Les Saunders (Cabinet Office), Mark Grey (DoH) and Caroline Brennan (Medicines and Healthcare Products Regulatory Agency).

Letter from Rt Hon Jane Kennedy to Lord Grenfell dated 12 November 2005

Thank you for giving me the opportunity to provide evidence about the European Commission’s proposal for a Regulation this morning. I promised to provide answers to the questions which were not reached during the oral evidence session this morning.

IDENTIFICATION/LABELLING

The committee will be aware that the original Commission proposal included a provision that medicinal products that were authorised through the Paediatrics Regulation would display a “P” on the product label. During the discussions in the Council working group it became clear that a number of Member States, including the UK, could not accept a “P” for different reasons. The current position agreed in the Council working group, which is in line with a European Parliament amendment, is that there will be a European symbol on the package label of all medicines authorised for paediatric use. The symbol will be selected by the paediatric committee within one year of the Regulation coming into force. The meaning of the symbol will be explained in the package leaflet. The symbol will be abstract, will not indicate a particular age group and there will be one symbol only. We do not believe that there is a danger of over-simplification.
RESEARCH

Under the proposals, the European Medicines Agency (EMEA) would act as a focal point to facilitate communication and collaboration between existing networks (such as the UK Clinical Research Collaboration paediatric clinical trials network) and act as an information point for pharmaceutical companies looking to conduct multinational trials. The proposed network will not affect the individual integrity of the existing national networks. It should help to disseminate good practice and communicate information on upcoming and ongoing trials. We are supportive this approach, The EMEA will receive the necessary funding to carry out its co-ordinating role.

The committee asked about the Medicines Investigation for the Children of Europe (MICE) research programme. This specific programme was mentioned in earlier informal draft proposals but not in the formal proposals adopted by the Commission in September 2004. There is, however, a proposal for funding for research into the paediatric use of off-patent medicines through the Community’s research framework programmes.

We believe there is indeed a need for such funding for research into the paediatric use of off-patent medicines and that this can be achieved through the Community’s research framework programmes.

EXPERIENCE ELSEWHERE

The committee asked about the legislation in place in the United States and my officials have already provided a summary note. The patent protection incentive (6 months) offered in the US is the same as that proposed under the European Regulation. However, there are some differences. In the US, a company is awarded an extra six months patent protection if it submits studies carried out according to a written request issued by the Food and Drugs Administration (FDA) based on public, health needs. The written request does not usually cover all appropriate age groups and formulations. Under the European proposals, a company would be awarded an extra six months patent protection if:

— it submits all studies contained in an agreed paediatric investigation plan (PIP);
— the PIP covers all appropriate paediatric age groups and formulations;
— the studies have been assessed and the appropriate information on paediatric use incorporated into the product information; and
— the product has been placed on the market in all Member States.

Both Australia and Canada face the same problem of a lack of medicines licensed for use in children. Neither have an existing legislative framework despite calls from their national professional and regulatory bodies.

I hope this information is helpful. I would like to re-iterate the point I made this morning about the importance the Government attaches to this proposal. We believe the proposal is long awaited and we hope to contribute to its progress by reaching political agreement under the UK Presidency at the Health Council next month. I hope the committee is able to grant scrutiny clearance on the proposal as soon as possible.

Letter from Lord Grenfell to Rt Hon Jane Kennedy dated 18 November 2005

We are grateful to you and your officials for the helpful oral evidence given to Sub-Committee G on 10 November, as well as for the very thorough reply in your letter dated 24 September. We are also grateful to you for supplying a summary of the consultation on this Proposal carried out by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Thank you, too, for your latest letter dated 12 November which supplies answers to the questions on Identification/Labelling, Research and Experience in other Countries, which were not fully covered in the oral evidence session.

We have also seen a copy of your letter dated 12 November to Jimmy Hood about the progress made in recent Council Working Group meetings, on which you touched in your oral evidence.

The next step is for Sub-Committee G to prepare and consider a draft Report on this short Inquiry and submit that to the Select Committee for approval and publication. We intend to do so as soon as possible, but that process is bound to take a few more weeks.
But we are aware that the Government is very anxious for scrutiny to be lifted in time to secure the expected “political agreement” at the Health Council meeting on 9 December and you have asked whether it might be possible to do so before the COREPER meeting which will consider the Proposal on 24 November.

It would be unusual to lift the scrutiny reserve in advance of the normal process of publishing an Inquiry Report. In this case, we have given very careful consideration to your request in the light of your own evidence and that given in the selected sample given to the Committee, as well as the results of the MHRA consultation. We have taken particular note of the assurances you have given us, especially about the protection of the health, welfare and rights of any children involved in paediatric testing. We have also taken account of the overwhelming weight of professional opinion we have seen and heard which broadly supports the Proposal and is anxious to see it implemented as soon as possible. We also have considered the indications of broad support from industry representatives in our evidence and the MHRA consultation and we have noted the endorsement of the European Parliament.

Ideally, we would have preferred to have spent more time considering this Proposal in greater depth. But, in view of your assurances, the evidence we have been given and the widely-felt need to move forward in the interests of children, we would be willing exceptionally to grant your request to lift scrutiny at this stage so long as you would be prepared to address the three principal outstanding concerns set out in the following paragraphs in the way that we propose.

Clinical Trials Database

Firstly, we understand from your oral evidence that the Commission has already made some concession over access to the Clinical Trials Database. But, from what was said in that evidence and from the report in your letter dated 12 November to Jimmy Hood it is not entirely clear what degree or other conditions of access the Commission are now proposing. Regrettably it appears to be less than the firm and unequivocal commitment to full access which the Committee would wish to see. We must therefore ask the Government to press for clarification of the Commission’s position at or before the Council meeting and to support the case for full access to the database vigorously at the Council meeting and in subsequent discussion of the guidelines.

Guidelines

Secondly, you will know from what was said at the oral evidence session that we continue to have some doubts about the adequacy of the ethical safeguards over the consent of minors to trials. Despite what you say in your letter dated 12 November, we also remain deeply concerned from the evidence we have had whether the proposed arrangements for labelling and identification of products, and for providing information on their suitability for use with widely-differing groups of children, will be a sufficient guarantee of safe practice.

We accept that the practical implementation of these and other important aspects of the safe and ethically-acceptable implementation of the Regulation will largely be determined by the guidelines which have yet to be worked out. We wish to keep that activity under review and therefore request that your officials should provide appropriate on-the-record briefing to the Committee in due course on the progress made in developing those guidelines.

Incentive Arrangements and Review Procedure

Thirdly, we must register our concern over the uncertainties surrounding the incentive arrangements proposed through the Supplementary Protection Certificate, the Paediatric Use Marketing Authorisation and the special provisions for orphan medicinal products. We have taken careful note of what you, your officials and others have said about those proposals. But we find ourselves unable to judge from the information we have been given whether those arrangements are likely to provide the necessary incentives to industry, whether they are likely to equitable and proportionate or whether they may give rise to excessive profits, penalise the health services of Member States or create unacceptable disadvantages for the manufacturers of generic products.

We were disappointed with the inadequacy of the costs estimates produced in your Partial Regulatory Impact Assessment (PRIA) and hope that the Department will continue to try to refine more reliable figures when the final RIA comes to be produced. But we accept to some extent the difficulties in doing so reliably in the circumstances and acknowledge that it may be some years before a clear picture will emerge of how well these arrangements are working.

For all these reasons, we welcome and attach great importance to the Government’s efforts in pressing for a full economic review of these proposals as soon as feasible. We look to the Government in its Presidency capacity to focus attention on this aspect at the Council meeting and to secure a firm and unambiguous
commitment from the Commission that either such a review should form part of the general report required by Article 49 within six years of implementation or that the Commission should be required to explain clearly to the satisfaction of the Council why it would be premature to do so at that stage and to ensure that is undertaken as soon as possible after that.

We are also anxious to ensure that the Commission’s six-year review will contain a full evaluation of all other aspects of the working of the Regulation. We would expect that review to be subjected to rigorous Parliamentary scrutiny.

**Scrutiny Reserve**

On receipt of your confirmation that you would be prepared to agree to proceed as proposed above, we would be willing to release scrutiny forthwith in the hope that the expected “political clearance” can be reached at the Council meeting as you have outlined. Should it not be possible to secure “political clearance” on the terms you have outlined we would expect scrutiny to be resumed.

We hope you will find this helpful. Naturally, we would expect you to report on the outcome of the December Council meeting and would ask you to set out in that report how you see the remaining steps leading to implementation if the expected “political agreement” is secured.

I should also make clear that, even if the scrutiny reserve is lifted as proposed above, we cannot guarantee that on such an important issue, with potentially far-reaching consequences for the welfare of children and with so many uncertainties inherent in the nature of the Proposal, a debate in the House may not be called for on publication of our Report.

**Legal Base**

Our other conclusions and recommendations on the proposed Regulation will be contained in our Report and we will look forward to the Government’s response to that. But we promised to let you have some further observations on the legal base. We note what you say in your letter dated 24 September and would be glad to know whether any further progress has been made on this important question in Working Group discussions or elsewhere in the meantime and how you propose to deal with it at the December Council meeting.

The Department’s original Explanatory Memorandum, dated 8 November 2004, and your letter dated 11 July both said that Article 95 would not be appropriate for measures which established a centralised EC procedure or body. In this case, the centralised body is the proposed Paediatric Committee, which would function under the aegis of the European Medicines Agency (EMEA). But it appears that the Government have not challenged the use of Article 95 as the legal base for the EMEA itself under Regulation 726/2004. We find this surprising and seemingly inconsistent with the challenges which you mention the Government is making in several other cases. We would welcome an explanation.

I am copying this letter to Jimmy Hood, MP, Chairman of the House of Commons European Scrutiny Committee, Simon Patrick, Clerk to the Commons Committee, Michael Carpenter, Legal Adviser to the Committee, Les Saunders (Cabinet Office), Mark Grey (DoH) and Caroline Brennan (Medicines and Healthcare Products Regulatory Agency).

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**Letter from Rt Hon Jane Kennedy to Lord Grenfell dated 22 November 2005**

I am writing in response to your letter of 18 November 2005. I am pleased to see that the Committee has agreed to grant scrutiny clearance at this time subject to our acceptance of the conditions that you have outlined in your letter. I can confirm that the conditions are acceptable. The issues for which you have sought reassurance are issues that are also important to the Government.

On the economic review of the Regulation, the Committee will be aware that the UK pressed hard in negotiations for a robust review of the incentives proposed under the Regulation. At this stage there is agreement that within six years of the Regulation entering into force the Commission will publish a general report on the operation of the Regulation as well as a detailed inventory of all medicinal products authorised for paediatric use under the Regulation. A full economic analysis of the incentives will be undertaken at six years provided there are sufficient data available at that time. If not, the full economic analysis will be undertaken within 10 years of the Regulation coming into force.
On the proposed paediatric clinical trials database, there is currently agreement in the Council working group that it will be for Member States, the European Medicines Agency (EMEA) and other interested parties to agree what parts of the database will be accessible to the public. The Council’s view is, that at the very least, the results of all paediatric trials, whether terminated prematurely or not should be publicly accessible. The Government believes this is a very positive development.

On the legal base issue, the Government’s view is that Article 95 of the Treaty is not an appropriate legal basis for this Regulation and that Article 308 should have been used instead for the reasons invoked in two cases brought by the UK before the Court of Justice of the European Communities (C-66/04 and C-217/04).

While we are strongly supportive of the content of the proposal on policy grounds, we intend to record our disagreement that Article 95 is an appropriate legal base for this measure in a minute statement at the Council.

While we await the outcome of the two UK challenges in the European Court of Justice, the Government believes that it would not be desirable to oppose every measure which uses Article 95 in this way and where we support the underlying policy. The Government intends to vote in support of the proposal at the Council on 9 December 2005.

A reply will follow separately about the query you have raised in relation to Regulation 726/2004.

I am copying my letter to the clerks of both scrutiny committees, Les Saunders at the Cabinet Office and Mark Grey, DH Scrutiny Co-ordinator.

Letter from Lord Grenfell to Rt Hon Jane Kennedy dated 25 November 2005

Thank you for your letter dated 22 November which was considered by Sub-Committee G on 24 November.

We are pleased that you have accepted the conditions outlined in my letter dated 18 November on which the Committee would exceptionally be prepared to grant scrutiny clearance. You may therefore take it that scrutiny clearance has now been lifted, so far as we are concerned, on that understanding. We welcome your reaffirmation that these issues are important to the Government.

What you say about the economic review of the Regulation is also noted. We continue to expect that the Commission’s review will also make a thorough evaluation of all aspects of the working of the Regulation.

We are glad to learn that the Council believe that the results of all paediatric trials, whether terminated prematurely or not, should be publicly accessible on the paediatric clinical trials database. We look to the UK Presidency to ensure that clear and firm agreement is secured on this at the Council meeting.

In due course we will want to agree with your officials when it would be appropriate for them to provide the agreed on-the-record briefing on progress in developing the guidelines, as also requested in my letter.

We also note what you say about the legal base and look forward to your response on the further comments about that made in my letter.

We will now proceed to prepare our Inquiry Report and will send you a copy in due course.

We also look forward to your report on the outcome of the December Council meeting.

I am copying my letter to the clerks of both scrutiny committees, Les Saunders at the Cabinet Office and Mark Grey, DH Scrutiny Co-ordinator.

Letter from Rt Hon Jane Kennedy MP to Lord Grenfell dated 14 December 2005

In my letter of 22 November 2005, I promised to reply separately about the query you raised in relation to our position on Regulation 726/2004. I can confirm that the Government raised objections to the use of Article 95 for this measure.

At the time we had concerns about the use of Article 95 as the legal base for fundamental changes that we believed required use of Article 308 of the Treaty. At the Council of Ministers meeting in June 2003 (when political agreement was secured), the Government voted in favour of the agreed package on policy grounds, but submitted a statement with a number of other Member States to highlight our concerns about the use of Article 95 for the Regulation. In December 2003 when Member States agreed the final compromise package, we also submitted a minute statement to register our objection to the proposed legal base.

I am copying my letter to the clerks of both scrutiny committees, Les Saunders at the Cabinet Office and Mark Grey, DH Scrutiny Co-ordinator.
Letter from the Government to Lord Grenfell dated 11 January 2006

I wrote to you at the start of the UK Presidency of the European Union to let you know about the programme of events that was planned and to update you on our priorities. I set out our plans for two main themes—patient safety and health inequalities, as well as the formal Council work to agree legislation and to set strategic policy direction. This note provides an end of term report on what has been achieved.

Legislation
The UK Presidency has made good progress on the legislative proposals currently on the table. We reached a political agreement amongst the 25 EU Health Ministers on the proposal on paediatric medicines. The paediatric medicines proposal provides incentives to the pharmaceutical industry to carry out better testing and will help significantly to improve the safety of healthcare given to children.

We are also pleased to have successfully taken forward the work under the Luxembourg Presidency on a set of proposals for food legislation designed to improve the information available to consumers about their food. These proposals can now move to the next stage of the negotiation with the European Parliament.

Presidency Themes
On health inequalities, we have been pleased to see a growing consensus around the need to ensure that the forthcoming EU alcohol harm strategy includes a focus on the marketing and promotion of alcohol to young people, and around the need for EU level work on diet and physical activity to address food promotion and marketing to children. Similarly encouraging was the interest generated in using the opportunity offered by next year’s negotiations to take forward the Framework Convention on Tobacco Control and focus on illicit trade of tobacco. Work was also progressed on ensuring that the evolving EU information and knowledge system includes information on the patterns and trends in health inequalities.

The work on patient safety has built on work during the preceding Luxembourg Presidency. A programme of future work has been agreed by the Member States and the Commission which will support Member States as they establish national patient safety programmes (including patient safety reporting and learning systems). Other projects that have been agreed in this area include work to bring together design experts from a range of industries to embed best thinking in systems design in patient safety, carrying out further research on patient safety as well as developing a skills and knowledge framework for patient safety education.

Setting and Influencing the Strategic Direction of Health Policy at EU Level
The UK Presidency has also been active in influencing and guiding the strategic direction for policy in a number of key health-related areas.

On Mental Health, EU Health Ministers discussed the Commission Green Paper on Mental Health that issued in October. The Green Paper sets out the links between mental health and important social challenges throughout the EU, such as alcohol and drug abuse, and the problems of discrimination against people suffering from mental illnesses.

The identification, in October, of the first cases of highly pathogenic avian flu in the European Union has prompted a significant amount of work to prepare for a possible human influenza pandemic. The Health Council has been active in addressing the human health aspects of a pandemic while pandemic influenza was the headline item at the Informal Meeting of EU Health Ministers held at the end of October. The Presidency has been working with the other Member States to identify the practical questions that would benefit from co-ordination, both in preparation for a pandemic and in managing a pandemic should one break out. These discussions, which culminated at the Health Council in December, have identified interest from the Member States in seeing a feasibility study of EU action on stockpiling anti-virals for targeted use in the event of a pandemic.

Working Together: Member States and the Commission and the Global Context
Progress in legislation and in policies was not the only objective that we set ourselves. We also set out to influence the way that EU business is managed.

We wanted to foster a strong voice for the EU in global health matters. It has been encouraging to see the extent to which the WHO has been involved in much of the work that has been taken forward, in particular, placing both health inequalities and patient safety in a global context, so that the EU work complements and
influences the WHO’s Commission on Social Determinants of Health, and the WHO World Alliance for Patient Safety. Similarly, there has been close involvement with the WHO in the work on pandemic influenza, laying the foundations for reinforced co-ordination between the Member States and the Commission.

We have also looked to promote non-regulatory ways of working. On both patient safety and health inequalities—but also in other areas such as recent proposals from the French Government for a Cancer Alliance—there has been interest from the Member States and the Commission in working together on practical projects that can release the benefits of closer co-operation across Europe without necessarily resorting to legislation as the first option. For example, it has been encouraging to see the project to get professional regulators to share information on professionals that work in different EU countries.

It is particularly welcome that the Commission has agreed to set up a new expert working group on social determinants of health inequalities, and is continuing the patient safety group. In the Council itself, the work of the UK Presidency to structure a work programme for the Health Working Group at Senior Level to take forward on the impact that the EU Treaties have on healthcare services was well received by Member States: progressing work for this Senior Level Group includes a further innovation, which is to use a group of past, current and future Presidencies to prepare future meetings.

I am writing in similar terms to the Chairman of the European Scrutiny Committee, the Chairman of the Departmental Select Committee, to the Clerks of both Scrutiny Committees, to Les Saunders, Cabinet Office European Secretariat and to Mark Grey, DH Scrutiny Co-ordinator.

Memorandum by European Federation of Pharmaceutical Industries and Associations

EFPIA VIEWS ON THE EUROPEAN COMMISSION’S PROPOSAL FOR A REGULATION ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE

A. INTRODUCTION

The European research-based pharmaceutical industry, represented by EFPIA (more: About EFPIA), is committed to playing a central role in developing and improving medicines specifically designed for children.

Children represent one fifth of the total EU population (more: children are not small adults). So far progress has been achieved in numerous paediatric therapeutic fields, thanks to medicines that provide cure or relief from many childhood diseases (more: examples of paediatric therapies). But pharmaceutical research in children presents a series of scientific, technical, practical and ethical challenges of importance (more: barriers to paediatric research).

Together with health professionals, patient and parent organisations, EU institutions, EFPIA support specific measures to be introduced at Community level to foster the research development and approval of medicines adapted to children’s use.

Against this background, EFPIA welcomed the release of the long-awaited European Commission proposal9 in September 2004 (Press release: EFPIA welcomes the Commission Proposal to Encourage Research and Development of Medicines for the Benefit of Children).

We agree with EU authorities that the current situation needs to be changed10:

— medicines regularly used to treat children’s medical problems should go through formal clinical trials specifically for paediatric use;
— the conduct of such trials must be carefully planned to protect the well-being of the young patients involved; and
— proper economic incentives also need to be set in place to make it realistic for a pharmaceutical company to undertake necessary work.

Our children must be able to benefit from medicines tailored to their special needs. This must be achieved by restoring a strong pharmaceutical research and development presence for Europe without delay.

For the sake of our children, we cannot afford to wait longer or fail.

9 Proposal for a Regulation on Medicinal Products for Paediatric Use (COM/2004/599), text available at the following address: http://dg3.eudra.org/F2/Paediatrics/index.htm
10 While all medicines used to treat children have been rigorously tested before their general use, not all of them have been authorised for use in children.
B. GENERAL BACKGROUND

The European Commission has provided information under the form of an overview and background explanation of the proposed regulation and Frequently Asked Questions.

EFPIA developed a “Q&A” in annex where you will find our responses to questions which you may have such as:

— What are the practical difficulties of conducting clinical trials in children?
— How are children participating in clinical trials recruited?
— How long does it take to conduct paediatric studies?
— Are the results of paediatric clinical trials published?
— Examples of achievements in paediatrics?

On the “patient room” section of the EFPIA website, we have identified a number of diseases that are the subject of active research and development within the research-based pharmaceutical industry. The section “Medicines for Mankind” provides an understanding of the condition, the nature of current treatments and, most importantly, the research the pharmaceutical industry is conducting to find even better medicines for the future benefit of patients, including children, both in Europe and worldwide.

C. EFPIA’S MESSAGES ON THE EUROPEAN COMMISSION’S LEGISLATIVE PROPOSAL

The research-based pharmaceutical industry subscribes to the EU health authorities’ request11: having better medicines for children must be a common, high priority goal in the improvement of Public Health for EU authorities, Member States and society in general.

For EFPIA, the EU initiative “better medicines for children in Europe” is a key opportunity to improve children’s health and for stimulating paediatric research.

EFPIA supports the European Commission proposal’s aim to:

— introduce scientific and regulatory measures to encourage the research, development and authorisation of medicines assessed for paediatric use;
— provide incentive measures to support paediatric investigations into new and older products; and
— create and support a paediatric R&D infrastructure in Europe.

The proposed measures should allow Europe to re-claim a central role in innovative drug development worldwide, and catch up with other world regions where paediatric research has been given effective means to meet the needs of the patient population. Europe cannot just stand and wait for research to be conducted in other regions (eg, the US) and eventually benefit children in the EU.

EFPIA stresses that the following issues must be considered:

— provisions on timing for submission of the paediatric investigation plans, and timing for submission of the paediatric results must not result in premature or unwarranted testing in children, nor delay the availability of medicines for other populations;
— incentives need to be strengthened, in support of paediatric R&D in Europe; and
— the proposal must not be a disincentive to conduct clinical studies on new medicines for children in Europe in the short term.

D. SPECIFIC POINTS UNDER CONSIDERATION

Timing of submission of paediatric results

The Commission’s proposal requires to submit the results of all studies, performed in compliance with an agreed paediatric investigation plan when filing a marketing authorisation application for a new medicinal product (Article 8). In some cases, at the discretion of the Paediatric Committee, the deadline for submission of paediatric data may be deferred to a later point (so-called “deferrals”).

11 This was already highlighted by the European Ministers of Health in a Council’s Resolution in December 2000, which invited the Commission to make proposals as soon as possible (Council Resolution on Paediatric Medicinal Products, 14 December 2000, JO C-17, 19/01/2001, p 1). The Council re-iterated its call for “incentives, regulatory measures and other supporting measures to encourage the development and marketing of paediatric medicines” in December 2003 (Council Resolution on Pharmaceuticals and Public Health Challenges—Focusing on the Patients, 2 December 2003, JO C-20, 24/01/2004, p 2).
Incentives to effectively stimulate paediatric R&D

The need for incentives is clear. In the United States, for example, specific incentive measures have significantly increased paediatric research and development activities.

In Europe, effective incentive measures are long overdue. They were requested by the European Health Council as early as the year 2000, when the Commission was invited to make proposals including appropriate incentive mechanisms as soon as possible. The G-10 High Level Group on Innovation and Provision of Medicines recommended in 2002 that Commission and Member States “put in place an effective policy in terms of incentives to research and support the development and marketing of orphan and paediatric medicines”, as a means to bolster innovation in Europe to the benefit of patients and public health. (more: G10 website).

Key elements of the European Commission proposal tabled in September 2004 are:

- a reward for studying medicines for children of six-months extension to the supplementary protection certificate (Article 36); and
- for off-patent medicines, 10-years of data protection for new studies awarded via a “Paediatric Use Marketing Authorisation” (PUMA).
- EFPIA welcomes the proposed fixed-term extension of the duration of intellectual property protection, but regrets that the proposal currently limits this extension to the Supplementary Protection Certificate (“SPC”). There are specific circumstances where for example, SPC protection is not available or where it would expire before RDP, thus neutralising the effect of a paediatric extension. To be fully effective, EFPIA recommends that the proposed incentive should consist of a fixed-term extension of the relevant protection for a given product (ie Patent, SPC or Regulatory Data Protection “RDP”, which are not cumulative rights), in return for the results of paediatric studies.
- The incentive should give a strong impetus to European paediatric research, taking into account the specificities of the European environment. Simply mirroring the US added protection period of six months would not be sufficient for allowing a paediatric research environment to emerge and develop in Europe. In order to achieve the shared and desired objective of developing better medicines for children in Europe, research-based pharmaceutical companies need a six-month fixed-term incentive as an absolute minimum, bearing in mind that the longer the term, the stronger the incentive to expand and potentially transfer additional research to the EU.

12 Except for very specific cases, sufficient data on the safety and efficacy of the medicine in adults should be generated before initiating clinical trials in children. Directive 2001/01/EC and ICH guideline E11 foresee that only limited paediatric data are available at the time of submission of the marketing authorisation application for products.


14 Back in 1998, the US introduced an incentive mechanism, allowing for six-month paediatric extension of all existing intellectual property rights. Almost 10 years later, the introduction of a strong incentive in Europe is of utmost importance, also in view of the EU goal to turn Europe into the most dynamic and competitive knowledge-based economy worldwide (Lisbon strategy). It is a well-known fact that the EU today offers a less attractive economic environment for pharmaceuticals than the US (eg differences in market access; price controls). Furthermore, the EU is lagging behind the US with respect to many measures to support pharmaceutical R&D (eg over 10 years difference in introducing supplementary protection certificates and protection of biotechnology inventions).
It should also be clear that a medicinal product shall be eligible to the incentive when the paediatric investigation plan has been completed and the results submitted after the application for marketing authorisation in compliance with a deferral granted by the Paediatric Committee.

Not hampering paediatric investigations in the immediate to short term

The measures proposed by the Commission will not come into effect before end of 2006 at the earliest.

— As such, EFPIA recommends that paediatric investigations initiated prior to entry into force of the Regulation should also be considered as part of an agreed paediatric investigation plan.