Paediatric Trials and Intellectual Property Incentives in the EU

A Report by Europe Economics for Merck Sharp and Dohme (Europe) Inc.
# TABLE OF CONTENTS

## EXECUTIVE SUMMARY

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1</td>
<td>Incentives for Paediatric Trials</td>
<td>1</td>
</tr>
<tr>
<td>1.2</td>
<td>The US Precedent and the EU</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>THE CONSEQUENCES OF LIMITED EVIDENCE SUPPORTING PAEDIATRIC MEDICINE IN THE EU</td>
<td>3</td>
</tr>
<tr>
<td>2.1</td>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>2.2</td>
<td>Why Evidence-based Medicine for Children Matters</td>
<td>3</td>
</tr>
<tr>
<td>2.3</td>
<td>Current Evidence Base for Paediatric Medicine</td>
<td>6</td>
</tr>
<tr>
<td>2.4</td>
<td>Ethical Issues with Paediatric Trials</td>
<td>9</td>
</tr>
<tr>
<td>2.5</td>
<td>Treatment Options in the Absence of Appropriate Paediatric Indications</td>
<td>12</td>
</tr>
<tr>
<td>2.6</td>
<td>Off-Label and Unlicensed Use of Medicines for Children</td>
<td>14</td>
</tr>
<tr>
<td>2.7</td>
<td>Can the Evidence Base for Paediatric Medicine in the EU be Improved?</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>INCENTIVES, PAEDIATRIC TRIALS AND PAEDIATRIC LABELLING</td>
<td>23</td>
</tr>
<tr>
<td>3.1</td>
<td>Introduction</td>
<td>23</td>
</tr>
<tr>
<td>3.2</td>
<td>Paediatric Drug Trials: the Business Decision</td>
<td>23</td>
</tr>
<tr>
<td>3.3</td>
<td>Private Benefits and Externalities</td>
<td>25</td>
</tr>
<tr>
<td>3.4</td>
<td>US Experience with Incentives</td>
<td>27</td>
</tr>
<tr>
<td>3.5</td>
<td>Incentives and Paediatric Trials in the EU: Products Already on the Market with Patents</td>
<td>35</td>
</tr>
<tr>
<td>3.6</td>
<td>Incentives and Paediatric Trials in the EU: Out-of-patent Products</td>
<td>40</td>
</tr>
<tr>
<td>3.7</td>
<td>Incentives and Paediatric Trials in the EU: Products not yet Licensed</td>
<td>44</td>
</tr>
<tr>
<td>3.8</td>
<td>Taking Account of Data Collected under the US Exclusivity Provision</td>
<td>46</td>
</tr>
<tr>
<td>3.9</td>
<td>Capacity for More Paediatric Trials in the EU</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>THE COMPETITIVENESS OF THE EU PHARMACEUTICAL INDUSTRY</td>
<td>52</td>
</tr>
<tr>
<td>4.1</td>
<td>The Evidence on Competitiveness</td>
<td>52</td>
</tr>
<tr>
<td>4.2</td>
<td>The Strength of the Market</td>
<td>53</td>
</tr>
<tr>
<td>4.3</td>
<td>The Effect on Competition</td>
<td>56</td>
</tr>
<tr>
<td>4.4</td>
<td>A Viable Research Community in Paediatrics</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>CONCLUSIONS</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>APPENDIX 1: BIBLIOGRAPHY</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>APPENDIX 2: EU HEALTH COUNCIL RESOLUTION ON PAEDIATRIC MEDICINAL PRODUCTS, 14 DECEMBER 2000</td>
<td>66</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY

1 Europe Economics was asked by Merck Sharp and Dohme (Europe) Inc. in March 2001 to produce an initial report on the options for introducing incentives to improve the availability of evidence-based drug treatments for paediatric patients in the European Union (EU).

2 This followed the December 2000 request of the EU Health Council to the Commission to bring forward as soon as possible proposals for the development of medicines for use with children.

US experience

3 The Pediatric Exclusivity Provision in Section 111 of the 1997 Food and Drug Administration Modernisation Act (FDAMA) introduced economic incentives for conducting paediatric studies in the US. A six-month extension to market exclusivity could be awarded to all the products containing a particular active substance for carrying out paediatric trials that met the terms of a Written Request received from the Food and Drug Administration (FDA).

4 The FDA's assessment is that this incentive led to a large increase in the number of paediatric product trials being carried out. Within three years, the benefits were already being felt in terms of improved guidance to doctors relating to the paediatric use of a significant number of products, with further amendments to paediatric labelling already in preparation and more to follow.

5 The FDA's Status Report to Congress on the Provision (January 2001) therefore concluded that giving incentives to pharmaceutical companies was proving effective in leading to better paediatric labelling, which would in turn lead to better treatment.

6 However, the EU is not the US. In developing and assessing a range of relevant options for the EU, this report draws on evidence from published written work and data, and from a small number of interviews with senior academic paediatricians, specialists in clinical paediatric trials, and regulatory specialists in the pharmaceutical industry.

The case for incentives

7 Leading European specialists in paediatric medicine agree that many products of potential use for children have not been subjected to paediatric trials and that there is an urgent need for more research – including clinical trials – into the suitability for use of medicines for the paediatric population, and into appropriate dosages and formulations.

8 The limited evidence base for paediatric medicine reflects post-war official restrictions on paediatric clinical trials and, for many medicines, the limited commercial returns to developing paediatric indications and formulations.
There is currently widespread off-label and unlicensed use of medicines for the paediatric population in the EU. The knowledge developed from unlicensed and off-label use is likely to remain localised, and Adverse Drug Reactions are likely to be under-reported.

The central public policy choice facing the EU is not that of “to experiment or not to experiment”: in the absence of properly regulated paediatric trials, off-label and unlicensed use represent uncontrolled experiments. Rather, the key choice is between ways of increasing the number of well-designed paediatric clinical trials to provide a better evidence base for paediatric medicine.

To provide incentives reflecting the positive externalities from the business decision to sponsor paediatric trials and develop and manufacture paediatric formulations is an appropriate course for public policy. There are potentially considerable gains to patients and to the community as whole from paediatric trials that lead to paediatric labelling for appropriate indications, in terms of better health over the short- and long-terms and savings in other medical costs.

The leading EU paediatricians we interviewed consider that where there is a need for more evidence to support better use of medicines in the paediatric population, well-designed studies can provide that evidence in ways that are ethically acceptable. Guidelines agreed through The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) reflect and consolidate the developing consensus in the US, EU and Japan.

For a programme to be effective in promoting research into better paediatric medicine in the EU, it must both provide incentives to pharmaceutical companies and ensure research is directed into the priorities considered important by clinical paediatricians.

In-patent medicines

For licensed products on the market with a remaining period of exclusivity, an additional period of exclusivity is the obvious instrument for providing financial incentives to companies to sponsor paediatric clinical trials. Additional data exclusivity by itself is unlikely to add to the effective period of a product’s market exclusivity.

A form of additional market exclusivity for the new indication or formulation, analogous to the US measure and to provisions in the EU Orphan Drugs Regulation, would provide a more powerful and flexible administrative instrument for providing incentives to develop paediatric medicines. To have an equivalent incentive effect, any such period of additional market exclusivity would need to be longer than in the larger US market.

Out-of patent medicines

Out-of-patent products are too important to be ignored by policy on the development of paediatric medicines. For these products, a period of exclusivity that could be applied to one of the company’s other products (a transferable exclusivity) would provide the most
powerful incentive to develop paediatric indications for out-of-patent medicines. However, designing the competition for a transferable exclusivity would be a significant challenge.

17 Another approach for out-of-patent products would be for public authorities to put research contracts to tender. Leading paediatricians believe it would be possible to agree a set of priorities at the EU level as a basis for prioritising such research contracts. The precedents of setting up and managing the Committee for Proprietary Medicinal Products (CPMP) and the Committee for Orphan Medicinal Products would be valuable in developing the machinery for such a prioritisation exercise.

18 A form of market exclusivity – for a period of several years as in the Orphan Drug Regulation - may provide a useful element of a policy for encouraging the paediatric development of out-of-patent medicines. This would be open to all, not just the research-based companies.

Licensing new medicines

19 For products not yet on the market, the EU licensing authorities have a greater opportunity to introduce new licence conditions requiring paediatric clinical trials to be carried out. Where the returns on paediatric development of a product would not justify the anticipated costs, a policy that combines close regulatory supervision of paediatric product development with incentives for carrying out trials is likely to be more effective.

20 An additional period of exclusivity for submitting paediatric data introduced for designated medicines already on the market could be applied equally to appropriate new medicines yet to be licensed. It would have a powerful effect in stimulating the earliest practical paediatric development of new products.

Products already granted additional exclusivity in the US

21 If the purpose of an EU incentive is defined as to ensure that paediatric data are submitted for review by EU authorities, then whether additional exclusivity has been awarded for a particular drug therapy in the US market does not have to be material to the structure of the new incentive. As long as the data are scientifically applicable to the paediatric population in the EU, whether or not additional exclusivity has already been awarded in the US in respect of such data need not affect the eligibility of the submission for an award of additional exclusivity in the EU.

22 A policy of free-riding, ie not awarding the incentive in respect of data forming the basis of a submission that had already led to the award of additional exclusivity in the US, may be ineffective. Paediatric data for many important medicines may not be submitted for review by EU authorities. Such a policy would also explicitly position the EU as a follower, rather than a leader, in the development of paediatric medicine.
The demand for and supply of paediatric clinical trials in the EU

23 An incentive for companies to seek additional paediatric indications for their products in the EU would lead to a dramatic increase in the demand for such trials to be carried out in the EU. The capacity is there to meet such demand, although in many cases initial training of paediatricians for their roles as trial investigators may be required.

Impact on industrial competitiveness

24 The impact on industrial competitiveness is a material secondary issue relevant to the design of policy to develop the evidence base for safe and effective use of medicines in children.

25 Offering an incentive in the EU with respect to paediatric drug trials would contribute to reducing the (in relative terms) declining opportunities presented by the home markets of EU pharmaceutical companies, without affecting the conditions underlying vigorous generic competition.

26 The full long-term consequences for research capacity if the EU continues to offer more limited opportunities for paediatric clinical research are unclear. However, the direction is clear enough: the EU would fall behind in its capacity for research, and given the close link between research and best clinical practice, would ultimately be less capable than the US of providing safe and effective treatment for paediatric patients.
1 INTRODUCTION

1.1 Incentives for Paediatric Trials

Europe Economics was commissioned by Merck Sharp and Dohme (Europe) Inc. to produce an initial report on the options for introducing incentives into the EU to improve the availability of evidence-based drug treatments for paediatric patients.

This followed a request by the EU’s Health Council, from its meeting of 14 December 2000, which “…Accordingly invite[d] the Commission to make appropriate proposals as soon as possible in the form of incentives, regulatory measures or other supporting measures in respect of clinical research and development, taking account of the ethical aspects of clinical trials on children, to ensure that new medicinal products for children and medicinal products already on the market are fully adapted to the specific needs of that population group, and taking into account also the internationally acknowledged standards for the protection of minors with regard to medical scientific research.”

(The full text of the Health Council's Resolution is at Appendix 2.)

This report draws on evidence from published written work and data, and from a small number of interviews with senior academic paediatricians, specialists in clinical paediatric trials, and regulatory specialists in the pharmaceutical industry. Comments are not attributed to individuals.

The natural starting point for such a study is evidence on the current state of paediatric labelling and why it matters. Section 2 provides a summary of the evidence.

Section 3 sets out in more detail the US experience with incentives for companies to carry out paediatric clinical trials, illustrating the significant gains to the short- and long-term of health of child patients from the better evidence base for the use of paediatric medicines. It then outlines different kinds of incentives that could in principle be offered in the EU, and explores how effective each would be in prompting paediatric trials and strengthening the evidence base for paediatric medicine.

Section 4 examines the likely effects on the competitiveness of the EU pharmaceutical industry of incentives to carry out more paediatric drug trials.

Section 5 sets out the conclusions of the analysis on the need for, and likely effects of, incentives to carry out more paediatric drug trials.

Europe Economics is an economics consultancy. While we have drawn on the medical literature and consulted clinical paediatricians in its preparation, this report focuses on the economic issues relating to the design and effect of incentives for carrying out paediatric trials. We provide no new analysis of the appropriate design of trials, or of the appropriateness of particular forms of treatment for paediatric (or adult) use.
1.2 The US Precedent and the EU

In 1997, the US introduced economic incentives for conducting paediatric studies, through the Pediatric Exclusivity Provision in Section 111 of the Food and Drug Administration Modernisation Act.

A six-month extension to market exclusivity could be awarded to all the products containing a particular active substance for carrying out paediatric trials that met the terms of a Written Request received from the FDA. The FDA's Written Requests would only be made where the medicine was identified as likely to bring significant benefit if approved for paediatric use (although such an outcome from the trials was not necessary for the additional exclusivity to be awarded). Written Requests were in most cases issued in response to Proposals submitted by the proposed sponsors.

The findings of the FDA's January 2001 Status Report to Congress are analysed further in Section 3.4 of this report, but the main messages are very clear:

- the incentive generated a large increase in the number of paediatric product trials; and
- within three years, the benefits were already being felt in terms of improved guidance to doctors relating to the paediatric use of a significant number of products, with further amendments to paediatric labelling already in preparation and more to follow.

The FDA's review concluded that giving incentives to pharmaceutical companies was proving effective in leading to better paediatric labelling, which would in turn lead to better treatment.

However, the EU is not the US. Incentives that have worked in the US may conceivably not work in the EU, because of differences in one or more of:

- the initial position on the extent of paediatric labelling;
- licensing procedures and licence terms;
- the nature of provision for patent and other forms of exclusivity;
- clinical practice (e.g., in the use of antibiotics);
- the capacity of the research community to carry out paediatric trials; or
- the markets into which products are sold.

This report explores the extent and significance of these differences between the EU and US, and in the light of this assesses the consequences of providing pharmaceutical companies with incentives to sponsor more paediatric drug trials in the EU.
2 THE CONSEQUENCES OF LIMITED EVIDENCE SUPPORTING PAEDIATRIC MEDICINE IN THE EU

2.1 Introduction

In its December 2000 Resolution, the EU Health Council:

“note[d] that nearly 20% of the Community population, i.e. seventy-five million people, is under the age of 16;

note[d] that, as regards their treatment, children have characteristics which vary with their age and which mean that in most cases they cannot be treated like adults. In particular, a medicinal product administered to a child has specific effects. Furthermore, a medicinal product intended for children requires appropriate pharmaceutical presentation, to ensure easy and safe administration.”

(See full text at Appendix 2)

Children in one age-group can react to drugs differently from adults, and differently from older or younger children:

• toxicity and metabolism may be quite different; and

• there need not be a simple linear relationship between size of body and the amount of a drug required to be an effective dose.

Good evidence of a drug’s effects in children is therefore an important priority for paediatric medicine. The greater vulnerability of children means that, if anything, society might be expected to give a higher weight to having a good base of evidence for their treatment than for treatment of adults.

This section illustrates some of the important differences in response between children and adults, drawing on published information. It then explores their significance, and the current position on paediatric medicine in the EU.

2.2 Why Evidence-based Medicine for Children Matters

It is generally acknowledged that drugs used in adults cannot always be assumed to have the same effect in children. Moreover, the effects are likely to vary between different age groups within the paediatric population. The differences in the effects of the drugs are due to changes in the developing body of a child. Drug metabolism, for instance, may be affected by changes in the maturity of the liver and kidneys.¹

There are important consequences for both the safety and the efficacy of paediatric medicines.

A classification of children for paediatric medicine

As already noted, children of different age groups may react differently to medicinal products. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) suggests that the paediatric population might be divided into five age groups:

- pre-term newborn infants;
- term newborn infants (0 to 27 days);
- infants and toddlers (28 days to 23 months);
- children (2 to 11 years); and
- adolescents (12 to 16-18 years (dependent on region)).

The ICH acknowledges, however, that there will be overlap between the categories. For example, while the division between children and adolescents at age 12 may be appropriate in terms of ability to give a degree of informed consent - historically, young people in some US states could marry at 12 – it does not represent any clear physiological distinction, as the onset of puberty often begins well before age 12, down to as young as eight.

For preterm newborn infants, the ICH states that “[o]nly rarely will it be possible to extrapolate efficacy from studies in adults or even in older pediatric patients to the preterm newborn infants.”

Similar issues can arise in term newborn infants. For example, “the blood-brain barrier is not fully mature and medicinal products and endogenous substances (eg bilirubin) may gain access to the CNS with resultant toxicity” (ICH). But, given that the bodies of term newborn infants will be more mature, the reactions to certain drugs may be different from those of pre-term infants.

Newborn infants differ from other age groups in important respects. For example, drug absorption is affected by:

- the pH level of the stomach, which is alkaline in new born babies but becomes acid within 48 hours;
- the gastric emptying time, which is significantly longer in the the pre-term infant;
- the degree of development of the epidermal barrier, which is low in the pre-term infant; and
- the ratio of body surface to weight, which is higher in the newborn infant.

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The higher percentage of body weight made up by water in a newborn infant affects the distribution of drugs. Together with a decreased plasma albumin concentration, this results in an increased volume of distribution and an increased free drug concentration.

In infants and toddlers there will be “rapid CNS maturation, immune system development and total body growth.” As a result, “[o]ral absorption becomes more reliable … [and] … [h]epatic and renal clearance pathways continue to mature rapidly.” (ICH)

The metabolic pathways in children tend to be mature. In fact, drug clearance can often be greater than in adults. The onset of puberty, particularly in girls at this age, can affect enzyme activity, which can in turn affect the metabolism of drugs.

Adolescents face a period of sexual maturation and “rapid growth and continued neurocognitive development” (ICH). The ICH notes that “many diseases are also influenced by the hormonal changes around puberty (e.g. increases in insulin resistance in diabetes mellitus).”

Implications for safety

The safety of medicines in children is central to good prescribing behaviour. Even where there are reliable safety data for adults, difficult issues arise with children in determining safe doses that reflect the action of a product on children of different ages.

For example, newborn infants have a higher surface area to weight ratio than adults and therefore absorb more of a topically administered drug. Combined with the newborn infant’s immature drug metabolism, this leads to greater risks of drug toxicity.3

Even for older children, metabolism of a product may be quite different from that of adults, leading to different concentrations that can affect health in quite different ways.

On safety, there are well-documented cases where the lack of evidence-based prescribing has led to severe adverse drug reactions (ADRs) in children. Examples of drug toxicity in children include:

- the possible link between the taking of salicylates and Reye’s syndrome;
- thalidomide causing phocomelia; and
- sodium valproate causing hepatotoxicity in children with abnormal drug metabolisms.

There will also be a larger number of less serious ADRs, which should nevertheless be taken into account when reviewing the need for improved labelling.

Implications for efficacy

From the outline given above of issues related to medicines in children of different ages, it will be clear that it cannot be assumed that appropriate doses for children of different ages can be derived by simply scaling down adult dosage guidance:

- some medicines effective in adults will not be effective in children, particularly younger children; and
- where they are effective, the dose-response relationship may vary according to a number of variables other than body mass.

### 2.3 Current Evidence Base for Paediatric Medicine

Ideally, a sufficient evidence base for the use of medicines in children, which took into account the different reactions of children to drugs, would be reflected in the licensed indications for pharmaceutical products and, in turn, in the labelling of the products.

However, as this section demonstrates, the current state of licensing and labelling of drugs used in children is far from satisfactory.

Impiccatore and Choonara (1999) studied medicinal products licensed by the European Medicines Evaluation Agency (EMEA) from January 1995 to April 1998. The results showed that, out of 45 medicines, 16 were not of potential use for children, 10 were licensed for paediatric use and 19 were of possible use for children but were not approved for such. The details of these 19 are shown in Table 2.1.

<table>
<thead>
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<th>Type of drug</th>
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<tbody>
<tr>
<td>Antiviral (HIV)</td>
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</tr>
<tr>
<td>Antiviral (Cytomegalovirus)</td>
<td>2</td>
</tr>
<tr>
<td>Coagulation disorder therapy</td>
<td>3</td>
</tr>
<tr>
<td>Diagnostic medicines</td>
<td>3</td>
</tr>
<tr>
<td>Insulins</td>
<td>2</td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
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On its own, 19 out of 29 is a high proportion of the drugs that could potentially be used for children, and represents a missed opportunity. Analysis of the types of drugs involved shows that important drugs were not licensed for use in children.

A French government working paper reached similar conclusions:

- most products used for the treatment of children in France had not been developed and evaluated for children. Only seven per cent of clinical trials declared in France under the “Huriel” Law from 1994-97 involved children; and
- of 110 Community authorisations for new or biotechnology products, only 15 gave indications for patients under 18 years old, even though 49 of the authorisations were for both children and adults.  

There is great concern over the limited extent of paediatric labelling. For instance:

“The UK Government’s Health Committee was said to be 'deeply shocked' by a 1997 report by the Royal College of Paediatrics and Child Health (RCPCH) and the Association of British Pharmaceutical Industry (ABPI), which showed that many medicines for children were given in a route, formulation or dosage which has not been controlled by the Medicines Control Agency (MCA).”

Roach (2000), when discussing the treatment of the risk factors of additional strokes in children, notes that there is no evidence-based guidance on the use of anticoagulants, antiplatelet agents or thrombolytic agents in children, even though their use is becoming more common.  

Weller et al (2000) calls for more studies on the use of anti-depressants and other psychotropics in children and adolescents given that psychiatric disorders in this group “carry considerable morbidity, impede development, and carry a significant mortality by suicide.”

Interviews with a small sample of leading EU clinical paediatricians revealed some common themes in terms of therapeutic areas where a stronger evidence base for paediatric medicine was important. Key areas included:

- analgesics;
- sedatives;
- immuno-suppressants;
- anti-convulsants; and

• the use of asthma treatments in infants and babies.

Nahata (1999) notes the lack of paediatric formulations in the US. He gives Captopril as an example, available as tablets of 12.5mg, 25mg, 50mg, and 100mg. A newborn infant, however, could require just 0.1 to 0.2 mg per kg per dose. Nahata notes that a major problem is that often the drugs are not in liquid formulations that would aid paediatric prescribing. Without this and research on stable liquid dosage forms for children, he argues that “it is unlikely that all drugs approved for adults will be labelled simultaneously for potential use in infants and children.” He concludes that:

“Numerous drugs used in infants and children are not available in suitable liquid dosage forms. The development of extemporaneous dosage form requires selection of appropriate drug concentration and excipients, assurance of stability and palatability, and adequate funding. Sharing of the research findings on formulations through presentations and publications should lead to their improved use in infants and children. Our [paediatric] patients should not be expected to wait for years and even decades for the drug to be labeled for the pediatric population.”

The importance of evidence-based prescriptions for children is clear, both from the results of the studies performed and from the strength of feeling of those involved in the treatment of children.

The next section discusses the reasons behind the current limited evidence base for paediatric medicine.

2.3.1 Reasons for the current limited evidence base for paediatric medicine

The low level of paediatric labelling reflects the consistently limited number of paediatric clinical trials.

There are three likely reasons given for the lack of paediatric labelling:

• past regulatory hostility to any trials on children, reflecting a high weight given to their protection from experiments that did not benefit them as individuals;

• the greater difficulty and cost of designing paediatric trials and of patient recruitment given the exacting guidelines designed to protect children; and

• for many products, the revenue from paediatric development of the product is not expected to justify the cost of the clinical trials and associated costs.

The pharmaceutical companies that responded to a letter from the Consumers’ Association in the UK regarding the lack of paediatric clinical trials said that a major difficulty for paediatric clinical trials was obtaining parental consent.10

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Conroy et al (2000)\textsuperscript{11} suggest the following reasons why pharmaceutical companies are disinclined to perform paediatric clinical trials:

- they are not economically viable (this is covered in Section 3.2 below);
- problems with blood sampling; and
- being unable to recruit sufficient patients.

Some interviewees identified a cultural gap between companies and researchers:

a) pharmaceutical companies may consider clinicians too slow to carry out trials within their tight timeframes – in some recent cases the dates for patent expiry have provided a hard deadlines for submissions to be completed - and not competent to do them well. Indeed, most paediatricians have limited experience of carrying out paediatric trials as there have been so few.

b) academic paediatricians have academic objectives, valuing the scope for interesting published papers, and funding for extra research posts. They may simply not be interested in mechanical trials on simple compounds. Paediatricians also have been known to remark that some proposals coming from US companies take insufficient account of European clinical practice, rendering them unworkable or unacceptable. For example, we were told that quite a few proposals from the US for placebo-controlled trials for children are rejected as unethical. Some paediatric specialists suggest that companies need to consider paediatric patients as more than just a market opportunity ie that given their resources and capabilities they should take more responsibility for providing safe and effective paediatric medicines.

One of our interviewees reported that in France, paediatric clinical pharmacologists had developed protocols themselves and tried to persuade pharmaceutical companies to sponsor trials. The results had been disappointing: in most cases the companies were simply not interested.

The significance of this cultural divide for policy design is discussed further below, as are the financial costs and benefits of developing paediatric medicines (Section 3.2). Here we discuss the ethical issues.

### 2.4 Ethical Issues with Paediatric Trials

It is immediately obvious that there are ethical problems with testing drugs on children. Children cannot give informed consent in the way an adult can, and causing them pain in the pursuit of research is generally considered acceptable, if at all, only under strict guidelines.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) now provides guidelines in response to these problems in its paper "Clinical Investigation of Medicinal Products in the Pediatric Population".

These guidelines, effective in the EU from 1 January 2001, represent a major step forward. Agreed between the regulatory authorities of the US, EU and Japan, and the pharmaceutical industry associations, they provide a framework that sets out:

- a set of factors that should be taken into account in deciding whether a product should be developed for paediatric use and the stage in the product’s development when the paediatric development work should take place;
- a set of high-level priorities for the conduct of paediatric clinical trials, eg for ways to minimise pain and distress;
- a framework for the assessment of efficacy and safety in paediatric medicine. Alongside other associated guidelines, this means that trial data adequate to support a submission for a paediatric indication in one of the three jurisdictions should also be sufficient to support an application in each of the others. Discussions with paediatric clinical researchers and industry managers suggest that this position has now been reached between the EU and US;
- a possible age classification for paediatric medicine: a degree of agreement on this is important if trial data are to be useful in more than one jurisdiction.

The process of international discussion and harmonisation – in the ICH and other fora – has important consequences. It means, for example, that data submitted in the EU or US in respect of a paediatric indication for a product should normally be sufficient to support a similar application across the Atlantic.

According to the ICH guidelines, the main considerations when deciding whether or not there should be a paediatric medicinal product development programme include:

- "[the] prevalence of the condition to be treated in the pediatric population;
- the seriousness of the condition to be treated;
- the availability and sustainability of alternative treatments;
- the need for the development of pediatric-specific endpoints;
- unique pediatric (developmental) safety concerns with the medicinal product; and
- the potential need for pediatric formulation development."

The guidance states that the timing of trials would depend partly on the disease being treated:
for those “diseases predominantly affecting pediatric patients,” the trials would all be conducted using children except for initial safety and tolerability data which could usually be obtained through testing adults;

- drugs relating to “[s]erious or life-threatening disease, occurring in both adults and pediatric patients, for which there are currently no or limited therapeutic options” should be developed early in children following initial safety trial and a review of the evidence for potential benefits; and

- paediatric trials for drugs for “other diseases and conditions” can generally be developed at a later stage in the process.

Tests on children can be limited through extrapolation from other data where appropriate. Where the disease process is similar and the result of therapy comparable, extrapolation from older to younger paediatric patients may be possible. For drugs that exhibit linear pharmacokinetics in adults, children can each be given single doses to provide data on dosage selection.

The form of these guidelines has important implications for the form and timing of paediatric clinical trials. Three implications may be particularly relevant:

- tests for paediatric safety can usually be carried out only after safety in adults is reasonably established;

- where there is already an effective treatment for children, tests for paediatric efficacy in children can usually be carried out only after the completion of Phase 3 trials in adults; and

- tests against placebo are generally considered unacceptable in children where there is already an effective treatment.

The ICH also provides guidelines to address the ethical problems identified earlier in this section. There should be no “inappropriate inducement”; “fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations,” and the risk and distress associated with the trial should be minimised.

Our small sample of leading EU paediatricians all emphasised the importance of designing and conducting paediatric trials on children within a clear ethical framework. All had seen paediatric trial proposals that they had declined to participate in on ethical grounds, particularly where protocols:

- suggested the use of placebos in trials for child patients when there were existing effective treatments that could be used;

- required more frequent blood sampling or other invasive procedures for individual children than strictly necessary; or
were for products with no likely therapeutic advantage over existing treatments, yet where some degree of pain or distress would be incurred during the trials.

Different ethical issues were raised in paediatric trials, and protocols for adult trials with minor adaptations, whilst easy for companies to produce, would often not be acceptable.

However, there was a consensus on two critical issues:

- for most of the post-war period, national and international guidelines on paediatric trials had given too high a weight to the protection of paediatric patients as against the benefit that trial subjects and subsequent paediatric patients would gain from a better evidence base for paediatric medicine. The result had been to stifle the possibilities for developing better medicines for children; and

- there were no no-go areas for paediatric clinical trials. Where there was a pressing need for better evidence about the safety and efficacy of particular medicines for use in children, the difficulties could be overcome in ways that were ethically acceptable.

Taking blood samples from children has been one controversial area. The British Paediatric Association initially regarded blood sampling as unethical but then decided that it is ethical if full informed consent is obtained from the carer or child. Conroy et al argue that the experience for the child, and the parent, can now be made more pleasant through the use of topical local anaesthetic creams and using the “population kinetics” approach whereby fewer blood samples are taken from a child, but more children are tested. This means, however, that more children are required for trials, which means that it will be less useful for new drugs than established ones where their application is being refined.

The critical issues for any expansion of paediatric trials are therefore not ethical issues – a framework is in place for dealing with these - but of the demand for trials and of the key skills in their design and implementation. We return to these questions of capacity in Section 3.9.

2.5 Treatment Options in the Absence of Appropriate Paediatric Indications

There is an important distinction to be made in the use of medicines for children between:

- off-label use, a drug used differently to the method recommended in the product licence; and

- unlicensed use, a drug that has been modified from the form given in its product licence.

Examples of off-label use include using medicines “at a different dose, by a different route, in a different age group or for a different indication than that authorised in the product licence” (Choonara et al, 2000).
Examples of the use of unlicensed drugs include “crushing a tablet and making it into a suspension suitable for a young child … [and] includes chemicals….. which have bypassed the licensing process” (Choonara et al, 2000).

The lack of evidence-based guidance results in off-label or unlicensed drugs being demanded by the paediatrician. The task of meeting those demands will typically fall to the pharmacist, in consultation with the paediatrician. There are several options when no suitable paediatric formulation is available. These include:

- supply of an alternative drug;
- use of soluble/dispersible tablets if available;
- crushing tablets or opening capsules;
- extemporaneous preparation of a liquid formulation;
- cutting tablets into fractions;
- withdrawal of liquid contents of capsules;
- use of injections orally;
- cutting suppositories into fractions;
- importing drugs from abroad; and
- refusal to dispense.  

All of these options carry difficulties. In some cases, none may be practical. The difficulties with cutting tablets into fractions are illustrated by the example of Captopril given above: precise measurement may be critical.

Preparing liquid formulations may also be problematic, beyond issues of the fineness of measurement: the medicine must be stable in the chosen vehicle, and the vehicle must be appropriate to the use of the medicine.

To help paediatricians and pharmacists facing the challenge of treating children with no suitable licensed formulation available, certain medical centres collect information and give advice. In the UK, the Alder Hey Children’s Hospital, for example, maintains a formulary and provides advice relating to unlicensed and off-label use. The written guidance available in the UK is becoming more fully documented, with the available data included or referenced.
Through such mechanisms, data and expertise on unlicensed and off-label use are made available to other paediatricians. However, the data available will in most cases fall short of the quality that would be derived from paediatric clinical drug trials leading to appropriately licensed indications.

Where a child needs a particular treatment, and there is no licensed treatment available, paediatricians can be expected to use unlicensed or off-label treatment insofar as they are sufficiently confident in the safety and efficacy of the medicines to believe that this is in the interests of the patient.

In doing so, they are often using a greater element of their own judgement, and relying on a more slender base of evidence, than when using a medicine for licensed indication.

To that extent, the alternative to having evidence and licensed indications based on clinical trials is that paediatricians will use medicines drawing on what is often a lesser evidence base.

2.6 Off-Label and Unlicensed Use of Medicines for Children

2.6.1 Extent

There is a growing body of evidence on the use of off-label and unlicensed paediatric drug use in the EU. Conroy et al (2000) noted this for Europe and the US and conducted a survey of paediatric medical wards in Derby (UK), Uppsala (Sweden), Marburg (Germany), Bergamo (Italy) and Rotterdam (Netherlands).

The definition of “unlicensed” used by Conroy et al (2000a)\textsuperscript{14} was:

- modification of licensed drugs;
- licensed drugs where the formulation is prepared under special licence;
- new drugs available under a special manufacturing licence;
- use of chemicals as drugs where no pharmaceutical grade preparation is available;
- drugs used before a licence has been granted; and
- drugs imported from a country where they are licensed.

Off-label use was defined as use:

- with a different dose or frequency to that defined in the patent licence or in line with the summary of product characteristics;

The Consequences of Limited Evidence Supporting Paediatric Medicine in the EU

- in different clinical indications;
- in different age groups;
- administered by an alternative route; or
- in a formulation not approved for paediatric use.

The findings of the survey on the extent of off-label and unlicensed use are reproduced in Table 2.2.

### Table 2.2:
Off-label and unlicensed drug use in five European paediatric wards

<table>
<thead>
<tr>
<th></th>
<th>Derby</th>
<th>Uppsala</th>
<th>Marburg</th>
<th>Bergamo</th>
<th>Rotterdam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>192</td>
<td>87</td>
<td>85</td>
<td>118</td>
<td>142</td>
<td>624</td>
</tr>
<tr>
<td>Age range</td>
<td>21 days-16 years</td>
<td>4 days-15 years</td>
<td>28 days-16 years</td>
<td>30 days-12 years</td>
<td>4 days-16 years</td>
<td>4 days-16 years</td>
</tr>
<tr>
<td>Prescriptions</td>
<td>798</td>
<td>185</td>
<td>224</td>
<td>398</td>
<td>657</td>
<td>2,262</td>
</tr>
<tr>
<td>Mean no. of prescriptions/patient</td>
<td>4.2</td>
<td>2.1</td>
<td>2.6</td>
<td>3.4</td>
<td>4.6</td>
<td>3.6</td>
</tr>
<tr>
<td>No. (%) of prescriptions unlicensed or off-label</td>
<td>239 (30)</td>
<td>57 (31)</td>
<td>91 (41)</td>
<td>264 (66)</td>
<td>385 (59)</td>
<td>1,036 (46)</td>
</tr>
<tr>
<td>No. (%) of prescriptions unlicensed</td>
<td>58 (7)</td>
<td>8 (4)</td>
<td>8 (4)</td>
<td>1 (0.3)</td>
<td>89 (14)</td>
<td>164 (7)</td>
</tr>
<tr>
<td>No. (%) of prescriptions off-label</td>
<td>181 (23)</td>
<td>49 (26)</td>
<td>83 (37)</td>
<td>263 (66)</td>
<td>296 (45)</td>
<td>872 (39)</td>
</tr>
<tr>
<td>No. (%) of patients receiving unlicensed or off-label treatment</td>
<td>109 (57)</td>
<td>37 (43)</td>
<td>46 (54)</td>
<td>101 (86)</td>
<td>128 (90)</td>
<td>421 (67)</td>
</tr>
</tbody>
</table>


Key findings are that

- off-label and unlicensed drug prescriptions account for nearly half of all drug prescriptions in the sample; and
- well over half of the patients received off-label or unlicensed prescriptions.

Whilst the level of unlicensed drug use appears relatively limited, off-label drug prescriptions represent a high proportion of total prescriptions.
As highlighted by the authors, it is interesting to note the variation across the different centres. This is shown in Table 2.3 below, reproduced from the article, which shows the five drugs in each centre most frequently used off-label.

**Table 2.3:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Cyclizine</td>
<td>38/42</td>
<td>13/13</td>
<td>Budesonide</td>
<td>10/12</td>
<td>Beclometasone</td>
<td>47/47</td>
<td>Heparin</td>
<td>28/28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>Salbutamol</td>
<td>27/42</td>
<td>13/41</td>
<td>Salbutamol</td>
<td>8/17</td>
<td>Salbutamol</td>
<td>28/32</td>
<td>Pancreatin</td>
<td>17/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>Morphine</td>
<td>26/33</td>
<td>13/10</td>
<td>Xylometazoline</td>
<td>8/15</td>
<td>Paracetamol</td>
<td>26/28</td>
<td>Spiromolactone</td>
<td>17/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>Ipratropium</td>
<td>15/15</td>
<td>3/5</td>
<td>Paracetamol</td>
<td>7/20</td>
<td>Betamethasone</td>
<td>21/38</td>
<td>Frusemid</td>
<td>16/18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>Diazepam</td>
<td>13/13</td>
<td>2/4</td>
<td>Chloral hydrate</td>
<td>5/5</td>
<td>Amoxycillin</td>
<td>18/23</td>
<td>Tobramycin</td>
<td>15/16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Number of off-label prescriptions/total number of prescriptions for drug in centre

Source: Conroy et al

Table 2.3 shows that in four of the five centres, off-label uses of treatments for asthma are amongst the most common of off-label drug uses. Bronchodilators were being used for children under two years, and in many cases more frequently than specified on the label. There are only limited data on the growth suppression effects of inhaled corticosteroids (e.g. beclametasone, budesonide) in this age group. Paracetamol is amongst the product most commonly used off-label in three of the five centres.

The nature of off-label use also varied between the centres in the study, as shown in Table 2.4 below.

**Table 2.4:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Derby</th>
<th>Uppsala</th>
<th>Marburg</th>
<th>Bergamo</th>
<th>Rotterdam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose and frequency</td>
<td>66(32)</td>
<td>53(88)</td>
<td>59(61)</td>
<td>255(58)</td>
<td>96(31)</td>
</tr>
<tr>
<td>Age</td>
<td>79(39)</td>
<td>1(2)</td>
<td>23(24)</td>
<td>33(7)</td>
<td>18(6)</td>
</tr>
<tr>
<td>Indication</td>
<td>36(17)</td>
<td>4(7)</td>
<td>7(7)</td>
<td>25(6)</td>
<td>13(4)</td>
</tr>
<tr>
<td>Route</td>
<td>24(12)</td>
<td>2(3)</td>
<td>3(3)</td>
<td>49(11)</td>
<td>4(1)</td>
</tr>
<tr>
<td>Formulation</td>
<td>0</td>
<td>0</td>
<td>5(5)</td>
<td>80(18)</td>
<td>176(58)</td>
</tr>
<tr>
<td>Total</td>
<td>205</td>
<td>60</td>
<td>97</td>
<td>442</td>
<td>307</td>
</tr>
</tbody>
</table>


Across the centres as whole, the most frequent forms of off-label paediatric use were:

- off-label use in terms of dose and frequency (more than half of all off-label use in the sample);
• off-label use in terms of age; and

• off-label use in terms of formulation.

The differences in the nature and extent of off-label use are in part explained by the different subspecialty interests of the different wards. However, prescribing behaviour is different in different European countries, and the design of the incentives for the pharmaceutical companies to test paediatric drugs may have to take into account the extent of different prescribing characteristics in each EU country.15

A study by Turner et al (1998)16 of unlicensed and off-label drug use in a regional children’s hospital in the UK found that over 20 per cent of drugs used were off-label in a paediatric medical ward and 22 per cent in a paediatric surgical ward. For unlicensed drugs, proportions for the medical and surgical wards were eight and six per cent respectively. 36 per cent of the patients received either off-label or unlicensed drug prescriptions.

Martin et al (1998)17 note that unlicensed and off-label drug use is not limited to paediatric wards. In a sample of 100 general practices in the UK, they found that 19 children aged 12 and under were prescribed Selective Serotonin Reuptake Inhibitors by general practitioners. According to the British National Formulary, these products are not recommended for children. Given that the data were collected from less than one per cent of all British practices, the authors conclude that the data suggest that “nationally there are probably hundreds of children who have been prescribed off-label antidepressants in general practice.”18

Further evidence on the use of off-label and unlicensed drugs in general practice in the UK comes from McIntyre et al (2000).19 From data in 1997 they found that, out of 3,347 prescriptions, 10 (0.3 per cent) were for unlicensed medicines, 351 (10.5 per cent) were for off-label use and for 158 (4.7 per cent) there was insufficient information to determine licence status. 16 per cent of systemic antibacterials prescriptions were off-label or unlicensed with the vast majority relating to prescriptions being off-label with respect to dose. For each of systemic antihistamines, laxatives, ophthalmological and otological preparations, anti-inflammatory/anti-rheumatics and anti-asthmatics unlicensed and off-label use was over 10 per cent, again with the vast majority relating to off-label use with respect to dose.

The authors note that these figures are lower than those from studies in hospitals but argue that, given the numbers of children treated in general practice, this does not make the results insignificant. They also note that the results will underestimate the use of unlicensed and off-label drug use in the community because of the use of the likely unlicensed and off-label use of over-the-counter medicines.

18 Note, however, that these medicines are considered fairly safe for use in older children and adolescents: the risk of mis-diagnosis of mental health conditions may be a more pressing concern.
2.6.2 Adverse Drug Reactions from unlicensed and off-label paediatric use

Where the use of medicines with children is unlicensed or off-label, the back-up information services provided by pharmaceutical companies may not be available or may not be used, and the necessary corrective action may not be taken.

Leach (2001) notes that serious Adverse Drug Reactions (ADRs) are well-documented in certain cases including:

- use of corticosteroids in the treatment of toxoplasmosis;
- off-label usage of salbutamol, captopril, cisapride, enalapril, dopamine, lorazepam, midazolam, morphine, ranitidine and warfarin; and
- grey baby syndrome in the 1950s from the use of chloramphenicol … ."

However, the recording of the prevalence of ADRs for off-label and unlicensed drugs in terms of percentage of related prescriptions/patients treated is limited. This may be partly due to the unwillingness of doctors to highlight areas where they may have prescribed incorrectly. Even though this is likely to be due to the lack of information on which they base their decisions, possibilities of being sued or being brought before medical authorities may act as a significant deterrent. As a result, reported ADRs from unlicensed and off-label paediatric use are likely to be underestimated, and the results of the studies reviewed in this section should be looked at in this light.

Much of the published evidence is on ADRs relating to all drugs used in children, rather than just those that are off-label or unlicensed.

Menniti-Ippolito (2000) studied ADRs in children in the Veneto region of Italy using 29 family paediatricians. Out of the 24,000 children registered with the paediatricians there was an incidence of 15.1 ADRs per 1000 children in the period April 1996 to March 1997. The highest incidence of ADRs was associated with cephalosporins and macrolides. None of the ADRs required hospital submission although the author notes that the design of the study may not have been suitable for the identification of rare or serious ADRs.

Morales-Olivas et al. (2000) analysed ADRs in children under 14 years old in Spain. The age distribution of the ADRs is given in Table 2.5.

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The Consequences of Limited Evidence Supporting Paediatric Medicine in the EU

Table 2.5:  
Age distribution of ADRs in paediatric patients

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>12.8</td>
</tr>
<tr>
<td>1-4</td>
<td>37.9</td>
</tr>
<tr>
<td>5-9</td>
<td>25.0</td>
</tr>
<tr>
<td>10-14</td>
<td>24.3</td>
</tr>
</tbody>
</table>

Source: Morales-Olivas et al. (2000)

The table shows that reports of ADRs decrease with the age of children. It should be noted though that the number of ADRs per report varies so that the distribution of actual ADRs across the age ranges may be different.

Antibiotics had the highest number of reports (nearly 40 per cent) followed by respiratory tract drugs (approximately 23 per cent) and vaccines and digestive tract drugs (just over 10 per cent). The products for which ADRs were most frequently reported are shown in Table 2.6.

Table 2.6:  
Products with frequent ADRs

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin-clavulanic acid</td>
<td>204</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>183</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>102</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>69</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>68</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>40</td>
</tr>
<tr>
<td>Ambroxol</td>
<td>36</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>39</td>
</tr>
<tr>
<td>Miocamycin</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>784</td>
</tr>
</tbody>
</table>

Source: Morales-Olivas et al. (2000)

Morales-Olivas et al. note, however, that the Sistema Espanol de Farmacovigilancia (Spanish Pharmacovigilance System) is “probably biased and incomplete” because it is a voluntary reporting scheme. They argue that reporting rates should be improved, particularly by hospital medical staff because hospitals are where the more serious ADRs are likely to occur.
The Morales-Olivas study looked at ADRs for all drugs. Turner et al. (1999),\textsuperscript{23} however, study ADRs in relation to just unlicensed and off-label used on paediatric wards. Their work focussed on five wards in a regional UK hospital.

The types of drugs associated with ADRs in the Turner study are shown in Table 2.7.

<table>
<thead>
<tr>
<th>Drug type</th>
<th>ADRs</th>
<th>Total</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>34</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Morphine and other opiates</td>
<td>33</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>31</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>10</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Antihypertensives/vasodilators</td>
<td>10</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Sedatives</td>
<td>8</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>8</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>TPN</td>
<td>5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Inotropic agents</td>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>14</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>157</td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>

Source: Turner et al. (1999)

Note: Severe is defined as fatal or potentially life-threatening.

While the authors report that multi-variate analysis demonstrated no significant relationship between the use of unlicensed and off-label drugs and the risk of ADR, the percentage of unlicensed and off-label drugs was significantly associated with the risk of an ADR.

The authors conclude that off-label and unlicensed drugs are used in children with “a variety of clinical conditions” and that the results are “suggestive of a higher risk of ADR in relation to unlicensed and off-label drugs.” They call for further work to be performed in both paediatric clinical trials and drug surveillance to reduce the risk of ADRs.

### 2.7 Can the Evidence Base for Paediatric Medicine in the EU be Improved?

Several points can be drawn out from the analysis of this Section.

There is general acceptance of the principle set out by the EU Health Council that the use of medicines in children should be solidly based on good-quality evidence.

Many products of potential use for children have not been subjected to paediatric trials and have no paediatric indication, or only limited paediatric labelling.

There is currently widespread off-label and unlicensed use of medicines for the paediatric population in the EU.

Paediatricians see a clear need for the more research – including clinical trials – into the suitability for use of medicines for the paediatric population, and appropriate dosages and formulations.

Because of the continuing and successful programme of international harmonisation through the ICH, data submitted in the EU or US in respect of a paediatric indication for a product are now almost always sufficient to support a similar application across the Atlantic.

Paediatricians we interviewed consider that where there is a need for more evidence to support better use of medicines in the paediatric population, well-designed studies can provide that evidence in ways that are ethically acceptable. There are few or no areas where medicines that children need cannot be researched. However, these trials may have to be carried out after adult trials, and there are often specific design issues to be solved.

The discussion on the solution to the lack of indications for paediatric use should, therefore, be focussed on mechanisms for increasing the demand for appropriate research, and for removing any obstacles (unjustifiable regulations, or skills or other capacity shortages) to an increase in the supply of that research.

2.7.1 Agreeing on priority areas for research

In several EU countries, including the UK, France, and Germany, paediatric clinical specialists have developed, or are developing, lists of therapeutic priority areas for paediatric clinical research.

These lists are in a developmental stage and not yet a firm basis for action. For this study, we have not sought to collate them or provide a detailed comparison. Nevertheless, two remarks are relevant.

The first is that the therapeutic areas identified as research priorities by EU paediatricians in our telephone interview included significant areas of overlap. As noted in Section 2.3 above, these therapeutic areas include:

- analgesics;
- sedatives;
The Consequences of Limited Evidence Supporting Paediatric Medicine in the EU

- immuno-suppressants;
- anti-convulsants; and
- the use of asthma treatments in infants and babies.

The second is that the paediatricians we spoke to were confident that, despite differences in clinical practice, it would be possible to achieve through negotiation and discussion agreement at the EU level on key research priorities.

One other specific suggestion made by paediatricians is that the CPMP should include an academic specialist in paediatric medicine when considering products of potential value to child patients. As well as advising on the potential suitability for paediatric use of a particular medicine, such a specialist could advise on the constraints on paediatric clinical trials that led to submissions being legitimately based on smaller studies.
3 INCENTIVES, PAEDIATRIC TRIALS AND PAEDIATRIC LABELLING

3.1 Introduction

Section 2 shows clearly that the central issue is not that of whether or not “to experiment on children”. The off-label and unlicensed use of medicines in the treatment of children is not best clinical practice. It is uncontrolled, and in such conditions there is no clear method of deciding which treatments are safe and effective, of informing other paediatricians of the safety and efficacy of medicines, or of capturing evidence on adverse events. Our interviews with a small number of leading paediatricians suggested that medical professionals are increasingly finding this position unacceptable.

Paediatric clinical trials for appropriate products will bring this unregulated use under proper control. Trials carried out under internationally agreed guidelines will either define appropriate usage and dosage, and enable better knowledge of adverse events and precautions to be assembled, or will establish that a particular medicine is not suitable for children.

The central public policy choice facing the EU is not that of “to experiment or not to experiment”: in the absence of properly regulated paediatric trials, off-label and unlicensed use represent uncontrolled experiments. The key choice is between ways of increasing the number of well-designed paediatric clinical trials to provide a better evidence base for paediatric medicine.

The starting point in developing such a policy is a clear understanding of the business decision of whether to conduct paediatric product trials.

3.2 Paediatric Drug Trials: the Business Decision

At some stage in the process of obtaining a licence for a new product and then marketing that product, a research-based pharmaceutical company has to make a decision whether to sponsor paediatric trials of the product.

A research-based pharmaceutical company with a licence for a new product faces the following trade-off:

“Do the additional earnings that will result from licences for paediatric indications justify the costs and risks of sponsoring the trial and of developing and maintaining the new paediatric formulation?”

The extent of the additional earnings will depend on the potential additional use that will follow from having paediatric indications in the product licence and in the product labelling.

The company can use its knowledge of the market to produce such estimates, but they will be subject to a high degree of uncertainty. In many EU jurisdictions, the price of a new therapeutic formulation is subject to control by the reimbursement authority.
For many products, there are potentially large paediatric markets and companies have a strong incentive to develop products for paediatric use. These include anti-infectives and treatments for asthma. Companies with new products in these markets are likely to be keen to sponsor paediatric product trials as part of their normal business.

For other therapeutic areas, the current gap in paediatric products available within the EU was shown in Section 2. Along with comparable evidence from the US cited below, that evidence suggests that, for most products, companies have taken the view that the expected additional earnings of developing paediatric indications and formulations did not justify the associated costs and risks.

3.2.1 Costs of developing paediatric medicines

In looking at the costs and risks, it is useful to break down the process in the manner of Gennery (2000). The costs of seeking and obtaining a paediatric indication include the following categories of cost.

Costs of developing and testing a range of paediatric formulations

In most cases, and almost certainly where this would include an indication for children of six and under who cannot take tablets, one or more new formulations must be developed that are palatable to children.

For children of different ages, different paediatric formulations may be necessary eg drops for neonates, and syrups for children aged from two to six.

All of these formulations must be tested for stability. A company seeking a licence must report the results of stability tests under a range of conditions over a period of a year.

Cost of carrying out trials and submitting data

In most cases, the ICH guidance for paediatric trials referred to in Section 2.4 above requires that such trials - both for toxicity or for effectiveness - should be carried out after the results of trials on adults are known.

Where there is already an effective treatment, clinicians or ethics committees may well decide that it is not ethical to give a placebo to children, so the test for the new product must be carried out against the existing treatment. This increases the necessary sample size.

The costs of sponsoring a paediatric trial, particularly of the time of medical professionals, may be significantly greater than for trials for adults, due to:

- consent procedures taking more time per patient;

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24 Gennery B, "Clinical research in Children – a pharmaceutical industry view" Paediatric and Perinatal Drug Therapy, 2000, 4, 67-70
25 Choonara et al 2000, Section 6.1.4
Incentives, Paediatric Trials and Paediatric Labelling

- smaller proportions of those presenting agreeing to take part;
- the possible need to include larger numbers of patients in a trial (see above); and
- the possible need to use multiple centres to ensure a sufficient number of child patients in the specified age group take part.  

Cost of preparing and submitting data

Once the trial is complete, it may become clear that the data would not support a submission seeking a paediatric indication. The costs of the trial then have to be written off.

Preparing and submitting the data in the form required by the regulatory authorities to approve a paediatric indication can be a lengthy and resource-intensive procedure (although there is now sufficient harmonisation between regulatory authorities, such that trial data submitted in the US should be sufficient to support submissions in the EU, and vice-versa).

Continuing costs: manufacturing

It can be expensive to continue to manufacture small amounts of a range of paediatric formulations. Choonara et al report examples of companies withdrawing such formulations presumably on just these cost grounds.  

Continuing costs: long-term follow up

Any company introducing new paediatric medicines faces risks to its reputation, whether from ill-informed criticism for “experimenting on children” or from longer-term adverse effects (e.g. developmental) that may have not have been identified in the trials.

3.3 Private Benefits and Externalities

From the company’s perspective, the business trade-off is:

“Do the additional earnings that will result from licences for paediatric indications justify the costs and risks of sponsoring the trial and of developing and maintaining the new paediatric formulation?”

However, this is not the trade-off faced by society as a whole. From a social welfare perspective, the full range of costs and benefits become relevant, and there are potentially considerable gains to patients and to the community as whole from paediatric trials that lead to a better evidence base for the paediatric use of medicines, with paediatric labelling for appropriate indications. These gains include:

26 Choonara et al Section 2.2.2.1
27 Choonara et al Section 7.3
• better short-term response of children to appropriate treatment, with reduced suffering and more rapid recovery;
• better longer-term health prospects for children from better-designed initial intervention;
• reduced absence from school;
• reduced costs of immediate and future primary and hospital medical care; and
• reduced anxiety and missed work time by parents and other carers.

Such benefits are positive externalities from the business decision, arising from better information about the use of particular products in the treatment of children. For the pharmaceutical company facing a decision on whether to sponsor paediatric trials, potential benefits of this kind cannot be captured and so may not influence the business decision.

Where there are significant potential social benefits to an action by a company or individual, such that the social benefits might outweigh the costs even where the private benefit does not do so, then it becomes appropriate to consider providing an incentive for the company or individual to undertake the action.

Indeed, if the social benefit could be known with certainty in advance, it may be appropriate to make a payment of up to that amount to induce the desired behaviour. In the subsidy on environmental grounds, for example, of the transfer of freight from road to rail, it is reasonable to consider subsidising the switch of freight from road to rail up the amount of the net positive externalities.

Of course, in the case of pharmaceutical paediatric trials (as in many other real-world examples) the value of the external benefit cannot be known in advance.

If an incentive is to be effective, it must be sufficient so that the decision is changed and the positive externalities generated.

For a business decision, it is natural that the incentive should be a financial one. This is the view, for example, of Choonara et al, practising clinical paediatricians:

> “Europe should learn from the FDAMA and introduce the principle of a financial incentive, while trying to ensure that this financial incentive is not restricted to the study of new medicinal products” (Choonara et al. 2000, Section 7.4).

Such incentives would sit alongside regulatory action to make sure that the right medicines were studied.

However, in designing efficient incentives in respect of positive externalities, there are important constraints:
• the incentive should be appropriately targeted at where it will induce the behaviour that will generate the externalities;

• for an incentive to be proportionate, the payment should reflect expected net social benefit;

• the design of the incentive should seek to minimise implementation costs and other unintended consequences, which costs should be counted against the expected gain.

The design of incentives is therefore necessarily a complex issue.

However, the EU does not have to start from scratch in designing an incentive for more paediatric trials. The next sub-section reports on the nature and effects of the incentives introduced in the US.

3.4 US Experience with Incentives

3.4.1 The Pediatric Exclusivity Provision

In 1997, the US introduced economic incentives for conducting paediatric studies, through the Pediatric Exclusivity Provision in Section 111 of the Food and Drug Administration Modernisation Act. The incentive took the following form:

A six-month extension to market exclusivity could be awarded to all the products containing a particular active substance for carrying out paediatric trials that met the terms of a Written Request received from the FDA.

This was achieved by adding the six months of exclusivity to any of the sponsor’s listed patents or previous non-expired grants of exclusivity on drug products containing the active moiety (active substance) that was studied, including combination products. The FDA’s Written Requests would only be made where the product was identified as likely to bring significant benefit if approved for paediatric use. Written Requests were in most cases issued in response to Proposals submitted by the proposed sponsors. To qualify for the additional exclusivity, the data then had to be submitted in the form, and within the time-frame specified in the Written Request. Note that it was not a condition for the additional market exclusivity that the additional studies identified a benefit justifying approval for paediatric use.

This incentive was introduced alongside a new presumption that new drugs should be studied in paediatric patients. Under the Pediatric Rule published by the FDA in December 1998, and effective from 1 April 1999, applications for new active ingredients or indications must “contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.”

There are provisions for deferral or waiver of the paediatric studies requirements of the Pediatric Rule under certain conditions. The intention is to focus on products deemed likely to be used to treat a substantial number of paediatric patients or to provide a therapeutic benefit for paediatric patients.  

The Pediatric Rule pertains only to indications an applicant is seeking for the product in the adult population, while the incentive program under Section 111 of FDAMA may be used to encourage studies in both existing approved indications as well as other indications, including indications that may be specific to the pediatric population. While the Pediatric Rule did not come into effect until April 1, 1999, it is likely to have affected observed behaviour since its announcement at the end of 1998, making the separate impact of the FDAMA incentive harder to identify.

### 3.4.2 Impact

In its January 2001 Status Report to Congress, the FDA provided an assessment of the effects of the Pediatric Exclusivity Provision over its first three years. The picture was a positive one.

“In general, the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.”

The incentive had led to a large increase in the number of paediatric clinical trials being carried out: 58 paediatric studies under the new arrangements had already been completed, submitted and received a preliminary review by September 2000. Sponsors had indicated that they had conducted or would conduct trials in respect of the treatments specified in 80 per cent or more of the 157 Written Requests issued by the FDA to September 2000, so the number covered under the new arrangements can be expected to continue to rise.

In contrast, only 11 post-marketing paediatric studies had been carried out between 1991 and 1996. The FDA reports that most of the 71 drug sponsors who promised to carry out such trials had not done so.

Some increase in the number of paediatric studies would have been expected anyway under the Pediatric Rule. Milne reports an FDA estimate that just under half the expected industry spending over the next few years would be spent on FDAMA-related paediatric studies that would also perform “double-duty” to fulfil the requirements of the Pediatric Rule.

The FDA concludes that the increase in paediatric drug trials showed the incentive had achieved its objective: the “pediatric exclusivity provision of FDAMA has been effective for obtaining pediatric studies for many drug products. An unprecedented number of pediatric studies have

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29 For a full description of both the Pediatric Exclusivity Provision and the Pediatric rule, see Chapter 16: “The Pediatric Studies Initiative” by C-P Milne in “M.Mathieu “New Drug Development: A Regulatory Overview”, Tufts Center for the Study of Drug Development, 2000

30 FDA Status Report page 12

31 Ibid page 8
been or are projected to be conducted under this provision. The flow of new paediatric submissions exceeded the FDA’s capacity to review them.

However, there were three classes of products for which the incentive was insufficient:

- drugs with no exclusivity or patent protection: here the FDA offered for discussion a suggestion that sponsors carrying out trials in respect of such products might be able to transfer an additional period of exclusivity to another product;

- drugs with insufficient sales; and

- drugs where sequential studies for different paediatric groups were necessary: here the FDA suggested that it should where appropriate be able to send a second Written Request, such that a second incentive – possibly another period of exclusivity - could be obtained.

### 3.4.3 Better paediatric labelling and child health

The benefits of these trials were already being felt in terms of improved evidence for doctors relating to the paediatric use of a significant number of medicines, with further amendments to paediatric labelling already in preparation and more to follow.

Table 3.1 below reproduces the list of active substances with new paediatric indications in the US under the Pediatric Exclusivity Provision provided in the Status Report.
### Table 3.1:
Therapies with new paediatric indications in the US under the Pediatric Exclusivity Provision

Paediatric exclusivity granted (as of September 2000)

<table>
<thead>
<tr>
<th>Granted</th>
<th>Moiety</th>
<th>Sponsor</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7/1/98</td>
<td>Ibuprofen McNeil</td>
<td>Fever, aches/pains cold symptoms</td>
</tr>
<tr>
<td>2</td>
<td>7/1/98</td>
<td>Ibuprofen Whitehall</td>
<td>Fever, aches/pains cold symptoms</td>
</tr>
<tr>
<td>3</td>
<td>9/18/98</td>
<td>Midazolam Roche</td>
<td>Sedation/anxiolysis/amnesia</td>
</tr>
<tr>
<td>4</td>
<td>12/14/98</td>
<td>Abacavir Glaxo</td>
<td>HIV</td>
</tr>
<tr>
<td>5</td>
<td>1/19/99</td>
<td>Ranitidine Glaxo</td>
<td>Gastro-esophageal reflux</td>
</tr>
<tr>
<td>6</td>
<td>7/12/99</td>
<td>Insulin glargine Aventis</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>7</td>
<td>8/11/99</td>
<td>Pemirolast Santen</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>8</td>
<td>8/11/99</td>
<td>Propofol Zeneca</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>9</td>
<td>8/11/99</td>
<td>Azelastine Astra</td>
<td>Itching associated with allergic conjunctivitis</td>
</tr>
<tr>
<td>10</td>
<td>10/1/99</td>
<td>Ammonium lactate Westwood-Squibb</td>
<td>Ichthyosis Vulgaris/xerosis</td>
</tr>
<tr>
<td>12</td>
<td>12/6/99</td>
<td>Etodolac Wyeth Ayerst</td>
<td>Juvenile Rheumatoid Arthritis</td>
</tr>
<tr>
<td>13</td>
<td>12/6/99</td>
<td>Oxaprozin Searle</td>
<td>Juvenile Rheumatoid Arthritis</td>
</tr>
<tr>
<td>14</td>
<td>1/3/00</td>
<td>Fluvoxamine Solvay</td>
<td>Obsessive Compulsive Disorder</td>
</tr>
<tr>
<td>15</td>
<td>1/6/00</td>
<td>Sotalol Berlex Lab</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>16</td>
<td>2/2/00</td>
<td>Gabapentin Parke Davis</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>17</td>
<td>2/2/00</td>
<td>Enalapril Merck</td>
<td>Hypertension</td>
</tr>
<tr>
<td>18</td>
<td>3/15/00</td>
<td>Remifentanil Abbott</td>
<td>Analgesic</td>
</tr>
<tr>
<td>19</td>
<td>3/15/00</td>
<td>Metformin Bristol-Myers</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>20</td>
<td>4/19/00</td>
<td>Tramadol R. W. Johnson</td>
<td>Analgesic</td>
</tr>
<tr>
<td>21</td>
<td>4/19/00</td>
<td>Bisoprolol/HCTZ Wyeth-Ayerst</td>
<td>Hypertension</td>
</tr>
<tr>
<td>22</td>
<td>5/22/00</td>
<td>Buspirone Bristol-Myers</td>
<td>Generalized Anxiety Disorder</td>
</tr>
<tr>
<td>23</td>
<td>8/2/00</td>
<td>Sevoflurane Abbott</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>24</td>
<td>8/14/00</td>
<td>Loratadine Schering</td>
<td>Seasonal allergic rhinitis &amp; chronic idiopathic urticaria</td>
</tr>
<tr>
<td>25</td>
<td>9/22/00</td>
<td>Lamivudine Glaxo</td>
<td>HIV</td>
</tr>
</tbody>
</table>

Source: FDA Status Report, Appendix B.

The significance of some of these new indications for paediatric medicine is illustrated in the examples below.
A. Over-the-counter medicines with potentially very large markets:

- extension down to six months for the over-the-counter use of ibuprofen products, widely used to relieve fever in children.

B. Treatments for life-threatening illnesses:

- directions for use of insulin glargine for paediatric diabetes patients six years and over;
- addition of information in the use of ranitidine in the neonatal population, for whom gastroesophageal reflux can cause serious and even fatal respiratory problems; and
- directions for use of abacavir in paediatric patients aged three months to twelve years.

C. Treatments for chronic conditions:

- new indication for etodolac, a treatment for children (approximately 100,000 in the US) with the frequently debilitating condition juvenile rheumatoid arthritis;
- proper dosing information for cromolyn in children aged two to six, a preventative treatment for allergies that does not act as either sedative or stimulant and therefore allows learning to be unaffected during treatment; and
- dosing and safety information for the use of fluvoxamine in children aged 8-17 with obsessive compulsive disorder (OCD).

The second two categories have potentially major long-term benefits for health. An obvious example is insulin glargine: where this combination therapy is more successful in controlling blood sugar levels, the long-term risks of organ failure are reduced. The new indications described by the FDA are expected to allow children with a range of conditions to lead more active lives, and to be better able to learn and develop.³⁵

³⁵ FDA Status Report pages 9-12

### 3.4.4 Products for which FDA Written Requests have been issued

Table 3.2 below, reproduced from the FDA Reports, shows the numbers of Proposed Pediatric Study Requests received by the FDA to September 2000, and the number of Written Requests, by therapeutic area.
Table 3.2: Proposed Pediatric Study Requests (PPSR) / Written Requests (WR)
(as at September 2000)

<table>
<thead>
<tr>
<th>Review Division</th>
<th>PPSRs Received</th>
<th>WRs Issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiorenal</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Neuropharm</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Oncology</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Medical Imaging</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anesthetic</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic &amp; Endocrine</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Anti-Infective</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Anti-Viral</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Dermatology</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Anti-Inflammatory</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>Over-the-Counter</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Reproductive</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Special Pathogens</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>191</strong></td>
<td><strong>157</strong></td>
</tr>
</tbody>
</table>

Source: FDA Status Report, Appendix B.

Notes: The FDA may have issued more than one Written Request for the same active substance if multiple sponsors hold licences. This table does not reflect incomplete actions FDA has taken on proposals submitted by industry.

The tight timelines for submitting data imposed by Written Requests have led to pressures on the conduct of trials. This may be particularly problematic in areas where diagnosis and measurement are difficult, such as the treatment of anxiety and depression in children.

Some of the EU paediatricians we spoke to considered that the list was not optimal in terms of the potential benefits for children; for example that it may contain too many heart treatments. The nature of the incentive – an additional period of exclusivity – is certain to lead pharmaceutical companies to focus on paediatric studies for medicines where there are significant potential monetary gains from that additional exclusivity.

However, each of these active substances has been approved by the FDA as of potentially significant benefit to children. The FDA’s own judgement is that fewer of these studies would have taken place without the provision.

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36 This suggestion is also reported in Choonara et al (2000) Section 7.2.
3.4.5 Effects on health care and pharmaceutical outlays

Reducing the demand for other medical treatment

A stronger evidence base for paediatric medicine would bring potential gains in reduced health care costs both in the short-term, where the need for other and more expensive interventions is reduced, and over the long-term, with more healthy teenagers and adults needing less treatment.

In many cases, the kinds of gains to health reported in Section 3.4.3 above from better-informed use of paediatric medicines would be associated with significant reductions in the demands on other health care services, eg:

- better treatment of HIV in infants would in many cases reduce the need for treatment of associated infections;
- better management of acid reflux in neonates would in many cases reduce the time and intensity of hospital treatment required; and
- better treatment of paediatric diabetes, with more stable blood sugar levels, would reduce the need for medical care resulting from the complications from the illness. For the UK, total health service costs arising from the treatment of diabetes-related conditions have been estimated at between 5 and 10 per cent of health service costs.37

The FDA anticipated that there would be substantial savings in future health care costs arising from the Pediatric Exclusivity Provision, but did not attempt to quantify these.

To illustrate the extent of the possible gains, the FDA reported the findings of a limited analysis initially published in the preamble to the Pediatric Rule. The FDA had examined hospitalisation rates for five serious illnesses (asthma, HIV/AIDS, cancer, pneumonia, and kidney infections). In each case, hospitalisation rates were higher for children than for adults. Eliminating 25 per cent of the difference between these hospitalisation rates for these five conditions would lead to direct medical costs savings of $228 million annually. These did not capture the potential cost savings from other serious illnesses affecting children, including hypertensive and renal conditions.38

So while the FDA considered that future cost savings in health treatment costs from a better evidence base for paediatric medicine would be large, it did not seek to estimate these savings, producing only illustrative projections for a subset of the potential cost savings.

Additional Resource Costs

The FDA Status Report did not seek to estimate the additional resource costs associated with developing formulations, carrying out trials, or of maintaining paediatric formulations in the formulary.

37 Source: ABPI
38 FDA Status Report page 14.
Nor did it seek to identify any other form of resource cost associated with the additional exclusivity, although it did note the costs that would be imposed on health insurance schemes and on those not covered by health insurance: these parties may have to change their behaviour at the margin where there is longer exclusivity period.

The FDA did note that the costs of extended periods of market exclusivity might hit hard those without medical insurance. This is likely to be less important an issue in the EU given the principle of universal health insurance.

Additional earnings of pharmaceutical companies

The FDA also provided an assessment of the additional earnings research-based pharmaceutical companies might be expected to earn from the additional six months of market exclusivity. This was based on an FDA analysis of a profile of drug prices and revenues following expiry, constructed from IMS Health Data.

For the 119 products subject to Written Requests for which the sponsors had indicated they were conducting trials or would conduct trials, the innovator drug industry was expected to gain additional sales revenues of approximately $29.6 billion (undiscounted) over the affected 20-year period. Consumers were expected to pay $13.9 billion of this; generics manufacturers to lose $10.7 billion in new sales, and retailers to lose $4.9 billion of lost revenues. Discounting to present values roughly halved these sums.

To set these amounts in context, the FDA calculated that the measure would add roughly 0.5 per cent to the nation’s annual drug bill.

It is important to note that these are estimates of future transfers not of additional resource costs. The $29.6 billion is not an estimate of the cost to the US, but of sums received by research-based pharmaceutical companies rather than available to consumers (patients and health insurers) or received by generics manufacturers or retail pharmacists.

It is not appropriate to compare this sum with any estimate of the reduced cost of future hospital care, which is a genuine saving in resources used and should be compared with the possible resource costs noted above.

However, it is relevant to assess the financial consequences for different kinds of individuals and companies. For example, for health insurers there are two effects on outlays that would work in opposite directions. Health insurers’ outlays would be reduced by the reduced needs for hospital treatment arising from better drug treatment of paediatric conditions, but increased by the delays in cheaper generic versions becoming available.

It would be entirely practicable to replicate the FDA’s calculation for the EU for the same set of medicines, or another illustrative set. Given that in many national pharmaceutical markets within the EU generics are not significant and prices do not decline sharply on the expiry of exclusivity,

39 FDA Status Report page 17.
the effect on total expenditure on pharmaceutical products would probably be proportionately lower.

3.4.6 Lessons from the US experience

The US experience shows that:

• an adequate incentive for paediatric clinical trials for products where this is considered appropriate by the authorities will lead to a dramatic increase in the number of such trials;

• such trials can rapidly feed through into new licensed paediatric indications and better labelling and hence into improved treatment of paediatric patients; and

• medicines at different stages of their lives may need different forms of incentive.

3.5 Incentives and Paediatric Trials in the EU: Products Already on the Market with Patents

This and the next two sub-sections focus in turn on:

• products already on the market with patents (Section 3.5);

• products no longer in patent (Section 3.6); and

• new products coming onto the market (Section 3.7).

3.5.1 Exclusivity

Exclusivity is a natural starting point for an incentive to pharmaceutical companies in respect of paediatric trials. This is because a form of exclusivity – patents - is the main device society uses to induce effort into developing new drug therapies, and the benefits to human health from the medicines developed have been - and continue to be – enormous.

The most obvious challenge is that an incentive of additional exclusivity will generate trials for medicines that stand to bring the largest gains, not necessarily those with the greatest potential value for paediatric use. This risk is assumed to be managed – as in the US - by a regulatory authority's prior approval (the equivalent of an FDA Written Request) being needed before a paediatric trial could qualify for an incentive of the additional exclusivity.

There are several forms of extension to marketing exclusivity that could in theory provide the compensation argued for. In the EU these are:

a) patent extension (a change from 20 years to some other agreed figure for qualifying active substances);

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b) amendment of the terms of the Supplementary Protection Certificate for qualifying products;

c) data exclusivity extension, whereby a second applicant may not refer to the originating company's data for a period less than 10 years (the currently anticipated EU "norm"); or

d) administrative extension of market exclusivity, whereby the relevant licence-granting body extends the period before which it will accept an application for a product licence from a second applicant seeking to market the same drug therapy.

In the USA the incentive for additional paediatric clinical trials is handled via (d), a form of market exclusivity.

For an incentive to be effective for a particular product, it must add to the effective period of market exclusivity of that product. For the policy to work, it must be possible to devise an appropriate instrument.

Data exclusivity

The Commission has set out its intention to move towards harmonisation of data exclusivity at ten years. This would clearly be a major step, and one that may give valuable protection to intellectual property in respect of applicant countries for EU membership.

However, even from a base of ten years, additional data exclusivity by itself is unlikely to add to the effective period of market exclusivity of the particular therapy. A second applicant is not prevented from repeating the trials for his or her own purposes within the period of data exclusivity, thereby annulling the originator’s exclusivity. If the originator’s patent has expired – or is about to do so – then the second applicant may be expected to enter the market on the back of his or her own data within the originator’s period of data exclusivity.

In this respect data exclusivity is always a weaker form of market protection. In the case of small market opportunities, such as those entailed by paediatric applications, an additional period of data exclusivity is in itself unlikely to provide sufficient incentive for the originator to do the necessary work.

Pharmaceutical products in the EU are protected by patents and the Supplementary Protection Certificate (SPC), which separately or together normally assure 15 years market exclusivity of the active substance. Data exclusivity runs for 6-10 years from the date of approved dossier, and on expiry is still likely to leave the therapy protected for a further period by the patent or SPC. In such cases, the extension of the period of data exclusivity by six or twelve months will normally have no effect at all on incentives to seek a paediatric indication for a product.

In such a situation, a second applicant may not commercialise his product until expiry of patent or SPC, and the period of data exclusivity is simply not the relevant factor.
Amending the Supplementary Protection Certificate provision is a more natural solution. Under the European Patent Convention, signatory states grant pharmaceutical patents for 20 years. The Council regulation on the “supplementary protection certificate for medicinal products” (EC 1768/92) became effective on 2 January 1993. With this certificate, a product’s exclusivity period can be extended by up to five years, subject to a maximum of 15 years of patent protection from the time of first product launch in an EU country.

The preamble notes that:

“Whereas pharmaceutical research plays a decisive role in the continuing improvements in public health…….;

Whereas at the moment the period that elapses between the filing of an application for patent for a new medicinal product and authorisation to place the medicinal product on the market makes the period of effective protection insufficient to cover the investment put into the research…”

This provision was adopted in order to give an appropriate degree of incentive to invest in the development of new drug therapies. It seems natural to make a marginal adjustment to that provision as means of providing an additional incentive to incur further costs and risks in following through their original innovation into the more difficult area of paediatric medicines.

Making such an adjustment in respective of paediatric trials would require a review of the SPC legislation, whereas achieving a corresponding effect in the case of patents would require a Treaty revision. In either case, it is hard to see any change being made within a short time-period, and the introduction of a new incentive through these routes could give rise to prolonged uncertainty.

**Market exclusivity**

Faced with ambiguity in the Pediatric Exclusivity Provision in Section 111 of the Food and Drug Administration Modernisation Act, the FDA reports that it interpreted the additional exclusivity in a broad fashion. It had added six months to any of the sponsor’s listed patents or previous non-expired grants of exclusivity on drug products containing the active substance that was studied. Copies are then not given marketing approval within that period. Effectively, this interpretation provides six months additional market exclusivity, adding six months to whatever had previously been the effective source of exclusivity that was due to expire last.

In the US context, this was the most direct way of giving an incentive to research-based companies to sponsor paediatric clinical trials.

For the EU, a form of market exclusivity may also represent a flexible instrument in a way that patents and SPCs may not be. For example, the FDA Status Report indicates that for paediatric

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41 FDA Status Report
patients to benefit to the full extent possible, it may be appropriate to grant a second period of exclusivity for some products. If this also proves to be so in the EU, market exclusivity may be a more appropriate form of instrument.

Introducing market exclusivity in the EU may require a new administrative mechanism, including the preparation of an official record of exclusivities similar to the FDA’s Orange Book.

There are practical challenges with such an approach:

- the range of products containing the same active substance will in many cases differ between EU Member States; and
- the effective periods of market exclusivity offered by patents and SPC will differ between EU Member States.

Policy development work at the EU level would therefore have to include the development of an effective mechanism for co-ordinating changes to the different exclusivities provided by different EU regulatory authorities.

3.5.2 The Orphan Drug Regulation: a useful precedent

There is a precedent for introducing market exclusivity into the EU. The Orphan Drug Regulation, introducing a new form of market exclusivity for medicines with limited sales, came into effect on 22 January 2000.

This Regulation is intended to encourage the development of products where markets are too small to encourage normal commercial development, known as orphan products.

For this purpose, the EU has agreed that a form of market exclusivity is the appropriate way of providing incentives to commercial development. In its work developing the Orphan Drug Regulation, the European Commission noted that:

“… experience in the United States of America and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered.”

For products designated as orphan products by a Committee of experts appointed by Member States, the form of the market exclusivity is as follows:

“Where a marketing authorisation of an orphan medicinal product is granted [whether under centralised or mutual recognition procedures], the Community and the Member

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States shall not, for a period of 10 years, accept another marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product”.

(Extract from Article 8 of the Orphan Drug Regulation) ……

The selection issues are similar to those raised in paediatric medicine – the lack of commercial prospects – and indeed it seems likely that applications for paediatric indications would in some cases meet the criteria of the Orphan Drug Regulation.

Compared to the form of market exclusivity awarded by the FDA under the Pediatric Exclusivity Provision, that under the Orphan Drug Regulation is different in important respects: it applies only to the particular therapeutic indication rather than protecting the active substance. It also provides protection against the entry of similar medicines,

From the analysis of Section 3.2 above, providing some additional market exclusivity in respect of a paediatric indication only would not provide a powerful incentive to develop paediatric indications for in-patent medicines: the potential additional revenues would typically be minimal. The precise form of exclusivity under the Orphan Drug Regulation would therefore not be appropriate for developing paediatric medicine.

However, the most pertinent point here is that the EU has established a form of market exclusivity and the mechanisms to enforce it. If it has done so for orphan drugs, then it can probably do so for paediatric medicines if the political will is there.

3.5.3 Duration of additional exclusivity

An additional period of market exclusivity was shown in the US to be an effective vehicle for giving an incentive to pharmaceutical companies in respect of paediatric clinical trials.

The additional market exclusivity under the FDAMA's Pediatric Exclusivity Provision was for six months. To provide the same reward for carrying out a trial, and hence the same incentive, the corresponding period in the EU would need to be longer:

- the EU pharmaceuticals market is smaller than that of the US;44
- the costs of submitting data to multiple authorities, and of maintaining formulations to the specification of different national authorities, are likely to be greater; and
- products in several EU markets experience relatively slow declines in sales revenue after patent expiry, in contrast to the US where the decline is more rapid.

This last point is shown vividly in a recent study for the European Commission.45 The analysis in Section 5 of that report shows that in France and Italy – after Germany, the second and third

44 As shown in Section 4 below, the combined value of sales in the five largest EU markets is about half that in the US.
largest EU pharmaceutical markets. Market shares of different kinds of products in a molecule did not change greatly on patent expiry over the period 1986-97. Competitors entered at prices similar to those of the original products, and the prices of the original branded products did not fall. This was in marked contrast to Germany and the UK, where the prices and market shares of original branded products did fall on patent expiry.46

US pharmaceutical markets are larger than the EU market, and US revenues decline more rapidly on the expiry of market exclusivity than revenues in most or all EU markets. The effect is that an additional period of exclusivity in the US is worth more than the same addition would be in the EU. To provide an incentive in the EU as powerful as that given in the US under the Pediatric Exclusivity Provision, a period of additional market exclusivity in the EU would need to be longer than six months.

3.5.4 Conclusions

For licensed products on the market, an additional period of exclusivity is the obvious instrument for providing financial incentives to companies to sponsor paediatric clinical trials. Of the different forms of exclusivity:

- additional data exclusivity is unlikely to offer any incentive;
- additional patent exclusivity or a longer SPC would require major new legislation; while
- a form of additional market exclusivity may provide a more flexible and powerful administrative instrument.

To have an equivalent incentive effect, any period of additional exclusivity would need to be longer than in the US.

3.6 Incentives and Paediatric Trials in the EU: Out-of-patent Products

3.6.1 Introduction

For products that are already out-of-patent, there is no obvious mechanism for granting market exclusivity in respect of an active substance.

Yet a high proportion of products for which there may be gains from paediatric trials that lead to paediatric indications are out-of-patent. One paediatrician we spoke to estimated that in 75-90 per cent of cases, medicines given to children in hospitals are out-of-patent. This class of products is too important to be ignored by policy on the development of paediatric medicines.

The policy challenge here is to give someone the incentive to sponsor or carry out such trials.

Here it may be appropriate to consider a wider range of options.

46 Ibid Table 23, Figures 7 and 8.
Brian Wright (American Economic Review, 1983) shows how different forms of information asymmetry make different forms of solution socially optimal.

Wright’s analysis identified several desirable properties of patents:

- their limited lifespan gives incentive to rapid commercialisation;
- the extent of the right to exploit the knowledge is clear, and the knowledge is in the public domain;
- the possibility of constructing a clear set of rules for judging patent applications, and these can be credible. For example, with a government commitment to award prizes firms would be suspicious that governments would wish to reduce the offered prize when the time came; and
- other potential systems (e.g., prizes or research contracts) being more subject to failings in the working of public sector institutions.

Nevertheless, prizes and research contracts were found to be appropriate mechanisms for rewarding innovative effort under certain circumstances, and are worth considering in reviewing alternative incentive mechanisms for out-of-patent products.

**Prizes and research contracts**

Under a “prize” model, public authorities might declare a prize for the first company or laboratory to submit data leading to a licence for paediatric use for one or other of a specified class of medicines. Apart from determining an appropriate level for such prizes, policy design would need to reflect the source of funding for the prize.

Any policy of giving “prizes” would also have to be set up so as to avoid wasteful and possibly unethical duplication. Prizes could therefore not be awarded for submitting data, but would probably have to relate to the submission of good-quality proposals.

A “research contract” model would take this a step further: public authorities would let a contract for the development of a particular paediatric medicine and/or carrying out a particular paediatric clinical trial.

These procedures will only be efficient if the public authorities – either different Member State governments or through a joint programme – have the expertise to decide which are the most promising lines of research, and to specify projects in ways that led to fruitful useful lines of investigation.

It was noted in Section 2.7 that the therapeutic areas identified as research priorities by EU paediatricians in our telephone interview included significant areas of overlap, and that the paediatricians we spoke to were confident that, despite differences in clinical practice, it would be possible to achieve agreement at the EU level on key research priorities.
Paediatricians and government in Germany are considering a model of funding such research through a Foundation. At the EU level, such a Foundation could be funded through contributions from Member States, health insurers and the pharmaceutical industry. A Board consisting largely of academic paediatricians might then agree a programme of research contracts, specify particular products most suited to paediatric medicine within the agreed set of therapeutic areas.

The precedents of setting up and managing the CPMP and the Committee for Orphan Medicinal Products would be valuable in developing the machinery for such a prioritisation exercise at the EU level.

**Transferable market exclusivity**

Building on the analysis above, one possible line of approach – one raised by the FDA in its Status Report – would be to offer market exclusivity in respect of trials on out-of-patent products that was transferable to another, patented, product.

For any research-based company, the value of approval of paediatric research work on any generic product could be as high as the value of an additional period of market exclusivity on its biggest-selling product in the EU.

Such an opportunity could be expected to generate strong interest from several research-based companies. Given that it would be wasteful – and unethical - for multiple versions of similar trials to be carried out, the transferable exclusivity in respect of a particular out-of-patent product could perhaps be awarded to the first party that submitted a satisfactory proposal, or the party that submitted the best proposal (according to criteria set out by the authority) within a given time period.

While the principle of rights or obligations being tradeable is well-established, particularly with the development of tradable emissions permits in the last decade, the design of such a competition would be demanding, and its supervision resource-intensive. Given that the link between the product studied and the product for which exclusivity is granted would be broken, a clear and robust procedure to determine which company benefited from a transferable exclusivity in respect of paediatric development of a particular out-of-patent product would be essential.

The policy would also have to be designed so as to ensure that any new formulations associated with the newly-developed paediatric indication remained in production. These formulations would be without the shield of exclusivity held by paediatric formulations of patented medicines.

**Exclusivity for the paediatric indication**

Another approach - compatible with either of those above - would be to award market or data exclusivity for the paediatric indication to the party that first submitted data resulting in a paediatric indication for an out-of-patent product.

The notion of market exclusivity with respect to an out-of-patent paediatric indication is close to that of market exclusivity awarded for an orphan drug indication (see Section 3.5.2 above).
A form of market exclusivity – for a period of several years as in the Orphan Drug Regulation - may provide a useful element of a policy for encouraging the paediatric development of out-of-patent medicines.

For example, for many older products used in the paediatric population, we are advised that there may be sufficient data from a long period of use to justify a submission in respect of a paediatric indication. A form of market exclusivity may be a good way of motivating the synthesis and submission of such data.

A period of exclusivity for a paediatric indication for an out-of-patent product would be most useful where there was some differentiation of the paediatric formulation, so that the product could effectively be marketed as a brand. Where this differentiation was impossible, competition from off-label use of unbranded generics would tend to nullify the advantage.

The European Medicines Evaluation Agency (EMEA) announced in March 2001 reduced licence and scientific advice fees for orphan products designated under the Regulation. This kind of measure may also be helpful in encouraging the paediatric development of out-of-patent medicines.

Conclusion

Out-of-patent products are too important to be ignored in EU policy for the development of paediatric medicine. Of the different approaches outlined above, a transferable exclusivity would be likely to provide by far the greatest incentive to develop paediatric indications for out-of-patent medicines. The potential rewards would probably be so much greater than any likely level of prize, and gains from other mechanisms (eg data exclusivity for the indication) are likely to be small and vulnerable to competition located just outside the protective mechanism.

Indeed, the regulatory authorities may face difficult choices in judging between competing bids from the research-based companies.

Such a policy may need to be supplemented by research awards let through a public body.

A form of market exclusivity for a paediatric indication – for a period of several years as in the Orphan Drug Regulation - may provide a useful element of a policy for encouraging the paediatric development of out-of-patent medicines.

3.6.2 Products with limited sales

Products with limited sales - such that an additional period of exclusivity is not valuable – were another set of products identified by the FDA for which the Pediatric Exclusivity Provision had not been effective.

As with out-of-patent medicines, a transferable exclusivity is likely to be the most effective way to generate research into the paediatric use of a particular medicine in this category.
The Orphan Drugs Regulation was introduced precisely to give an incentive for the commercial development of products with only limited commercial potential.

3.7 Incentives and Paediatric Trials in the EU: Products not yet Licensed

A regulatory requirement?

For products that do not yet have a licence, the policy challenge is to have the right balance between regulation and incentives.

Where the prospective returns do not provide sufficient reward for companies to undertake paediatric development, companies are unlikely to be energetic in meeting such a requirement, unless some incentive is also offered for them to do so. This is indeed the experience of the US, where the results of the 1994 Pediatric Labeling Regulation - requiring companies to survey existing data and determine whether those data were sufficient to support additional paediatric use information – are reported by the FDA as having been disappointing.47

Hence the adoption in the US of a policy characterised by Milne as a “carrot and stick” policy, with the Pediatric Rule for new indications introduced alongside the Pediatric Exclusivity Provision, as discussed in Section 3.4.

At one end of the spectrum, regulatory authorities in the EU could designate certain new products as of potential value to children, and make providing data on paediatric trials - and submitting data for paediatric indications if such indications were appropriate – a condition of having an initial product licence.

If such a regulation was not well-designed, it could potentially have undesirable effects:

- regulatory authorities could be forced to make judgements about the suitability of a product for children before its effects on adults were fully understood; and
- given the internationally-agreed guidance on conducting paediatric trials, the licensing of products, and their availability to adult patients, could be delayed.

Earlier Europe Economics work on patient access showed that patients in many EU Member States face long delays before important new medicines become available.48 Introducing an additional regulatory requirement that would add to those delays would be highly undesirable, both for adult patients and for pharmaceutical companies.

Policy design for new products should seek to avoid any regulatory requirements that lead to delays in new products becoming available to patients. Any requirement to submit paediatric data along with submissions for new products or indications deemed likely to be of therapeutic

47 FDA Status Report Page 3.
benefit would need to accommodate the different timing of paediatric development appropriate for different kinds of products, as illustrated in Section 2.4 above.

Companies with product licences in the EU are required to keep their dossiers up-to-date. Part of this process – for designated products - could be a requirement to have completed paediatric trials within a certain time of the licence being awarded (time-lag to be agreed, reflecting the ICH guidelines), and to maintain any resulting paediatric indications, along with any associated formulations.

Given that the pharmaceutical companies have signed up to the ICH guidelines on clinical trials in children, regulatory authorities will now have a strong basis for pressing them on their paediatric development programmes. For many products, particularly where there are other effective treatments, this will be after they are on the market. In the UK, licences have to be renewed every five years. This provides an opportunity for pressure to be applied, as the review at licence renewal can include paediatric development.

The design of regulatory policy on paediatric trials for products not yet licensed may perhaps be most appropriately considered as part of the review of pharmaceutical legislation that is already under way in the EU. But in doing so, it will be important not to lose sight of the question of incentives.

Incentives for new products

An additional period of exclusivity for submitting paediatric data introduced for designated medicines already on the market could be applied equally to appropriate new medicines yet to be licensed. It would have a powerful effect in stimulating the earliest practical paediatric development of new products.

The prospect of an additional period of patent or market exclusivity in the EU to carry out paediatric trials on products not yet licensed would also, at the margin, increase the incentive to engage in pharmaceutical R&D on products for which the regulatory authorities may wish paediatric product trials to take place.

This could be expected to lead to:

- an increase in the total amount of pharmaceutical R&D investment undertaken in the EU; and
- a shifting of the research programme at the margin towards medicines which the authorities might be expected to designate as potentially of benefit for the paediatric population.
3.8 Taking Account of Data Collected under the US Exclusivity Provision

As of September 2000, 25 additional periods of market exclusivity had been awarded under the US Pediatric Exclusivity Provision (see Table 3.1 above) with more expected to follow.

As all were products for which the FDA had issued a Written Request under the Provision, it is likely that many of these products would be considered suitable candidates for any incentive developed in the EU.

However, for these products the trial data already exist.

Given the progressive harmonisation in guidelines for clinical trials, robust trial data accepted by the FDA will in most cases also be accepted by EU authorities. In a minority of cases, a different comparator treatment may be required by a particular EU licensing authority, but in broad terms the submissions under which an additional paediatric indication has been granted in the US will also support such a submission in respect of such an indication in the EU. The ethical justification for insisting on separate studies in children to generate paediatric labelling in the EU is questionable if data submitted in the US are sufficient to support paediatric labelling in the EU.

However, if the purpose of an EU incentive is defined as to ensure that paediatric data are submitted for review by EU authorities, then whether additional exclusivity has been awarded for a particular drug therapy in the US market does not have to be material to the structure of the new incentive. As long as the data are scientifically applicable to the paediatric population in the EU, whether or not additional exclusivity has already been awarded in the US in respect of such data need not affect the eligibility of the submission for an award of additional exclusivity in the EU.

Some participants in the EU debate may be attracted by the idea of “free-riding” on the US data, by introducing a restriction that no further incentive should be offered in respect of data forming the basis of a submission that had already led to the award of additional exclusivity in the US. The development work and clinical trials have already taken place: why should the EU also pay for the data to be submitted?

However, such an approach would be short-sighted. Under a policy of not awarding the incentive in respect of data forming the basis of a submission that had already led to the award of additional exclusivity in the US, companies with in-patent products would then face the following trade-off:

“Do the additional earnings that will result from licences for paediatric indications justify the costs and risks of preparing and submitting the data for EU authorities and of developing and maintaining the new paediatric formulation?”

For many products, the answer would still be no, even though, compared to the position before the trial, some of the development work had been done. Free-riding in this way would therefore lead at best to patchy results, because for many products the paediatric dossiers would not be
submitted. A policy of free-riding may be ineffective in that paediatric data for many important medicines may not be submitted for review by EU authorities.

Companies that take the risk of investing in new pharmaceutical products are able to patent the resulting chemicals in a number of jurisdictions, not just their jurisdiction of residence. It could be argued by analogy that the development of a new paediatric medicine should similarly be rewarded more widely than the original jurisdiction. Of course the investment and degree of risk involved is much less than in the development of a new therapeutic molecule, so the analogy is valid only up to a point.

A policy of free-riding on US funding for the development of paediatric medicine would also:

(a) explicitly position the EU as a follower, rather than a leader, in the development of paediatric medicine; and

(b) represent a missed opportunity to demonstrate the political will to improve the relative position of the pharmaceutical research and investment climate in the EU as against that in the US.

However, there is a further set of important questions that need to be considered first: whether the EU has the capacity to respond to a new incentive and actually carry out a greater number of clinical paediatric trials.

3.9 Capacity for More Paediatric Trials in the EU

3.9.1 Would an incentive generate increased demand for paediatric trials in the EU?

The harmonised guidelines on the conduct of clinical trials, negotiated under the ICH, have important implications for the location of clinical trials:

- such trials can now be carried out anywhere in the world; and

- there is sufficient regulatory harmonisation that data providing the basis of a submission in the US can support submission in respect of an indication in the EU, and vice-versa.

Hence the conduct of paediatric clinical trials is in principle global. A global pharmaceutical company wishing to conduct a clinical trial may seek patents in any or all of the countries in which it operates.

To protect themselves, regulatory authorities naturally reserve the right to inspect research units providing the data submitted in respect of clinical trials. This activity too is becoming global.

However it is reasonable to presume that the availability of an adequate incentive in the EU for conducting paediatric clinical trials would lead to a significant increase in the demand for paediatric clinical trials in the EU.

Corroborating evidence from our discussions with EU paediatricians is that the FDA's Pediatric Exclusivity Provision has led to increases in the demand for paediatric trials in the EU only in a
small number of therapeutic areas. This is despite the proportionately large increase in trials and submissions reported by the FDA.

More than one EU paediatrician interviewed suspected that the increase in demand for paediatric trial subjects in certain therapeutic areas in the EU reflected the exhaustion of the US supply of such patients, ie it was an overflow. This was suggested, for example, in the area of hypertension.

Compared to the multinational US companies, many EU companies that may wish to carry out trials are smaller and have less of a global presence. They are thus more likely to wish to sponsor trials close to their domestic markets and research centres.

The implication is that an incentive that led companies to wish to apply for paediatric indications in the EU would also lead to a dramatic increase in the demand for such trials to be carried out in the EU.

3.9.2 The EU’s capacity to carry out more paediatric clinical trials

A variety of skills is needed to run successful paediatric drug trials. These include:

- skills in designing the trials in an appropriate way for the relevant paediatric population, in turn requiring using appropriate dosage and formulations for the trial given adult data, and appropriate measurement metrics and technologies; and

- skills of recruiting patients with informed consent and of carrying out the investigations.

Given the limited number of trials in the past, it is a legitimate question to ask whether the EU has the capacity to carry out more paediatric clinical trials.

**Number of patients**

For some trials, the limiting factor is the number of patients. Where there are relatively small numbers of paediatric patients, or where recruitment is particularly difficult, this may prove a powerful limiting factor.

However, trials can be designed to minimise the number of paediatric patients required, and the experience of the paediatricians we consulted was that where there was a medical need, such trials could be developed and carried out.

**Trained medical professionals to carry out trials**

The potential number of doctors able to act as investigators in clinical trials is large. Outside the teaching hospitals, it includes many other paediatricians and primary care physicians.

Given the limited numbers of such trials carried out in the past, many EU paediatricians have little experience of paediatric clinical trials. This may be less of an issue with measuring short-term responses to anti-infective treatment, but more of an issue with more complex protocols for chronic diseases.
Limited amounts of training may therefore be needed on how to build such an investigative role into their clinical practice. With such training, there is unlikely to be a shortage of paediatricians able and willing to participate in trials they consider acceptable and of likely benefit to their patients.

In many paediatric drug trials the necessary consent can best be achieved by nurses, and some departments or investigators may not be able to call on any excess capacity of research nurses to lead in achieving informed consent and in the management of patients on the trial. This constraint can be eased by appointing nurses, or where necessary doctors, specifically to manage the process of recruiting patients to the trials.\textsuperscript{49}

None of those we spoke to considered these obstacles to be insurmountable.

\textit{Incentives for paediatricians}

The willingness of paediatricians to participate is sometimes suggested as a further difficulty. However, the advice we consistently received that if there is a medical need and the trial is well-designed so as to be ethically acceptable, paediatricians will be willing to take part.

One possible exception - and one area where sponsoring companies may face frustration - is that paediatricians may decline to participate in trials where several products of a class already have similar paediatric indications. Here there may be little of potential interest and little potential benefit for paediatric patients.

Analysis of clinicians' motives and incentives supports the view that for a programme to be effective in promoting research into better paediatric medicine in the EU, it must provide both incentives to pharmaceutical companies and research directed into the priorities considered important by clinical paediatricians.

A further potential difficulty is that, at present, clinicians tend to receive the same payment for paediatric and adult trials. Clinicians may then be unwilling to carry out paediatric trials, because the trials are usually more difficult to perform. Incentives in the form of payment schedules that reflect the resources required to carry out paediatric trials should overcome any such unwillingness.

\textit{Capacity of laboratories}

One of our interviewees highlighted the limitations of the centralised laboratory facilities used by the pharmaceutical companies for clinical trials. These laboratories tend only to be equipped for adult trials and not, for example, for testing microsamples from children. Further investment in laboratory and equipment may be required for more paediatric clinical trials.
Design skills

One potential bottleneck is of the specialised skills necessary for the appropriate design of paediatric trials, given the different challenges they present. These challenges are both technological and ethical:

- different forms of measurement may have to be used where metabolism is different (e.g. for infants or newborns) or where data collection methods (e.g. repeated blood sampling) used for adults are considered unacceptable; and

- trials against placebo will not normally be considered acceptable where there is an effective alternative treatment.

Expertise in paediatric clinical pharmacology may be valuable in the design of a trial as well as its implementation. It is valuable if there is such expertise within the sponsoring company as well as in the research institutes or hospitals.

From discussion with a small sample of paediatricians, the picture may vary across Europe. The Netherlands, France, and Italy are amongst EU countries thought to be well-equipped for designing and carrying out more paediatric clinical trials.

Within France, there is an active network of paediatric clinical pharmacologists and paediatricians willing to help devise suitable protocols. For some products, this network has developed its own protocols for paediatric research. Pharmaceutical companies have not necessarily wished to sponsor such projects, but it shows that the capacity is there.

There is limited capacity or expertise in Germany in carrying out paediatric clinical trials. However, there have been training courses and many teaching hospitals are now aware of the issues. With training now under way, including at Marburg, a network of younger paediatricians with competence in carrying out such trials is beginning to take shape.

Within the UK, the number of trained paediatric clinical pharmacologists has been limited, although the industry is supporting training programmes in paediatric clinical pharmacology.

However, the qualitative picture emerging here is of a large number of EU health professionals able - often with some initial training - to participate in designing and carrying paediatric clinical trials.

Possible legal impediments

The legal frameworks of certain EU Member States may serve to limit the development of paediatric clinical trials. Two such elements in France are:

- the requirement that informed consent of both parents be sought; and

49 Choonara et al Sections 6.2.6; 6.2.7.
• the requirement that companies sponsoring a trial take full legal responsibility for any adverse consequences.

The first makes recruitment more difficult; the second makes companies reluctant to sponsor trials. Both may limit the extent to which additional trials would be carried out in France.

Legislation in Germany does not allow trials that do not benefit the individual child. Hence trials against placebo are not normally possible; nor is it possible to carry out pharmacokinetic studies to study the rate of metabolism of a product. Blood sampling is difficult.

For any significant medical intervention relating to a child in Germany, informed consent of both parents is required, to be given in the presence of the investigator. This is practically difficult. In many families, it is not easy to establish who the relevant parties are.

The European network

Voluntary associations of research institutes and professionals have been formed within the EU to argue the case for, and strengthen the capacity to do, more paediatric drug trials.

The European Network for Drug Investigation in Children (ENDIC) was formed in December 1998 and at the end of 2000 included 11 European centres in nine European countries, including Switzerland and Israel as well as EU members states France, Germany, Finland, Italy, the Netherlands, Sweden and the UK.

The number of paediatric clinical specialists with experience in designing clinical trials of medicinal products in the EU is limited, but they can be readily identified though their publications or membership of networks.

The ENDIC network has shown itself capable of carrying out clinical trials together and of assisting the training of research fellows.

Conclusion

While we have no rigorous quantitative measure of capacity, nothing arising from our interview programme was inconsistent with the published view of a member of the ENDIC network:

“There is considerable potential for the pharmaceutical industry in association with academia to investigate clinically relevant medicines in paediatric medicines in Europe.”

Even setting aside the fundamental point that trials can be conducted anywhere in the world provided the necessary clinical standards of their conduct are maintained, there do not seem likely to be strong arguments on capacity grounds for the EU to delay proceeding with additional incentives for paediatric clinical trials.

50 Choonara et alSection 2.2.2.4.
4 THE COMPETITIVENESS OF THE EU PHARMACEUTICAL INDUSTRY

This section considers the likely effect on the competitiveness of the EU pharmaceutical industry of offering an incentive for paediatric trials.

It does this at two different levels.

The first relates to changes over time in the relative positions of the EU and US pharmaceutical industries, and at how changes in intellectual property protection in different markets might affect their relative growth. Evidence on this issue is considered in Sections 4.2 and 4.3, following a summary in Section 4.1 of key evidence on competitiveness.

The second level of analysis relates to the underlying capacity for research into paediatric medicines of the two national research communities. Evidence on this issue is considered in Section 4.4.

The central issue of policy design here is of improving the evidence base for safe and effective use of medicines in children, not industrial competitiveness.

Nevertheless, the impact on industrial competitiveness is a material secondary issue relevant to the design of policy to develop the evidence base for safe and effective use of medicines in children.

4.1 The Evidence on Competitiveness

Competitiveness can be defined as the capability of a firm or an industry to face and respond to external competition. The concept of competitiveness, therefore, is intrinsically a relative one, because it consists of the evaluation of the performance of the unit considered compared to the performance of its competitors. The analysis of competitiveness is also a forward-looking analysis, seeking patterns that point to future success or decline.

The question of the competitiveness of the EU pharmaceutical industry has been central to debate within the EU Council on policy towards the sector.

In its Resolution of 23 April 1996, the Council states that “…sufficient profitability is necessary if the European pharmaceutical industry is to cover the investment required to guarantee its capacity for innovation and thus ensure its competitiveness at the international level…”. And in its Resolution of 18 May 1998 the Council states that “…the Council considers that the Community policy should address the need to strengthen the competitiveness of the European pharmaceutical industry, in particular by encouraging research and development which is required for therapeutic improvement and cost-effectiveness…”.

One important issue in the data is of what defines the EU or US industry. This is also an issue of substance for the analysis. OECD and Eurostat data are country data. These series show activity (whether production, trade, or R&D expenditure) within those borders regardless of the origin of the companies. In contrast, the commonly-used IMS HEALTH data are of companies,
and analysis is most readily carried out by company nationality. Both concepts are relevant to the analysis of competitiveness. Which is the more relevant depends both on the particular issue and how far it is activity within the borders that influences future prospects, and how far the industry in the country of a company’s origin benefits from the company’s development.

This section briefly summarises the relevant findings of two analyses of the competitiveness of the EU pharmaceutical industry:

- “Benchmarking the Competitiveness of the EU Pharmaceutical Industry”, prepared by Europe Economics for EFPIA in November 1998 and circulated to those present at the Bangemann round table in December 1998, henceforth Europe Economics 1998;

- “Global Competitiveness in Pharmaceuticals: a European Perspective” by Fabio Alfonso Gambardella, Luigi Orsenigo, and Fabio Pammolli, prepared for the Commission in November 2000, henceforth Pammolli et al.

Both analyses concluded that the EU industry had performed well in terms of R&D investment effort and international trade in pharmaceuticals; and that EU-based multinationals had made R&D investment comparable to those of their US counterparts and in new chemical entities placed on the market.

However, both identified declining competitiveness of the EU industry over time, shown inter alia by:

- the lead in the development of new products passing to US-based companies;
- the EU industry’s greater dependence for market share on older products; and
- the EU industry’s weaker position in terms of new technology.

4.2 The Strength of the Market

Both Europe Economics (1998) and Pammolli et al included an analysis showing that:

- the US market had been growing more rapidly than the EU market; and
- in both the US and different EU national markets, national firms had leading shares.

Extracts from the tables from Pammolli et al are reproduced below.

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51 IMS HEALTH collects data on the pharmaceutical sector through continuous and periodic market surveys based on statistically representative samples. IMS coverage of pharmaceuticals include ethical and over-the-counter pharmaceuticals, as well as some nutritionals and herbal remedy products sold by pharmacies. IMS HEALTH data covers about 90 per cent of the existing ethical drugs, whilst coverage of over-the-counter drugs is lower. Despite the efforts of IMS to standardise collection procedures, how the data is collected varies from country to country, reflecting local distribution channels and requirements.

52 Europe Economics 1998 Table 4.4 and 4.6, Pammolli et al Tables 12 and 14.

53 Europe Economics 1998 Table 4.5, Pammolli et al Table 15.

54 Europe Economics 1998 Section 5, Pammolli et al Chapter IV.

55 Europe Economics 1998 Table 4.8, Pammolli et al Table 2.

56 Europe Economics 1998 Table 3.2 and A3, Pammolli et al Table 9.
Table 4.1:
Sales in the US and five largest EU Markets, US$ million

<table>
<thead>
<tr>
<th>Country</th>
<th>1989 (US$m)</th>
<th>1994 (US$m)</th>
<th>1999 (US$m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>44789</td>
<td>75425</td>
<td>130069</td>
</tr>
<tr>
<td>Five largest EU markets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>9984</td>
<td>16725</td>
<td>18500</td>
</tr>
<tr>
<td>France</td>
<td>9326</td>
<td>15152</td>
<td>17751</td>
</tr>
<tr>
<td>Italy</td>
<td>8260</td>
<td>8829</td>
<td>11332</td>
</tr>
<tr>
<td>UK</td>
<td>4526</td>
<td>6821</td>
<td>11029</td>
</tr>
<tr>
<td>Spain</td>
<td>3349</td>
<td>4710</td>
<td>6596</td>
</tr>
<tr>
<td>Total EU - 5</td>
<td>35445</td>
<td>52237</td>
<td>65208</td>
</tr>
</tbody>
</table>

Source: Pammolli et al., 2000, Table 2

The data in Table 4.1 show that while in 1989 the US market was about 25 per cent larger than the total of the five largest EU markets (Germany, France, Italy, Spain, UK), by 1999 it was twice their combined value.

In 1989 the North American market accounted for 34 per cent of the world market, and the EU market 31 per cent. By 1999 the comparable figures were 40 per cent and 27 per cent.57

Table 4.2:
Market shares in selected countries, by nationality of corporation (per cent)

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
<td></td>
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<tr>
<td>USA</td>
<td>74.7</td>
<td>69.6</td>
<td>63.3</td>
</tr>
<tr>
<td>EU-15</td>
<td>12.8</td>
<td>20.4</td>
<td>24.6</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Germany</td>
<td>56.6</td>
<td>55.0</td>
<td>45.1</td>
</tr>
<tr>
<td>Other EU-15</td>
<td>12.8</td>
<td>15.0</td>
<td>19.7</td>
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<tr>
<td>USA</td>
<td>17.8</td>
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<td>22.1</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
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<tr>
<td>UK</td>
<td>33.4</td>
<td>42.7</td>
<td>24.5</td>
</tr>
<tr>
<td>Other EU-15</td>
<td>17.2</td>
<td>19.03</td>
<td>23.8</td>
</tr>
<tr>
<td>USA</td>
<td>35.3</td>
<td>28.44</td>
<td>32.1</td>
</tr>
</tbody>
</table>

57 Pammolli et al Table 1.
The Competitiveness of the EU Pharmaceutical Industry

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Other EU-15</th>
<th>USA</th>
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<tbody>
<tr>
<td>FRANCE</td>
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<td></td>
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<tr>
<td>France</td>
<td>51.6</td>
<td>48.5</td>
<td>36.9</td>
</tr>
<tr>
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<td>23.7</td>
<td>29.3</td>
</tr>
<tr>
<td>USA</td>
<td>20.6</td>
<td>20.2</td>
<td>24.0</td>
</tr>
</tbody>
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<table>
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<th>Other EU-15</th>
<th>USA</th>
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<tr>
<td>ITALY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>39.6</td>
<td>42.4</td>
<td>25.8</td>
</tr>
<tr>
<td>Other EU-15</td>
<td>27.8</td>
<td>27.3</td>
<td>32.4</td>
</tr>
<tr>
<td>USA</td>
<td>17.6</td>
<td>19.3</td>
<td>27.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Spain</th>
<th>Other EU-15</th>
<th>USA</th>
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</thead>
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<td>SPAIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>37</td>
<td>30.7</td>
<td>24.8</td>
</tr>
<tr>
<td>Other EU-15</td>
<td>32.6</td>
<td>38.1</td>
<td>40.0</td>
</tr>
<tr>
<td>USA</td>
<td>15.3</td>
<td>16.8</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Source: Pammolli et al, 2000 Table 9. Original data from IMS International. Data to each country do not add to 100, as “Others” are not included.

The data in Table 4.2 show that corporations of US nationality held 63.3 per cent of the US market in 1998, whilst in the five largest EU markets the market shares of EU-based firms varied from 48 per cent (UK) to 66 per cent (France).

Both *Europe Economics* and *Pammolli et al* conclude that given the strong home bases of EU and US corporations, the more rapid growth of the US market can only have strengthened the competitive position of the US pharmaceutical industry against the EU industry. EU companies faced not only slower growth in their domestic markets, but also:

- a multitude of different national pricing and reimbursement procedures (and also different licensing procedures, although this is diminishing), making it difficult to secure economies of scale;

- different patent authorities and the continuing effects of previous differences in the form of intellectual property protection; and

- different degrees of competition in national EU final product markets, with some national markets (as shown vividly by the analysis in Section V of *Pammolli et al*) not functioning in a competitive way on patent expiry.

These differences in the growth and structure of EU and US markets represent a material handicap for EU pharmaceutical companies seeking to compete with US companies.
In strengthening the US domestic market, the Pediatric Exclusivity Provision will have aided US pharmaceutical companies in competing with EU companies. Offering a similar incentive in the EU with respect to paediatric drug trials would contribute to reducing the declining opportunities (in relative terms) presented by the home markets of EU pharmaceutical companies.

Of course, any action that increased the profitability of sales to EU pharmaceutical markets could be presented as minimising the harmful effects of the US pharmaceuticals market becoming over time a progressively more attractive market relative to the EU. The justification for a particular measure to stimulate the competitiveness of the EU pharmaceutical industry must depend on a more detailed and rigorous analysis of the effects of the measure.

4.3 The Effect on Competition

Manufacturers of generic products have an apparent interest in opposing any extension to market exclusivity for major pharmaceutical products.

While accepting the principle of incentives for paediatric trials, the position paper on the subject prepared by the European Generics Association emphasises a list of restrictive conditions that it proposes must be met before any additional exclusivity could be awarded. (It simultaneously proposes measures to reduce the degree of effective protection afforded by patents and SPCs for pharmaceutical products in the EU market.)

The conditions to be applied to any additional period of exclusivity will be central to the policy debate. The relevant conclusion from Section 3 is that for such a policy to work, the incentive has to be an effective one. For an incentive to be effective, it will have to be of sufficient magnitude, and a sufficient degree of certainty, to justify the allocation of resources.

To the extent that an additional period of exclusivity that contributed to the development of safer and effective medicines for children led to a transfer from generics manufacturers to research-based companies, the effects would be neutral in overall terms. What would be a matter of concern would be if competition in pharmaceutical markets were weakened by the introduction of an additional period of exclusivity.

The evidence from Pammolli et al. shows that the current intensity of generic competition varies across the major EU markets. In some EU countries, including France and Italy, generics have only a limited role in the market. The underlying causes of the limited extent of generic competition in these pharmaceutical markets lie outside the scope of this report, but for these a short additional period of market exclusivity for patented products would tend to be less valuable.

Where there are competitive markets and generics do take substantial shares on the expiry of exclusivity – as in Germany or the UK – the health of generic competition requires that the conditions for generic competition are maintained.

See Pammolli et al Chapter V.
Key conditions for effective generic competition are:

- a demand-side that is responsive to relative prices: this implies that doctors’ behaviour is influenced by relative prices;
- many potential producers of generics; and
- free entry for generics manufacturers and wholesalers subject only to their meeting the standards necessary for product quality and pharmacovigilance.

These underlying conditions would not be adversely affected by the award of an additional period of market exclusivity to certain patented medicines.

It is possible that the conditions for competition may be improved where research results in a paediatric drug being available over the counter, where demand is likely to be more responsive to prices.

This analysis suggests that introducing an additional period of market exclusivity for certain patented medicines would not damage generic competition, and that it should therefore not be held up on such grounds.

### 4.4 A Viable Research Community in Paediatrics

Chapter IV and VI of *Pammolli et al* show clearly the extent to which the EU is falling behind the US in the generation of new technologies and the development of efficient markets in licensing research on new chemical entities.

Key influences identified include:

- the public funding of a network of biomedical research in the US, compared to a more limited development of research capacity and networks in the EU;
- the national lines of EU funding support and networks; and
- the greater mobility of personnel in the US between academia and industry.

In many ways, the position in expertise in paediatric clinical trials and pharmacology may be similar:

- in both cases, the existence of an effective network of specialists and researchers is important to the development of research capacity and expertise;
- the US has a funded national network, while until recently the EU had only a loose association of specialists; and
- labour markets in the US probably allow greater movement and cross-fertilisation of ideas between academia and industry.
In the US, the network of Pediatric Pharmacology Research Units (PPRUs) comprised (as of 2000) 13 academic medical centres and children’s hospitals, up from seven in 1997. These PPRUs are organised under the auspices of the National Institutes of Health (NIH) and have been operational since 1994. The number of Contract Research Organisations and Site Management Organisations in the US specialising in paediatric studies rose sharply in the late 1990s.\(^5^9\)

There is now an established EU network capable of co-operating to conduct paediatric clinical trials and best practice, but this is relatively small and under-developed compared to the US network.

While the FDA has a specialist team contributing to the development of policy on paediatric medicine – a Paediatric Implementation Team and a Pediatric Exclusivity Review Board - the EMEA has no such dedicated resources. EU paediatricians we spoke to considered that a specialist paediatric committee within EMEA would be an important development, ensuring that the smaller sample sizes and different measurement techniques reported in paediatric submissions were appropriately evaluated.

The recent increase in the number of paediatric drug trials in the US can be expected to lead to the development of greater expertise in the US. If not matched by similar incentives to carry out such trials in the EU, this could be expected to lead to:

- an increase in the differentials in capacity and expertise, with the US becoming relatively more attractive as a place to hold such trials;
- an increased US focus of pharmaceutical research and development activity, particularly for medicines that may have paediatric application; and
- migration of high quality researchers and research expertise in paediatric medicine to the US, where the opportunities were greater.

The leading paediatricians we spoke to noted the attractions to academic researchers of the way that funding for paediatric clinical research is more readily available in the US.\(^6^0\)

The precise long-term consequences for research capacity if the EU continues to offer more limited opportunities for paediatric clinical research are unclear. However, the direction is clear enough: the EU would fall behind in its capacity for research, and given the close link between research and best clinical practice, would ultimately be less capable than the US of providing safe and effective treatment for paediatric patients.

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60 One prominent EU professor had recently accepted a post in the US, a move regarded as considerable loss by his colleagues. There is also a significant pull of researchers into industry.
5 CONCLUSIONS

From Section 2:

There is general acceptance of the principle set out by the Council that the use of medicines in children should be solidly based on good-quality evidence.

Many medicines of potential use for children have not been subjected to paediatric trials and have no paediatric indication, or only limited paediatric labelling.

There is currently widespread off-label and unlicensed use of medicines for the paediatric population in the EU.

Where the use of medicines with children is unlicensed or off-label, the back-up information services provided by pharmaceutical companies may not be available or may not be used. The knowledge developed from unlicensed and off-label use is likely to remain localised. Reported Adverse Drug Reactions are likely to underestimate the actual numbers, and the necessary corrective action may not be taken.

From our interviews with leading European specialists in paediatric medicine, paediatricians themselves see a clear need for more research – including clinical trials – into the suitability for use of medicines for the paediatric population, and into appropriate dosages and formulations.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) now provides guidelines on the conduct of paediatric clinical trials. These guidelines provide a major step forward. They are agreed between the regulatory authorities of the US, EU and Japan, and the pharmaceutical industry associations, and provide a widely accepted framework for the paediatric development of particular products and for handling the ethical issues that arise in paediatric clinical trials.

Because of the continuing and successful programme of international harmonisation through the ICH, data submitted in the EU or US in respect of a paediatric indication for a medicine are now almost always sufficient to support a similar application across the Atlantic.

The leading EU paediatricians we interviewed consider that where there is a need for more evidence to support better use of medicines in the paediatric population, well-designed studies can provide that evidence in ways that are ethically acceptable. There are few or no areas where medicines that children need cannot be researched. However, elements of these trials will normally have to be carried out after adult trials, and there are often specific design issues to be solved.

In several EU countries, paediatric clinical specialists have developed, or are developing, lists of therapeutic priority areas for paediatric clinical research.

The therapeutic areas identified as research priorities by EU paediatricians in our telephone interviews included significant areas of overlap, and those paediatricians were confident that,
Conclusions

despite differences in clinical practice, it would be possible to reach agreement at the EU level on key research priorities for paediatric medicine.

The discussion on the solution to the lack of indications for paediatric use should, therefore, be focussed on mechanisms for increasing the demand for appropriate research, and for removing any obstacles (unjustifiable regulations, or skills or other capacity shortages) to an increase in the supply of that research.

From Section 3:

The central public policy choice facing the EU is not that of “to experiment or not to experiment”: in the absence of properly regulated paediatric trials, the widespread off-label and unlicensed use of medicines represents uncontrolled experiments. The key choice is therefore between ways of increasing the number of well-designed paediatric clinical trials to provide a better evidence base for paediatric medicine.

The starting point in designing such a policy is a clear understanding of the business decision of whether to conduct paediatric clinical trials.

A research-based pharmaceutical company with a licence for a new product faces the following trade-off:

“Do the additional earnings that will result from licences for paediatric indications justify the costs and risks of sponsoring the trial and of developing and maintaining the new paediatric formulation?”

Where the potential paediatric market is limited, the answer will often be no.

However, there are potentially considerable gains to patients and to the community as whole from paediatric trials that lead to paediatric labelling for appropriate indications. Such benefits are positive externalities from the business decision, arising from better information about the use of particular medicines in the treatment of children. For the pharmaceutical company facing a decision on whether to undertake paediatric trials, these benefits are remote as they cannot be captured.

In 1997, the US introduced economic incentives for conducting paediatric studies, through the Pediatric Exclusivity Provision in Section 111 of the Food and Drug Administration Modernisation Act.

A six-month extension to market exclusivity could be awarded to all the products containing a particular active substance for carrying out paediatric trials that met the terms of a Written Request received from the FDA.

The experience of the additional market exclusivity in the US shows that:

- an adequate incentive for paediatric clinical trials for products where this is considered appropriate by the authorities will lead to a dramatic increase in the number of such trials;
Conclusions

• such trials can rapidly feed through into new licensed paediatric indications and better labelling and hence into improved treatment of paediatric patients; and

• drug therapies at different stages of their lives may need different forms of incentive.

For licensed products on the market with a remaining period of exclusivity, an additional period of exclusivity is the obvious instrument for providing financial incentives to companies to sponsor paediatric clinical trials. Of the different forms of exclusivity:

• additional data exclusivity by itself is unlikely to add to the effective period of market exclusivity of a patented medicine;

• additional patent exclusivity or a longer SPC would require major new legislation; while

• a form of additional market exclusivity, analogous to the US measure and to provisions in the EU Orphan Drugs Regulation, would provide a more powerful flexible administrative instrument for providing incentives to develop paediatric medicines.

To have an equivalent incentive effect, any period of additional exclusivity would need to be longer than in the US.

With the Orphan Drug Regulation, which came into effect in January 2000, the EU has established a form of market exclusivity and the mechanisms to enforce it. As it has done so for orphan drugs, then it can probably do so for paediatric medicines if the political will is there.

The Orphan Drug Regulation is more limited as it applies only to the particular therapeutic indication, not the active substance. Providing some additional market exclusivity in respect of a paediatric indication only, rather than in respect of the active substance, would not provide a powerful incentive to develop paediatric indications for in-patent products: the potential additional revenues would typically be minimal.

However, the precedent of the Orphan Drug regulation shows that market exclusivity can be introduced into the EU regulatory framework.

Many of the products for which paediatric trials and subsequent paediatric indications may be most valuable are out-of-patent. One paediatrician we spoke to estimated that in 75-90 per cent of cases, medicines given to children in hospitals are out-of-patent. This class of products is too important to be ignored by policy on the development of paediatric medicine.

For out-of-patent products, a transferable exclusivity would be likely to provide by far the greatest incentive to develop paediatric indications for out-of-patent medicines. The potential rewards would probably be so much greater than any likely level of prize, and gains from other mechanisms (eg data exclusivity for the indication) are likely to be small and vulnerable to competition located just outside the protective mechanism.

The design and supervision of a mechanism for transferable exclusivity would be resource-intensive. Given that the link between the product studied and the product for which exclusivity is
granted would be broken, a clear and robust procedure to determine which company benefited from a transferable exclusivity in respect of paediatric development of a particular out-of-patent product would be essential.

Another approach for out-of-patent products is for public authorities to put research contracts to tender. As noted above, paediatricians believe it would be possible to agree a set of priorities at the EU level as a basis for prioritising such research contracts. The precedents of setting up and managing the CPMP and the Committee for Orphan Medicinal Products would be valuable in developing the machinery for such a prioritisation exercise.

A form of market exclusivity – for a period of several years as in the Orphan Drug Regulation may provide a useful element of a policy for encouraging the paediatric development of out-of-patent medicines. This would be open to all, not just the research-based companies.

For example, for many older products used in the paediatric population, we are advised that there may be sufficient data from a long period of use to justify a submission in respect of a paediatric indication. A form of market exclusivity may be a good way of motivating the synthesis and submission of such data.

For products not yet on the market, the EU licensing authorities have a greater opportunity to introduce new licence conditions requiring paediatric clinical trials to be carried out. However, this would not change the underlying economics of paediatric product development. Where the returns on paediatric development of a product would not justify the anticipated costs, a policy that combines close regulatory supervision of paediatric product development with financial incentives for carrying out trials is likely to be more effective. An additional period of exclusivity for submitting paediatric data introduced for designated medicines already on the market could be applied equally to appropriate new medicines yet to be licensed. It would have a powerful effect in stimulating the earliest practical paediatric development of new products.

Given the progressive harmonisation in guidelines for clinical trials, robust trial data accepted by the FDA will in most cases also be accepted by EU authorities, and vice-versa. In a minority of cases, a different comparator treatment may be required by a particular EU licensing authority, but in broad terms the submissions under which an additional paediatric indication has granted in the US will also support such a submission in respect of such an indication in the EU.

If the purpose of an EU incentive is defined as to ensure that paediatric data are submitted for review by EU authorities, then whether additional exclusivity has been awarded for a particular drug therapy in the US market does not have to be material to the structure of the new incentive. As long as the data are scientifically applicable to the paediatric population in the EU, whether or not additional exclusivity has already been awarded in the US in respect of such data need not affect the eligibility of the submission for an award of additional exclusivity in the EU.

A policy of free-riding, ie not awarding the incentive in respect of data forming the basis of a submission that had already led to the award of additional exclusivity in the US, may be ineffective. Paediatric data for many important medicines may not be submitted for review by EU authorities. This is because in many cases the business decision would still show prospective
Conclusions

sales revenues below the costs of submitting the data, maintaining the licence, and continuing to produce the formulations. A free-riding policy would also explicitly position the EU as a follower, rather than a leader, in the development of paediatric medicine.

An incentive for companies to seek additional paediatric indications for their products in the EU would lead to a dramatic increase in the demand for such trials to be carried out in the EU.

For a programme to be effective in promoting research into better paediatric medicine in the EU, it must both provide incentives to pharmaceutical companies and ensure research is directed into the priorities considered important by clinical paediatricians. Training may be needed for medical professionals, eg for those cast for the first time in the role of investigators in clinical trials.

Nothing arising from our interview programme was inconsistent with the published view of a prominent member of the ENDIC network:

“There is considerable potential for the pharmaceutical industry in association with academia to investigate clinically relevant medicines in paediatric medicines in Europe.”

Even setting aside the fundamental point that trials can be conducted anywhere in the world provided the necessary clinical standards of their conduct are maintained, there do not seem likely to be strong arguments on capacity grounds for the EU to delay proceeding with additional incentives for paediatric clinical trials.

From Section 4:

The impact on industrial competitiveness is a material secondary issue relevant to the design of policy to develop the evidence base for safe and effective use of medicines in children.

In strengthening the US domestic market, the Pediatric Exclusivity Provision will have aided US pharmaceutical companies in competing with EU companies. Offering a similar incentive in the EU with respect to paediatric drug trials would contribute to reducing the (in relative terms) declining opportunities presented by the home markets of EU pharmaceutical companies.

The current intensity of generic competition varies across the major EU markets. In some EU countries, including France and Italy, generics have only a limited role in the market. Where there are competitive markets and generics do take substantial shares on the expiry of exclusivity – as in Germany or the UK – the health of generic competition requires that the conditions for generic competition be maintained. The report’s analysis suggests that introducing an additional period of market exclusivity for certain patented medicines would not damage the conditions of generic competition, and that it should therefore not be held up on such grounds.

The full long-term consequences for research capacity if the EU continues to offer more limited opportunities for paediatric clinical research are unclear. However, the direction is clear enough: the EU would fall behind in its capacity for research, and given the close link between research and best clinical practice, would ultimately be less capable than the US of providing safe and effective treatment for paediatric patients.
APPENDIX 1: BIBLIOGRAPHY


Europe Economics “Benchmarking the competitiveness of the EU pharmaceutical industry”, Report to EFPIA, November 1998.


APPENDIX 2: EU HEALTH COUNCIL RESOLUTION ON PAEDIATRIC MEDICINAL PRODUCTS, 14 DECEMBER 2000

"THE COUNCIL OF THE EUROPEAN UNION,

1 RECALLS that a high level of health protection is to be ensured in the definition and implementation of all Community policies and activities and that Community action, complementing national policies, is to be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to human health;

2 NOTES that nearly 20% of the Community population, i.e. seventy-five million people, is under the age of 16;

3 NOTES that, as regards their treatment, children have characteristics which vary with their age and which mean that in most cases they cannot be treated like adults. In particular, a medicinal product administered to a child has specific effects. Furthermore, a medicinal product intended for children requires appropriate pharmaceutical presentation, to ensure easy and safe administration;

4 NOTES that a large number of the medicinal products administered to children have not been assessed specifically for paediatric use and may therefore not meet the criteria of quality, safety and effectiveness required in the case of adults;

5 OBSERVES that the prescription of medicinal products to children is therefore very often not covered by the marketing authorisation and that, taking into account the shortage of paediatric pharmacovigilance data, safety of use in this population group cannot therefore be documented by monitoring studies after marketing;

6 RECOGNISES that making paediatric medicinal products available involves difficulties of pharmaceutical development and of clinical development. The necessary research and development costs are not amortised because of the small number of children affected by each disorder in each age bracket;

7 CONSIDERS that the development of paediatric medicinal products and clinical trials involving children may give rise to specific ethical concerns and that children must benefit from special protection;

8 CONSIDERS that all Member States face this problem and that a European approach offers advantages from the epidemiological, public health and economic points of view;

9 ACCORDINGLY INVITES THE COMMISSION to make appropriate proposals as soon as possible in the form of incentives, regulatory measures or other supporting measures in respect of clinical research and development, taking account of the ethical aspects of clinical trials on children, to ensure that new medicinal products for children and medicinal products already on the market are fully adapted to the specific needs of that population
group, and taking into account also the internationally acknowledged standards for the protection of minors with regard to medical scientific research.”