Draft European Parliament and Council Regulation (EC) on medicinal products for paediatric use – DG Enterprise

Extended Impact Assessment

This is an extended impact assessment (EIA) to support a Commission proposal for a European Parliament and Council Regulation on Medicinal Products for Paediatric Use (hereafter referred to as the draft paediatric regulation). The draft paediatric regulation responds to the Council Resolution of 14 December 2000 which called on the Commission to make proposals in the form of incentives, regulatory measures or other supporting measures in respect of clinical research and development to ensure that new medicinal products for children and medicinal products already on the market are fully adapted to the specific needs of children.

This EIA, conducted by the Commission is based primarily on:

- experience with the existing EU pharmaceutical market and regulatory framework,
- experience with legislation on paediatric medicines in the United States (US),
- experience with orphan medicines in the EU,
- the published literature,
- cost estimates provided by the European Medicines Agency (EMEA)
- extensive consultation with stakeholders, and,
- an independent, externally contracted study (hereafter referred to as the Rand Study)[1].

1. WHAT ISSUE IS THE PROPOSAL EXPECTED TO TACKLE?

1.1 The issue, the risks and the causes

The issue

In the previous 15 Member States of the European Union (EU), the paediatric population (0-19 years) represented about 84 million people, i.e. about 22% of the total population. Following enlargement of the EU in May 2004 this number has increased to just over 100 million children. This is a vulnerable group with developmental, physiological and psychological differences from adults. Because of these differences, the results of tests of medicines in adults can not necessarily be extrapolated directly to children and specific research, including clinical trials, in children is usually required to establish the safe and effective use of medicines in children. Because the diseases suffered by children may differ from those suffered by adults and because children's bodies handle drugs differently from adults, the dose of a medicine to treat a childhood disease is not always predictable from the adult dose. Furthermore, because doses are generally smaller for children and for the very young, and tablets or capsules may not be practical, specific pharmaceutical forms (formulations) of a medicine, such as a solution or syrup or very low dose tablet or injection, may be required. Again, specific testing will usually be required in the development of such specific formulations.

It is estimated that between 50 and 90% of medicinal products used in the paediatric population have never been specifically studied or authorised (licensed) for use in that age group. The range reflected by these figures represents the differences between non- specialist

[1] Extended Impact Assessment of a draft EC Regulation on Medicinal Products for Paediatric Use. Rand Europe. April 2004. http://pharmacos.eudra.org

and specialist situations and differences between therapeutic areas (for example cancer treatments compared to treatments for AIDS). This leaves no alternative to the prescriber than to use products "off-label" (i.e. use of product authorised for adults - products that have not been tested or authorised for paediatric use) or use of completely unauthorised products with the associated risks of inefficacy and/or adverse reactions (side effects).

Risks of the current situation

Why should it matter if the medicines use to treat children have not been tested or authorised for such use? The answer is clear. The health and therefore quality of life and future of the children of Europe may suffer from a lack of testing and authorisation of medicines for their use. Every time a doctor in Europe writes a prescription for a child for an untested, unauthorised product, that doctor may not be sure the medicine will be effective, may not be sure what dose is appropriate and may not be able predict what adverse reactions the child may suffer. Furthermore, new innovative products developed by the pharmaceutical industry to meet the therapeutic challenges we face today are denied to children. Think of HIV infection: untreatable in the early 1990s and now considered by many as a chronic disease (amongst those with access to treatment). Innovative medicines can and do save lives and the children of Europe deserve at least the same access to innovation as that enjoyed by adults. All medicines can, in some individuals, cause adverse reactions (side effects). One study conducted in the United States[2] of hospitalised adults estimated that adverse drug reactions are the 5th largest cause of death. This study was conducted in adults. Considering that there is accumulating evidence that off-label and unlicensed use of medicines is associated with a higher risk of adverse drug reactions than licensed use[3] [4] and that children are growing, developing physiologically and mentally and are therefore particularly vulnerable to adverse drug reactions, the potential public health implications of not testing and authorising medicines for children are apparent. Untested and unauthorised products are associated with increased risks and these may not be balanced by any benefit of treatment.

Causes of the current situation

The absence of suitable authorised medicinal products to treat conditions in children is an issue that has been of concern for some time. It results from the fact that frequently pharmaceutical companies do not perform the necessary research and development to adapt medicinal products to the needs of the paediatric population. This is particularly ironic considering that our modern system of medicines regulation was developed primarily in response to therapeutic disasters, such as the thalidomide tragedy of the 1950s and 60s, that occurred in children.

To reach the market place a medicine has first to be discovered, then researched and developed to establish that it is of high quality, efficacious and is acceptably safe (considering the disease it is intended to treat). Once data establishing quality, efficacy and safety have been generated companies then have to obtain a marketing authorisation (licence) before placing the product on the market. The marketing authorisation includes approved information for healthcare professionals and patients on the safe and effective use of the

[2] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalised patients: A meta-analysis of prospective studies. *Journal of the American Medical Association*, 1998; 279(15): 1200-1205.

[3] Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrics*, 1999; 88(9): 965-968.

[4] Horen B et. al. Adverse drug reactions and off-label drug use in paediatric patients. British J. Clin. Pharmacology. 2002; 54: 665 – 670.

product. Because of the extensive, frequently-costly and time-consuming testing required for market access, it can take many years from drug discovery to first marketed use. This fact led in 1992, to the regulation creating the supplementary protection certificate[5], an EU-wide mechanism to extend the time-period of patents of medicinal products to compensate for the time required to access the market.

Industry has a free choice as to what medicines to develop, authorise and market. Industry bases its choice on potential revenue from sales balanced against the costs of research and development, manufacturing and marketing. The main drivers of overall return on investment are the size of the pharmaceutical market and the price achievable within the market-place. The control of the price of medicines by many EU governments is a main reason why, despite a larger population, the EU is less profitable for industry than the US. The number of children suffering specific diseases is generally lower than the number of adults and, in terms of research, "children" can not be considered a single population (consider a premature new-borne compared to a fifteen-year old) so studies may be more complex. The current situation in the EU regarding medicines for children is clear evidence that market forces alone are insufficient to stimulate adequate research, development and authorisation of medicines for children. The industry has considered that for many childhood diseases the potential return on investment is insufficient to justify such investment in research and development.

The result of no action

Without specific action to stimulate research, development and authorisation of medicines for children, the available evidence suggests that the current situation will persist: a situation where innovation is denied to our children, ineffective treatments are given, incorrect doses are prescribed, and adverse reactions, which may be serious or fatal, will occur at an increased rate. The evidence to support this conclusion comes from a number of sources, including: the current EU pharmaceutical market including experience in the Member States, experience in US and experience with orphan medicines.

The current situation regarding medicines for children in the EU has persisted for decades despite clear evidence that medicines specifically tested in and developed and authorised for children are required. A similar situation exists in other world markets supporting the notion that market forces alone can not and will not resolve this important public health issue. Certain EU Member States have attempted to increase the authorisation of medicines for children by encouraging (on a voluntary basis) industry to conduct research in children and, where data on use of a medicine in children already exist, to submit applications for marketing authorisations. This has included encouraging industry to submit applications in the EU based on data generated as a result of the actions taken in recent years in the US (described below). Such actions by the Member States have largely been unsuccessful. Without either legislative requirements or clear financial incentives or rewards, the pharmaceutical industry has generally refused to research or authorise medicines for children.

In the US, the situation regarding a lack of tested, authorised medicines for children led, in the 1980s and early 1990s, to the US authorities introducing various initiatives to encourage the pharmaceutical industry to research and authorise medicines for children. These, mainly voluntary initiatives, were largely unsuccessful[6]. The situation in the US changed dramatically

[5] Council Regulation EEC No 1768/92 of 128 June 1992 concerning the creation of a supplementary protection certificate for medicinal products. OJ No L 182 of 2.7.1992, p.1

[6] Schreiner MS. 2003. Paediatric clinical trials : redressing the balance. Nature Reviews; Vol. 2: 949 – 961.

with the introduction of specific legislation to encourage the performance of clinical trials in children: introduced by the so-called "paediatric rule" and "paediatric exclusivity" adopted in 1998 and 1997 respectively. These pieces of legislation are complementary.

The "paediatric rule[7]" requires companies to perform paediatric studies and/or to develop paediatric formulations for new and already marketed medicinal products if the product is likely to be used in a substantial number of paediatric patients or if it would provide a meaningful therapeutic benefit to paediatric patients over existing treatments. The requirements in the paediatric rule are not directly linked to any incentives or rewards for the pharmaceutical industry, although it may be possible for companies to satisfy the requirement while also being granted the incentive described in the next paragraph. Between September 1999 and 31 December 2002 the paediatric rule lead to 12 labelling changes impacting on the safe and effective use of products. In October 2002 the US District Court overturned the "paediatric rule", however, on 3 December 2003 the "paediatric rule" requirements were again passed into US law via the Paediatric Research Equity Act[8].

The "paediatric exclusivity" provision in the Food and Drug Administration (FDA) Modernisation Act 1997[9] provides an incentive (6 months of further market exclusivity is added to market exclusivity or patent protection on the active moiety) for companies who perform clinical studies in the paediatric population. The incentive is granted when the studies, conducted according to a written request from the FDA based on public health needs, are submitted to the FDA. The incentive is granted irrespective of whether the results have demonstrated safety and efficacy. In addition, the Act required the FDA to draw up guidelines and a "paediatric list", i.e. a list of drugs for which additional paediatric information is expected to be beneficial. The "paediatric exclusivity" provision, which had a sunset clause of 1 January 2002, was reviewed by the US Congress after three years of operation[10]. Due to its success in stimulating new studies on medicinal products to treat children of different age groups (as of February 2004, 63 new paediatric labels and 661 studies requested), the paediatric exclusivity provision has been retained in the Best Pharmaceuticals for Children Act 2002[11]. The new Act also includes a requirement to develop a prioritised list of medicines for which paediatric studies are needed. In addition, the Act establishes a fund of $200,000,000 for fiscal year 2002 and such sums as are necessary for each of the succeeding five years for the study of the use in the paediatric population of medicinal products for which there is no patent protection or market exclusivity.

Overall, the combined measures of incentives and obligations have been extremely successful in the US in stimulating the development of medicinal products for paediatric use. It is disappointing to note that despite the trends towards globalisation in the area of pharmaceuticals, the success of the measures taken in the US has brought little benefit to the children of Europe. International companies do not appear to be willing to voluntarily submit data collected in the US to support the authorisation of paediatric indications in the EU.

An orphan medicine is a medicine to diagnose, prevent or treat a rare disease. The 1983 US Orphan Drug Act[12] guarantees the developer of an orphan-designated product several

[7] 21 CFR Parts 201, 312, 314 and 601. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in paediatric patients. Final Rule. Federal Register 63, 66632 – 66672 (1998).
[8] Paediatric Research Equity Act 108th Congress edn. (2003)
[9] Food and Drug Modernization Act of 1997. 105th Congress edn. (1997)
[10] The Paediatric Exclusivity Provision. January 2001 Status Report to Congress : US Food and Drug Administration (2001).
[11] Best Pharmaceuticals for Children Act. 107th Congress edn. (2001)
[12] Orphan Drug Act: Public Law 97 – '414, January 4, 1983, or Title 21, U.S. Code, Sect. 360aa.

incentives: seven years of market exclusivity following US market approval in the same indication; tax credits for clinical research in the product's development; and, available funding from the US orphan products grant program. In addition, orphan-designated products have exemption from application fees for US FDA approval. This legislation has been very effective in bringing products for rare diseases to the market. During the 10 years before the Orphan Drug Act the American pharmaceutical industry developed approximately 10 orphan medicines. In contrast, between 1983 and 2003, 242 orphan-designated products have received FDA marketing approval[13]. The EU Orphan Regulation[14] was introduced in 2000 and is having a similar effect on stimulating the authorisation of medicines to treat rare diseases.

The Rand study has conducted a projection of the size of the paediatric population in 2015. By 2015, the proportion of children (between 0 and 19 years), compared to the total population of Europe, will decline. However, in 2015 there will be over 150 million children in the EU. Rand estimated that by 2015 the total size of the pharmaceutical market will be more than 1,000 billion dollars. Even if an increasing proportion of the market will be geared towards adults and the elderly, the paediatric population will most likely continue to be a significant market.

On the basis of the available evidence it is very unlikely that the current public health issue regarding medicines for children will be resolved in the EU until a specific legislative system is put in place.

The stakeholders

Children and their parents: children, their parents and their families are the ultimate stakeholders affected by the draft paediatric regulation. Children are currently denied robustly tested, authorised medicines to meet all their therapeutic needs and the main objective of the draft paediatric regulation is to improve the health of the children of Europe by ensuring an adequate supply of such medicines to the EU market. In some sectors of the healthcare market and more in some Member States than others, the public may pay for their medicines out of their own pockets. Any effect of the draft paediatric regulation on the cost of medicines will therefore impact on the costs of some individuals. However, as will be described later, any marginal increase in costs of medicines have to be considered in the light of savings from improved overall healthcare and consequent quality of life and personal economic productivity.

Healthcare professionals (clinical doctors, pharmacists, nurses and researchers): healthcare professionals are also key stakeholders. They want to provide their patients with tested, effective, safe and high quality products. Furthermore, the current situation forces doctors to take personal legal liability for the effects of the untested, unauthorised medicines that they are forced to prescribe. Health professionals are also involved in research into the effects of medicines in children and measures to increase research will clearly impact on those involved.

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[13] Haffner ME (2003) The current environment in orphan drug development. Drug Information Journal, 37, 373 – 379.

[14] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Official Journal of the European Communities L18/1 22.1.2000.

Governments and health insurance companies: In much of the EU, governments, either directly or through government sponsored insurance schemes, pay for healthcare, including medicines. Member State governments have a responsibility for promoting the health of their citizens and also have an economic interest in having a healthy population with low healthcare and social security needs able to work and generate wealth. Where governments pay for healthcare and medicines, the draft paediatric regulation may impact on them through the costs of medicines and healthcare.

Pharmaceutical industry: the pharmaceutical industry is made up of both large global companies (a few of which are predominately based in the EU) and smaller companies (far more of which are firmly based in the EU). The industry can also be divided into the innovative industry, responsibly for the discovery, research and development of innovative medicines and the generics industry which is responsible for only limited research but undertakes the manufacture of generic copies of off-patent innovative medicines. Some pharmaceutical companies focus on specialised medicines (e.g. predominantly used in hospitals), others on products prescribed mainly by general practitioners, whilst others market products available without the prescription (so-called "over-the-counter" medicines). In addition to dividing the industry by type of product, parts of the industry may also focus on different aspects in the production of medicines. Although, historically, big pharmaceutical companies have undertaken the discovery, research and development, authorisation, manufacture and marketing of their products in-house, more and more, companies may specialise in these different functions. For example, certain companies operate almost exclusively as "contract research organisations" (CROs) conducting clinical trials on behalf of traditional pharmaceutical companies.

Regulatory authorities: regulatory authorities are responsible for regulating the pharmaceutical industry. More specifically (although not exhaustively), regulatory authorities are responsible for: the approval of clinical trials in Europe; the authorisation of medicines; authorisation of manufacturing facilities; inspecting manufacturers, laboratories, clinical trials and market authorisation holders; maintaining marketing authorisations, and; pharmacovigilance (monitoring the safety of marketed medicines and taking action to increase benefit and reduce risk from medicines). The laws regulating medicines in the EU are a mixture of EU regulations and directives and national laws. That said, the overall framework of medicines regulation is governed by Community law and most of the key regulatory steps are covered by Community law. In the EU, two parallel systems of authorisation exist: the centralised pan-European system operated by the EMEA and the de-centralised or mutual recognition system operated by the Member State competent authorities. If a pharmaceutical company wants to have a marketing authorisation in more than one EU Member State then one of these two Community systems for obtaining an authorisation has to be used.

2. WHAT MAIN OBJECTIVE IS THE PROPOSAL EXPECTED TO REACH?

2.1 The overall policy objective

The overall policy objective is to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children.

2.2 General objectives

General objectives are to:

- increase the development of medicines for use in children,
- ensure that medicines used to treat children are subject to high quality research,
- ensure that medicines used to treat children are appropriately authorised for use in children,
- improve the information available on the use of medicines in children.
- achieve these objectives while avoiding unnecessary studies in children.

Ensuring that children have access to high quality, effective and safe medicines, accompanied by high quality information based on robust evidence is key to allowing children and their doctors the ability to make informed decisions about the treatment of disease and to ensuring that the medicines chosen, improve health. To achieve this, new and established medicines have to undergo research, including clinical trials in children, pharmaceutical companies have to obtain marketing authorisations based on the data generated, medicines authorised for children have to be marketed and clear and robust information about how and when to use the medicine has to be available and accessible. The draft paediatric regulation sets out to address all of these factors through the specific objectives described in section 3.1 and listed in section 7.

3. WHAT ARE THE MAIN POLICY OPTIONS AVAILABLE TO REACH THE OBJECTIVE?

3.1 The proposed approach to reach the objective

In selecting the measures included in the draft paediatric regulation, the Commission has looked for solutions that provide as many wins and winners as possible. The proposal builds on and links existing Community and Member State laws, structures, institutions and mechanisms. In so doing, the draft paediatric regulation respects the division of competencies between the Community and the Member States and ensures that the measures are efficient, effective and consistent.

To ensure that all the medicines required by children fall within the scope of the draft paediatric regulation and to fully understand the measures proposed, it is necessary to break medicinal products down into three groups:

1. products in development and yet to be authorised
2. authorised products still covered by intellectual property rights (IPRs)
3. authorised products no longer covered by IPRs

The draft paediatric regulation contains a package of measures to achieve its objectives. Most apply to all medicinal products whereas others are specific to products falling into one of the three groups listed above.

The US experience and the experience gained from the EU Regulation on orphan medicinal products indicates that a system of both obligations and incentives/rewards is necessary to achieve the objective of stimulating the development of medicinal products to meet the therapeutic needs of the paediatric populations in the Community. They also underline the

importance of striking the right balance between the two. The precise nature of the obligations and incentives will depend on the status of the particular medicinal product. It is easier to find answers to the question of how to introduce effective obligations and incentives/rewards for new products or products that are still covered by IPRs than for those that are not.

For the first two categories of medicines, extensions of the period of patent can be used to provide incentives/rewards, and requirements to provide the results of a paediatric study programme can be imposed on the marketing authorisation holder. The draft paediatric regulation proposes a requirement for new medicinal products (other than generics, similar biological medicinal products and those authorised through the well-established medicinal use procedure) and authorised medicines covered by a patent or a supplementary protection certificate to present the result of studies in children according to an agreed paediatric investigation plan at the time of marketing authorisation application or application for a new indication, new dosage form or new route of administration. A system of waivers will ensure that research in children is only conducted to meet the therapeutic needs of children. A system of deferrals will ensure that research is done only when it is safe and ethical to do so and deferrals will also ensure that the requirement for data in children will not block or delay the authorisation of medicines for other populations. Unlike the situation in the US where the requirement is not directly rewarded or incentivised, the draft EU regulation proposes linking the submission of data in children (whether the results are positive or negative) and updating of the product information, to a mixed reward/incentive in the form of a six-month extension of the supplementary protection certificate (SPC). The SPC is a type of patent extension harmonised across the EU, the creation of which is set out in Article 13 of Council Regulation No (EEC) 1768/92, of 18 June 1992. SPC extension was proposed at the time the Rand Study and the 2004 part of the public consultation were conducted, however, based mainly on the results of the public consultation (see section 6) it should be noted that the final Commission proposal, presented in section 7, proposes extended marketed exclusivity rather than SPC extension for orphan medicines. Under the EU orphan regulation, medicinal products designated as orphan medicinal products gain ten-years of market exclusivity on the granting of a marketing authorisation in the orphan indication. As such products are frequently not patent protected the reward of SPC extension can not be applied and when they are patent-protected, SPC extension would provide a double incentive. Therefore, for orphan medicines, rather than extend the SPC, in the final Commission proposal presented in section 7 it is suggested to extend the ten-year period of orphan market exclusivity to twelve-years if the requirements for data on use in children are fully met.

For the third category of product i.e. those not covered by IPRs, it is more difficult to introduce incentives and requirements. With respect to incentives, there is no period of patent protection, market exclusivity or data protection to be extended. Furthermore, although a number of different marketing authorisation holders tend to market products containing the same active substance they are usually generics manufacturers and, in addition, the innovator may no longer market the product. Individual manufacturers of generic products may not to have large resources for research and development or expertise in conducting clinical trials beyond the studies required to demonstrate that their product is equivalent to the innovator product. The opportunities to introduce requirements are also fewer as the generic product tends to follow that of the innovator and once the innovator has stopped developing the product few changes are made independently to the marketing authorisations for generic products. However, this is an important category: an FDA survey found that 6 of the 10 products used most frequently off-label or on an unlicensed basis in the US were off-patent. Different tools will be necessary, therefore, to improve the availability of medicines for use in

the paediatric population of off-patent medicines compared with protected products. The draft paediatric regulation proposes to use the incentive of data protection (of 10 years) on any new studies on the safety, quality and efficacy of the product in children linked to a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), together with a study program to fund or part fund research into the paediatric use of off-patent medicines (Medicines Investigation for the Children of Europe: MICE). The paediatric study program is only referenced in the Explanatory Memorandum of the draft paediatric regulation: it will be the subject of a separate proposal.

In addition to requirements, rewards and incentives, the draft paediatric regulation contains a number of other measures that can be categorised roughly into the following groupings: infrastructure, knowledge sharing, transparency, pharmacovigilance, and market access.

With regard to infrastructure, an expert committee, the Paediatric Board (PB) is proposed within the EMEA and procedures are established regarding paediatric investigation plans, waivers and deferrals from the requirements described above and marketing authorisations. Clinical trials in the paediatric population may require specific expertise, specific methodology and in some cases, specific facilities and should be carried out by appropriately trained investigators and paediatricians. Therefore, it is proposed to create a network to link together existing national and European initiatives (of trial centres / investigators) in order to build up the necessary competences at a European level and to facilitate co-operation and avoid duplication of studies.

In addition to being central to the agreement of paediatric investigation plans, the PB will be central to knowledge sharing as will free scientific advice from the EMEA to companies, a survey of the use of medicines in children in the Member States and an inventory of the therapeutic needs of children.

The inventory, developed primarily by the PB, will also serve as an important transparency measure as it will form, in part, the basis for waivers from the requirement for data in children and deferrals of the timing of the implementation of studies in children. Other proposed transparency measures include a database of the studies conducted as a result of agreed paediatric investigation plans and based on the database set up in relation to the EU Clinical Trials Directive, a requirement for industry to submit to competent authorities pre-existing studies relating to the use of medicines in children and published annual reports on the companies that have benefited or failed to comply with the measures in the draft paediatric regulation.

Pharmacovigilance measures are included over and above the existing requirements in the pharmaceutical legislation. These are a requirement to outline the pharmacovigilance plans as part of a marketing authorisation application and the authority for regulators to require a risk management system and post-authorisation data collection for a particular product associated with a safety concern.

With regard to market access, the draft regulation proposes access to the centralised procedure for applications containing the results of studies resulting from an agreed paediatric investigation plan, access to an optional centralised procedure via the existing Community referral procedure to obtain a Commission Decision on paediatric use for nationally authorised products and a requirement for authorised products newly granted a paediatric indication to market the product, taking into account the new indication, within two years.

Additional explanation of the individual measures proposed is provided in the explanatory memorandum and the recitals that precede the draft legislative text.

3.2 The trade-offs associated with the proposed approach

Proportionality regarding new medicines and patent-protected, authorised medicines

Some of the greatest debate regarding the proposal has centred on striking the right balance between requirements placed on the industry and whether any requirement should be rewarded and, if rewarded, by how much? The proposal attempts to strike the right balance. Intervention is necessary as the forces of the free market have failed to deliver medicines for children. However, for new medicines and patent-protected, authorised medicines, a requirement without rewards would place the entire burden of this public health issue on industry and could reduce or hamper innovation for adults. A system of reimbursement to industry for the costs of developing, authorising and marketing medicines for children is theoretically possible. However, such a system would be near impossible to administer. Such a system would require, in particular, the costs of research and development of medicines to be known in advance. It would also require a precise knowledge of the market before the product is launched. Furthermore, the largest sales of medicines are usually up to ten years after first marketing, as a product nears patent expiry. When, therefore, would reimbursement be calculated and how could the sales for children be accurately divided from the sales for adult use? On this basis the Commission has opted for a far simpler system based on an existing EU-wide instrument: extension of the supplementary protection certificate (SPC).

Extension of the SPC will provide for a mixed reward and incentive. By extending the patent life of the active moiety, generic competition will be delayed for the entire product range based on that active moiety and this will occur at the end of the patent life when sales are generally at their greatest. For successful products, whether sales success is in child or adult markets, the SPC extension will result in increased sales for the innovator company that may significantly outweigh the costs incurred as a result of the requirements in the draft paediatric regulation. However, for other, less successful products, the SPC extension may not fully compensate the costs incurred as a result of the requirements. Overall it is likely that for most products, industry will be more than compensated for their costs (see section 4). In this way, the SPC extension can be viewed as a mixed reward and incentive. Based on the Rand study, public consultations and discussions with industry, it is likely that for most products industry will want to access the SPC extension, so willingly conducting high quality research in children. This therefore represents a clear win for the innovative industry and a clear win for child-health.

The draft paediatric regulation proposes a *six-month* extension to the SPC. This is the same extension as is provided in the US by the paediatric exclusivity provision. The innovative industry has argued for a longer period of SPC extension based mainly on the fact that sales in the EU are less valuable than in the US. However, the proposed reward / incentive must strike a balance between the gain for the innovative industry and the potential costs to society, the burden on healthcare costs and the costs to the generics industry. Furthermore, the same research and development will be eligible for both US paediatric exclusivity and EU SPC extension and the EU SPC extension will already adequately compensate industry costs in most cases. Section 4 presents estimates of the value of the proposed six-month extension to the innovative industry and the potential costs to society and the generics industry.

In summary, the duration of *six-month* for the SPC extension is justified on the following basis:

- a precedent of six-months extension already exists in the United States,
- the costs of testing medicines for children are estimated to be, on average, four million Euros per product. However, the requirement for testing medicines for children will result in additional costs to the innovative industry including administrative costs and the costs of manufacturing specific formulations for children (an estimate of the size of these costs is not available),
- the Rand study has estimated that the six-month SPC extension will result in a profit for the innovative industry of between 0.8 and 9.1 million Euros per product, however, this estimated profit range does not take into account these additional administrative and manufacturing costs,
- the loss of profit to the generics sector resulting from the six-month SPC extension has been estimated by Rand to be between 4 and 51 million Euros across the entire generics sector.
- The Rand study has estimated that the six-month SPC extension will result in only a very modest increase in spending on medicines of between 0.06 and 0.25% of European pharmaceutical expenditure.

It can therefore be seen that the six-month SPC extension may result in a profit for some companies for individual products but that the size of the profits estimated by Rand Europe are over-estimates. Furthermore, the loss of profit to the generics sector and the increase in the costs of medicines resulting from the six-month SPC extension are relatively modest. Considering the public health advantages of having safe and effective medicines for children, these costs are considered justified.

Any measures to promote medicines for children should not delay access to medicines for other populations

The draft paediatric regulation aims to remedy the situation for children but in so doing, it must not compromise the access of other populations to new medicines. The draft paediatric regulation includes a requirement for new and existing patent-protected medicines to present the results of studies in children according to an agreed paediatric investigation plan at the time of marketing authorisation application (usually for adults) or application for a new indication, new dosage form or new route of administration. Although the draft paediatric regulation encourages industry to research their products in children early in product development, the results of studies in children will not always be available as early as the results in other populations (notably adults). The draft paediatric regulation contains a specific measure to ensure that the requirement does not delay the authorisation of medicines for adults. The Paediatric Board will be empowered to grant deferrals from the timing of the requirement. Such deferrals might be granted because study in children is judged to be safer if delayed until after some study in adults or because the trials in children may take longer to conduct. Deferrals from the requirement will allow a medicine to be authorised for adults and the results of studies in children to be presented at a later date.

Difficulties in stimulating research and development for off-patent medicines

There has been some debate on how best to stimulate research, development and authorisation of off-patent medicines for children. In order to establish a vehicle for providing incentives

for off-patent medicines, the proposal includes a new type of marketing authorisation: the Paediatric Use Marketing Authorisation (PUMA). A PUMA utilises existing marketing authorisation procedures but is specifically for off-patent medicinal products developed exclusively for use in children. The PUMA provides a vehicle for awarding the incentive of data protection.

Awarding data protection for research, development and authorisation of off-patent medicines is considered the best option by the Commission. However, during consultation, some stakeholders have proposed a system of market exclusivity, like that used for orphan medicines. Such a system of "administrative" market exclusivity has also been considered by the Commission for off-patent medicines for children. However, the orphan regulation aims to stimulate, through incentives, the development and authorisation of specific treatments for rare diseases. Orphan medicines are few in number; the exception rather than the rule. The opposite is true with paediatric medicines. The majority of diseases effecting adults affect children to some degree and the majority of medicines for adults could be of therapeutic benefit to children. The aim of this proposal is for many medicines on the EU market to be tested (other than generics) and authorised (including generics) for use in children. Therefore a system of market exclusivity would be contrary to the objectives of this proposal. Another central argument against a system of market exclusivity is that generics will already be on the market. Unless generic marketing authorisations for a particular active drug substance were revoked following authorisation of one off-patent product for children then market exclusivity is impossible in a multi-product environment. Revocation of an existing marketing authorisation is only justified if it is to protect public health (such as with a safety concern). A system of market exclusivity could only operate for a new formulation of a medicine specific to the needs of children if no suitable formulation was already authorised. In contrast, a data protection scheme is practical for all off-patent medicines for children even if the incentive is less when no child-specific formulation is required.

Data protection means that the data generated to support the marketing authorisation can not be used to support the authorisation of any other medicine for a set period. Data protection is the form of IPR established in pharmaceutical legislation to delay generic competition and therefore stimulate innovation. The system works independently of the patent system. Data protection is an IPR than can be applied to off-patent medicines and it has stimulated innovation for off-patent medicines, allowing their use to treat new diseases and new populations. However, data protection is weaker than patent protection as a competitor can, if they judge that the market is valuable enough, conduct their own research and development on the same active substance. Therefore, data protection does not *guarantee* market exclusivity.

As the proposed PUMA is based on the existing system for granting marketing authorisations in the Community, the existing period of data protection (ten years) has been chosen. This is the period on which the Extended Impact Assessment and the 2004 consultation were based. However, both the Extended Impact Assessment and the 2004 consultation concluded that this incentive might prove insufficient. To address this, an additional incentive has also been added to the PUMA since the 2004 consultation in the form of amended data requirements (described later). In view of the challenges involved in stimulating research, development and authorisation of off-patent medicines for children, an additional stimulus and incentive for conducting high quality, ethical research is considered necessary and it is considered that this should be the provision of funding for studies, including clinical trials, into the paediatric use of medicines not covered by a patent or a supplementary protection certificate. The

Explanatory Memorandum of the draft paediatric regulation includes a reference to the creation a paediatric study program: Medicines Investigation for the Children of Europe (MICE). The creation of the funding and its operation will be included in separate legislation. With relevance to MICE, the existing Committee on Proprietary Medicinal Products Paediatric Expert Eroup has developed a provisional list of sixty-five off-patent medicines considered priorities for research and development.

Balancing wins and losses for different sectors of industry

Overall, the draft paediatric regulation provides important opportunities for the innovative industry. The main opportunity is the extended patent protection which has already been described and the value of which is explored in section 4. Another opportunity for the innovative industry relates to the use of the data generated as a result of the draft paediatric regulation to capitalise on markets outside the EU.

Many of the measures in the draft paediatric regulation will benefit all sectors of the industry. The availability of free scientific advice and the expert Paediatric Board will benefit all sectors of the industry but may be particularly valuable to small and medium sized enterprises (SMEs) with limited in-house expertise. The same is true for the inventory of therapeutic needs for medicines in children. This information resource will provide industry with identified therapeutic gaps and therefore market opportunities. The EU network of paediatric investigators and trial centres will provide industry with easier access to the infrastructure required to conduct research. As the number of studies in children increases, the infrastructure and knowledge base for conducting research will increase with it with economies of scale and experience. The draft paediatric regulation presents major opportunity for companies specialising in clinical research and companies specialising in the development of specialist formulations of medicines. Where such companies do not today exist, companies will be created or existing companies will diversify to fill the gaps.

The impact on the generics industry is more mixed. While all of the general opportunities will apply to the generics industry and indeed, certain generics companies have already expressed an interest in capitalising on the paediatric market with niche products, the SPC extension will result in lost opportunity costs for the generics sector. These losses are estimated in section 4.

3.3 Why a regulation is necessary and why action needs to be European

Previous sections have described the public health issue and the risks associated with it and have explained why action is required. A European solution to this public health challenge is warranted on the following basis. Firstly, the lack of tested, authorised medicines for children is a Europe-wide issue. Surveys of off-label and unlicensed use of medicines are available from many EU Member States and all show the same result: children are denied innovation and children are being treated with medicines meant for adults and those medicines may not work in children and may present safety hazards. The Rand study report presents the results of a literature search to support this conclusion. Secondly, the current system for the regulation of medicines is a Europe-wide system. Therefore, the most efficient and effective way to improve the availability of medicines for children across the Community is via the existing Community system of pharmaceutical legislation (including granting marketing authorisations) and the Community system of supplementary protection certificates. Indeed, given the Community nature of the existing pharmaceutical legislation, the scope for unilateral action by individual Member States is limited.

3.4 The discarded options

No action

The results of no action were explored in Section 1. On the basis of the available evidence it is concluded that the current public health issue regarding medicines for children will not be resolved in the EU until a specific legislative system is put in place.

Industry self-regulation

One potential option to increase the research, development and authorisation of medicines for children is to work with industry to develop a code of practice by which the industry could self-regulate. However, such a system would relay entirely on the good-will of industry and, as was explained in Section 1, industry has generally been unwilling to make the investment required to authorise medicines for children in the EU even when the data to support authorisation have already been generated as a result of the laws that exist in the US. Furthermore, self-regulation would place the entire burden of this public health issue on industry with no mechanisms for rewards. In addition, government intervention is required to ensure the right studies are done for the benefit of children rather than studies being conducted only because the market returns are likely to be high.

The possibility of an industry code of practice operating *in parallel* to the draft paediatric regulation could be considered. Issues for a voluntary code might include the marketing of authorised medicines for children (the draft paediatric regulation has a requirement only for authorised products newly granted a paediatric indication to market the product, taking into account the new indication, within two years) and information and resource sharing.

Member State action

As has already been stated, the public health issue is Community wide and the regulation of medicines is Community based. The draft paediatric regulation does, however, leave room for complementary Member State actions. Some examples: the infrastructure for conducting paediatric clinical trials in the EU is currently limited. Member State investment in clinical trial centres and training of doctors and trialists would be welcome complementary measures; the paediatric study program (Medicines Investigation for the Children of Europe) will be the subject of separate Community legislation. The size of the program is yet to be agreed although it is very unlikely to be sufficient to support all the research required. Furthermore, it is likely to only part-fund individual studies. Therefore, additional funding for research from the Member States will be required; the major competencies regarding the setting of taxes and therefore tax incentives lie with Member States. The draft paediatric regulation leaves scope for such incentives; finally, delivery of health care including the prescription of medicines is outside Community competence. Member States may choose to preferentially reimburse or include in formularies, tested authorised medicines, once these are available.

Requirements without rewards and incentives without requirements

A justification for balancing the requirements contained in the draft paediatric legislation with rewards / incentives has been provide under the heading “Proportionality regarding new medicines and patent-protected, authorised medicines”. What about incentives without requirements? Providing an incentive in the form of IPRs would lead some companies to do the necessary research, development and authorisation of some medicines for children.

However, the main driver for research would remain market forces i.e. the potential for industry to profit from the research conducted and the IPR awarded. This would mean that the therapeutic needs of children, which are the drivers of the research, development and authorisation of medicines in the draft paediatric legislations, might come second to consideration of profit. Important public health needs might remain unmet and the objective of improving the health of the children of Europe would only be partially met.

New products: why not reward with data protection

Data protection could be used to reward industry for meeting the requirements for new and patent-protected authorised products in the draft paediatric regulation. However, as has previously been explained with regard to the PUMA, data protection is less valuable to the innovative industry than SPC extension and the draft paediatric regulation is already offering the innovative industry a shorter period of SPC extension than it is demanding. In consultation (see section 6), with the exception of the generics industry, all main stakeholder groups have been supportive of SPC extension (although the period of extension is debated). The Commission predicts that, based on the experience gained during the recent review of the pharmaceutical legislation, further extension of data protection for new products will be strongly opposed by some Member States, particularly some of the new Member States. Finally, data protection does not prevent competitor companies generating their own data to support marketing authorisation applications. Repeating clinical trials in children, if those trials add nothing or only a limited amount to society's knowledge about the use of a medicine for children is considered undesirable. A system of data protection for new products would encourage the repetition of studies. On the basis of all of these factors, the Commission considers SPC extension to be the preferred option.

New products: why not reward with administrative market exclusivity

Some have argued that a system of "administrative" market exclusivity, as is operated under the EU orphan regulation should be considered for new paediatric medicines. As with data protection, market exclusivity is an alternative to SPC extension. However, the Commission consider SPC extension to be the preferred option on the following basis. The orphan regulation aims to stimulate, through incentives, the development and authorisation of specific treatments for rare diseases. Orphan medicines are few in number; the exception rather than the rule. The opposite is true with paediatric medicines. The majority of diseases effecting adults affect children to some degree and many medicines for adults could be of therapeutic benefit to children. The aim of the draft paediatric regulation is for many medicines on the EU market to be tested (other than generics) and authorised (including generics) for use in children. Therefore a system of market exclusivity would be contrary to the objectives of the draft paediatric regulation. Orphan medicines are few in number and therefore the operation of a system of "administrative" market exclusivity is possible. Such a system for paediatric medicines, considering their number and the multiple competent authorities in Europe responsible for the authorisation of medicines, would be administratively impossible. Furthermore, such a system would require the EU competent (regulatory) authorities to check patents. At present they do not possess this competence. Finally, a system of "administrative" market exclusivity would create a third type of IPR in a system where two types (patents including SPCs and data protection) already operate. To introduce a third type of IPR would be less transparent and less fair on generic competitors.

Older products: why not use market exclusivity as the incentive

Awarding data protection for research, development and authorisation of off-patent medicines is considered the best option by the Commission. However, some of the weaknesses of this option have already been explored under the section "Difficulties in stimulating research and development for off-patent medicines". A system of "administrative" market exclusivity has also been considered by the Commission, for off-patent medicines for children. The central argument against such a system is that generics will already be on the market. Unless generic marketing authorisations for a particular active drug substance were revoked following authorisation of one off-patent product for children then market exclusivity is impossible in a multi-product environment. Revocation of an existing marketing authorisation is only justified if it is to protect public health (such as with a safety concern). A system of market exclusivity could operate for a new formulation of a medicine specific to the needs of children if no suitable formulation was already authorised. In contrast, a data protection scheme is practical for all off-patent medicines for children even if the incentive is less when no child-specific formulation is required. As has already been stated, the final Commission proposal, described in section 7, proposes amended data requirements for marketing authorisation applications that should make the development of off-patent medicines for children particularly attractive to generic companies.

4. THE IMPACTS EXPECTED FROM THE DIFFERENT MEASURES IDENTIFIED

The Commission's assessment of impacts from the different measures identified is based on an independent, externally contracted study, specifically designed to estimate the economic, social and environmental impacts of the draft paediatric regulation (the Rand Study). The assessment of impacts also draws on experience with the existing EU pharmaceutical market and regulatory framework, experience with legislation on paediatric medicines in the US, experience with orphan medicines in the EU, extensive consultation with stakeholders, and the published literature.

The Rand study has performed a detailed assessment of the possible impacts, in economic, social and environmental terms, of the different measures in the draft paediatric regulation (see Annex 1). The Rand study utilised the following methods: identification of the key stakeholders and interviews with the stakeholder groups to assess their views on the issue of medicines for children and on the potential impacts of the solutions proposed in the draft paediatric regulation; identification and assessment of data relevant to quantifying the size of the problem and the impact of the proposed solutions; a qualitative description of the extent of the impacts, distinguishing between stakeholders, social groups, regions, sectors and external impacts; quantitative estimates of selected indicators (e.g. numbers of patients treated, number of deaths avoided, number of patent applications, number of companies involved); and, a monetary valuation of the quantitative impacts, distinguishing costs and benefits and paying separate attention to the costs of compliance with requirements (to the extent that the data allow such a valuation). The Rand study assesses the impacts in the short and long term, identifies the theoretical risks and uncertainties and assesses whether the proposals in the draft paediatric regulation will be effective in achieving its objectives.

It should be noted that at the time of the Rand Study, the "working proposal" of the Commission included orphan products in the scope of the SPC extension and 10-years of data protection linked to the PUMA. These remain part of the "working proposal" for this section. However, based on the Rand Study results and the later part of the public consultation (see section 6), two-years of additional market exclusivity has been proposed as an alternative to

SPC extension for orphan products and amended data requirements have been added to the PUMA as an additional incentive in the final proposal presented in section 7.

4.1 Impacts of the key proposed measures

Impacts of the core requirements

The core requirements in the draft paediatric regulation concern: the paediatric investigation plan; the requirement to present data on use in children with marketing authorisation applications for new products, and; the requirement to present data on use in children with applications for new formulations, new dosage forms and new indications ("line-extensions") for authorised but patent-protected medicines. The impacts of these requirements are assessed together.

Operationalisation

Unless a waiver from the requirements has been granted, companies will have to develop and carry out studies in children according to an agreed paediatric investigation plan for new products and for line extensions of existing patent-protected products. The Paediatric Board (supported by the EMEA) will have to assess draft paediatric evaluation plans, requests for waivers and requests for deferrals. The EMEA and National competent authorities will have to assess the data from studies in children together with data in adults when authorisation applications are submitted. Healthcare professionals and researcher will need to take part in studies and provide scientific advice to industry and regulators. Children will need to be enrolled in studies with the support of their families.

Short-term effects

The workload of the EMEA and National Competent Authorities will increase. There will be a need to secure the services of additional experts able to assess paediatric investigation plans and the data generated from studies in children. The EU pool of available resource is relatively limited and, in the short term, this will put some pressure on the system. The Rand study has estimated the potential impact of the core requirements on the budget of the EMEA. Rand have estimated that, based on the increase in the number of marketing authorisation applications the EMEA will have to handle, the EMEA budget would have to increase by 67 – 150%. Assuming constant costs per application and considering that the EMEA budget for 2003 was 78 million Euros, Rand estimate a worst-case scenario of the EMEA's budget needing to increase to between 130-195 million Euros. However, these estimates do not take account of the fact that many of the EMEA's costs are fixed. Furthermore, the costs of many marketing authorisation applications will be covered by the existing fees structure of the EMEA so revenue from fees will also increase. The Commission does not support the estimates proposed by Rand. The Commission believes that the main increase in costs to the EMEA will relate to the operation of the Paediatric Board, free scientific advice regarding medicines for children and the transparency measures included in the draft paediatric regulation (such as the database of paediatric studies). The Commission requested a detailed costing of the proposed measures by the EMEA. The EMEA has estimated that following the initial introduction of the regulation, its costs will increase by up to five million Euros per year. The Commission judges that the EMEA projections of its own costs are likely to represent a more robust estimate and should be the estimate on which readers rely.

Based on information provided by stakeholders, the Rand study has estimated that the costs of developing the paediatric investigation plan and conducting phase III studies in children will increase the costs to industry of 1-7 (average 4) million Euros per product. These figures are

supported by separate estimates of the costs of paediatric studies provided to the EMEA by various academic centres involved in paediatric research. They are also supported by a survey[15] carried out in the US of the overall costs of trials conducted to meet FDA Written Requests. This survey gave a result of an average cost of $3.87 million per written request (range 500,000 – 20,000,000). The Rand study extrapolates these figures, based on the EMEA estimate of the increased number of marketing authorisation applications, to the total costs of the paediatric study requirements to the entire pharmaceutical industry (i.e. costs for all medicines). This gives a figure of 560 million Euros for the total costs of paediatric testing in the first year, falling to between 160 and 360 million Euros in subsequent years. In 2000, European pharmaceutical companies spent $17 billion (€15.2 billion) on research and development. American data suggest that Phase III clinical trials account for c. 15% of the total drug development costs. This translates to $2,550 million (€2,274 million) for European manufacturers. Assuming that the estimated cost of paediatric testing is accurate, the requirements would involve an increase in expenditure on Phase III clinical trials of 25% in the first year and between 7% and 16% in the following years. Total expenditure on drug development would therefore rise by almost 4% in the first year and between 1% and 2.5% in subsequent years. These figures represent a reasonable estimate of the costs of phase III clinical trials. It should be remembered that the costs of developing a new drug have been estimated to be $802 million on 2000[16]. Industry has argued that the costs of the requirements in the draft paediatric regulation are higher than the costs of the specific studies required. Industry argue that the cost of capital, costs of manufacturing and packaging child-specific formulations and costs of marketing products should also be included. Although these additional costs are valid, the Commission believes that the cost estimates of the requirements in the draft paediatric regulation provided by the Rand study are likely to be in the correct order of magnitude.

The Rand study has also estimated the costs of medicines if the marginal costs of drug testing are passed directly on to customers. The total retail value of European pharmaceutical consumption (in the EU-15 and the new Member States) is about €166 billion, while from an industrial perspective (turnover in producer prices) market size is $88 billion (€78.5 billion). From both perspectives the burden of paediatric testing is relatively light. If the costs are carried forward directly, the Rand study estimates that consumers (or their insurers) would be confronted with an increase in costs of 0.1% to 0.3%, while for industry the costs amount to between 0.2% and 0.7% of turnover. If pharmaceutical producers apply a risk premium to the costs of paediatric testing, the effect on consumers (or their insurers) will be slightly larger than was estimated above. The increase in costs would then translate into a price rise of 0.1% to 0.4%. However, it should be remembered that in many EU Member States, the price of medicines is controlled by governments. Therefore these increases in prices estimated by Rand remain theoretical and may not occur in practice.

Long-term effects

The costs of paediatric medication and paediatric health care may theoretically increase as the costs of testing are carried forward. The impact on the revenues and profits of pharmaceutical companies will depend on the price elasticity of paediatric medicines and on the willingness-to-pay of households and the willingness-to-reimburse of insurance companies. Healthcare professionals appear willing – and may even feel obliged – to switch to tested medicines. National governments may decide to negotiate or enforce price reductions.

[15] Milne C. Food and Drug Law Journal. 2002; 57: 491-517.

[16] DiMasi JA, Hansen RW, Grabowski HG. The price of innovations: New estimates of drug development costs. Journal of Health Economics, 2003; 22: 151-185.

An increasing proportion of the available medicinal products will be tested for use in children. From the time of entry into force of the proposed Regulation, the currently available patent-protected products that are not tested for use in children will be caught by the requirement relating to applications for new indications, new pharmaceutical forms and new routes of administration. It will take approximately between 10 and 15 years before the last patent expires. However, after the patent expires generic drug manufacturers can enter the market without having to perform paediatric tests. The proposed Regulation does not impose a requirement after the expiry of the patent, but intends to attract manufacturers of off-patent drugs by means of an incentive (linked to the PUMA). The effect on the availability of paediatric tested off-patent medicines will consequently be more modest.

The supply of licensed medicines for use in children will increase, resulting in better treatment, a higher quality of life, and possibly lower overall healthcare costs. The expected increase in the supply of licensed medicines for use in children will allow healthcare professionals to provide better treatment, reduce the frequency of adverse drug reactions, and lower the chance of liability suits. It will also provide the opportunity to reduce prescribing of off-label and unlicensed products. Children are provided with a wider range of new and existing products tested for use in children, improving the quality of their treatment and raising the quality of their lives.

To estimate the financial value of social savings from improvements in medical treatment resulting from the draft paediatric regulation is very difficult. The difficulties result from a lack of robust data on the financial consequences of unlicensed and off-label use of medicines in children, the lack of robust data on the direct improvements in health from the use of tested, effective and safer medicines and the lack of robust data on the financial value of improved health. The Rand study has attempted to partially estimate the value, in terms of reduced hospital stay from eradication of unlicensed and off-label use of medicines in children. The Rand study estimates the total costs for the entire EU-15 of an additional two-day stay in hospital related to an adverse drug reaction would amount to between $11 and $40 million (€10-36 million). In the upper range of the Rand study estimates –where ADRs occur more frequently, children have to stay in hospital for an additional three days, and more children are hospitalized annually, the costs would rise to between $157 and $283 million (€140-252 million). These could be considered social savings, if off-label and unlicensed prescription were made unnecessary as a result of the proposed regulation. However, the Commission urges caution in interpreting these figures. Firstly, the figures are based on a number of assumptions linking unlicensed and off-label use of medicines in children to adverse drug reactions. Secondly, the figures relate only to reduced hospital stay from avoided adverse reactions and do not include the value of lives saved as a result of avoiding fatal adverse reactions or the value of improved quality of life from avoiding adverse reactions from unlicensed and off-label use of medicines in children. Lastly, the Rand study figures do not include the value of more effective medicines in terms of: lives saved; quality of life improvements for children and their families; lost-work days avoided through ill-health of a child, and; healthcare costs avoided. On this basis, the Commission considers the Rand study figures to be of interest but incomplete (because of the unavailability of relevant data) and therefore unrepresentative of the true financial benefits from improved health that will result from the draft paediatric regulation. The Commission considers that the impact of the draft paediatric regulation will be very large in both positive social effects and financial value to society. However, in this extended impact assessment, it has been impossible to apply a robust estimate of the financial value of these social benefits. As we have estimates of costs and

benefits to industry but no robust estimate of the financial benefits from improvements in health, then, unavoidably, this impact analysis is unbalanced and undervalues the true value of the draft paediatric regulation.

Core requirements: risks and uncertainties

The Rand study has suggested a theoretical risk of the time of assessment of marketing authorisations increasing as a result of the requirements in the draft paediatric regulation. However, the maximum time for assessment is set in law and therefore the EMEA and National Competent Authorities will have to avoid increased assessment time through securing greater resources. The Rand Study suggests that when the draft paediatric regulation first comes into force there may be a backlog of applications (i.e. of draft paediatric investigations plans, waiver requests and deferral requests) for the Paediatric Board to consider. This is foreseen and specifically dealt with in the draft paediatric regulation in the form of a staggering of implementation dates for the different elements, including requirements.

The Rand Study suggests that difficulties might arise if the Paediatric Board, responsible for agreeing paediatric investigation plans, and the committees (notably the Committee for Proprietary Medicinal Products - CPMP) responsible for authorisation, disagree on how to study a medicine in children. This issue is again specifically addressed in the draft paediatric regulation: membership of the two committees will overlap; the EMEA is tasked with effective co-ordination between them, and; a mechanism is included to allow modification of paediatric investigation plans, should implementation issues arise.

The Rand study highlights a theoretical risk that the requirement for studies in children may potentially lengthen the drug development process. The draft paediatric regulation deals with this theoretical risk head-on. The draft paediatric regulation introduces an important derogation from the requirement for studies in children to be submitted at the time of marketing authorisation application. This derogation relates to the granting of deferrals by the Paediatric Board. Deferrals relating to the starting, finalisation and submission of studies in children will allow marketing authorisation applications for adults to be processed and marketing authorisations granted while studies in children are ongoing. This may be necessary if it is considered safer to start studies in children after some study in adults or if studies in children take longer to conduct. The granting of deferrals by the Paediatric Board will prevent the requirements in the draft paediatric regulation from causing any delay in market access for products for other populations.

The Rand study has raised the theoretical possibility of the requirements leading to more research in the most profitable areas rather than to meet the unmet medical needs of children. This will not be the case for new drugs and patent-protected products covered by the requirements in the draft paediatric legislation. The requirements are absolute unless a waiver is granted by the Paediatric Board. The Paediatric Board is empowered to grant waivers, based on the therapeutic needs (or lack of them) of children, even if waivers are not requested by companies. Therefore, if companies do propose to study medicines in children of no or limited therapeutic value to children, these will be blocked by the Paediatric Board. The risk of incentives driving research and medicines development towards more profitable areas is discussed under the heading “Impact of the Paediatric Use Marketing Authorisation (PUMA)”.

The Rand study has also raised the possibility of industry "cutting corners" to meet the requirements. Specific safeguards against this are included in the draft paediatric regulation: all paediatric investigation plans will need to be agreed by the Paediatric Board. This is one of the absolute requirements of the draft paediatric regulation. Furthermore, the EU Clinical Trials Directive will apply to all EU conducted studies, providing additional and robust safeguards.

The Rand study suggests that, because of the paediatric testing requirements, there is a risk that some companies will become reluctant to develop new indications, new pharmaceutical forms and new routes of administration in small markets and for products with low sales. However, the costs of paediatric testing are relatively modest compared to total drug development costs and will be adequately compensated for by the six-month extension of the SPC. Indeed, the opposite may be true. The draft paediatric regulation may drive innovation for adults as companies will want to satisfy the paediatric requirements for their existing patent-protected products in order to gain from the six-month extension of the SPC (as has been seen in the United States).

The costs of developing a new indication, new pharmaceutical form or new route of administration are lower than the costs of developing a new drug, but the reward from the draft paediatric regulation (6-months SPC extension) is the same. The Rand study suggests that the industry may be drawn towards the second requirement, that is, find ways to adjust existing authorised products first, and focus on new products later. This may have the effect of stimulating innovation for already authorised patented products as companies may develop new indications specifically to benefit from the SPC extension. The Commission supports that this may be a business decision taken by some companies. However, as the share value of companies is heavily dependent on a company's pipe-line of new products, it is considered unlikely that companies will divert the major portion of their Research and Development funds to further developing existing products.

The Rand study points out that authorised, patent-protected product that are not the subject of applications for new indications, new pharmaceutical forms or new routes of administration will not be caught by the requirements of draft paediatric regulation. This is entirely correct, however, it will represent the minority of products (as line-extensions are commonplace), companies may develop line extensions specifically to access the SCP extension, and if they do not, once the patent expires competitors will be free to develop the medicine for children and apply for a PUMA.

The Rand study points out that the draft paediatric regulation targets the production of paediatric medicines (supply) rather than the way in which they are used (demand). In the short term (until the draft paediatric regulation has significantly impacted on the availability of tested and authorised medicines for children) unlicensed and off-label use of medicines can continue. Healthcare professionals are expected to favour tested products over untested products. If the Regulation is successful, an increasing proportion of the available medicines will be tested and prescribing practices will automatically shift in the desired direction. This proportion will increase over time. There is an opportunity here for those responsible for the delivery of healthcare in the Member States to use formularies and reimbursement mechanisms to swing demand towards tested, authorised products. However, the Commission wishes to stress that until the supply side of the problem is completely resolved, unlicensed and off-label use of medicines will have to continue for some medicines in order to meet all the therapeutic needs of children.

Impacts of the six-month supplementary extension certificate extension

The draft paediatric regulation proposes that companies that comply with the core requirements for new and authorised patent-protected products will gain a six-month extension of the duration of the SPC. The justification for this and an explanation as to why this should be considered as a mixed reward and incentive were provided in earlier sections. Here we explore the possible impacts of this measure.

Granting of the SPC extension will take place in response to submitting the results of studies according to an agreed paediatric investigation plan *and* when the results are included in the product information of the product. Competent authorities will then include a statement in the marketing authorisation stating that the requirement has been met, and this can then be submitted to the patent offices to have the SPC extended.

The value to the innovative industry

The Rand Study has estimated the value to the innovative industry of the six-month SPC extension. The Rand study has estimated this value in two ways: firstly, per drug and secondly for total drug production (i.e. value to the entire innovative industry sector).

The Rand study estimates of the value to the innovative industry per drug

Profits associated with the turnover required to recover the costs of drug development during a drug's patent life while maintaining current levels of profitability and R&D intensity:

Whereas the costs of Phase III paediatric testing amount to an estimated €1 to 4 million, the lower range of estimated profits associated with the six-month extension vary between *$0.9 and $10.2 million (€0.8-9.1 million).*[17]

The data refer to the development of medicines for use in adults. When taking into account the possibility of applying for an SPC, the increase in market size when the paediatric market becomes more accessible (tested products will be superior), and the potential economies of scale inherent in EU enlargement, profits will have to be adjusted upwards. In contrast, these estimates of profit do not include the costs to industry of separate manufacturing of paediatric formulations, additional costs of packaging or marketing costs, therefore, the profit estimates will have to be adjusted downwards.

Overall, given the number of assumptions involved, using this methodology to estimate the profit to the innovative industry should be viewed with caution.

The Rand study estimates of the value to the innovative industry for total drug production (the entire market)

The turnover and profits associated with the products for which the patent expires have been estimated by the Rand study:

- Off-patent products account for 13% of the global pharmaceutical market. Assuming that the same percentage applies to Europe, the size of the market for generic products can be estimated at $11.4 billion (€10.2 billion) and that of patented products at $76.6 billion (€68.3 billion).

[17] See table 3.10 of the Rand study report for the calculations. The lower estimate of $0.9 million assumes $200 million (€178 million) development costs, 71 months time-to-market, while the upper estimate of $10.2 million assumes $800 million (€713 million) development costs, 71 months time-to-market. Both only take into account the real patent life of 20 years. The EGA estimates the social costs at €50 million per drug per year for the entire EU.

- The patent life of a drug is 20 years. If on average every year 5% ($1/20^{th}$) of all patented products becomes available for off-patent production with an annual turnover value of $3.83 billion (€3.42 billion) at original (patent-protected) prices. It should be noted however, that the patent life of authorised medicines will be less than 20 years.

- The Rand study then estimates the value of a six-month extension of the SPC to 5% of $76.6 billion (€68.3 billion) divided by two (as the SPC extension is 6-months not a year), or *$1.92 billion (€1.71 billion)* of turnover per year. Assuming a profit margin of between 10% and 25%, the annual value (profit) of the extension is *between $192 and $480 million (€171-€428 million).*

However, after a patent expires companies will continue to sell their branded product and may even apply for the paediatric use marketing authorisation for off-patent products. Real gains will consequently be lower. On the other hand, companies invest in paediatric testing well before they reap the financial benefits of a six-month extension of the SPC. If, on average, they test five years before patent expiry, the discounted value of the total costs of paediatric testing of €160-€360 million will be €132-€296 million; for a ten-year period these values will amount to €108-€243 million.[18] Using this second method to estimate the value of the 6-month SPC extension, the Rand study estimates that the pharmaceutical industry will be able to recover the costs of testing and make a profit on the SPC extension of between €63 and €205 million (market profit minus the costs of paediatric testing). It is important to stress again that these Rand study estimates relate to the entire innovative industry sector and are total values not values per year. It is also important to note that the costs of separate manufacturing of paediatric formulations, additional costs of packaging and marketing costs have not been subtracted from these profit estimates. Therefore, these figures should probably be revised downwards, however, we can not estimate by how much as no reliable data are available on these costs.

<u>The Rand study estimates of the cost to the generics industry</u>

Rand have assumed that every year 5% ($1/20^{th}$) of all patented products become available for off-patent production with an annual turnover value of $3.83 billion (€3.42 billion) at original (patent-protected) prices. In principle, the proposed Regulation may make this portion of the market unavailable for generic drug manufacturers for an additional six months. However, many products will be excluded from the reward associated with the requirement as a result of waivers. In addition, the size of the paediatric market is estimated by Rand at only *15%* of the total pharmaceutical market. Rand then assume a paediatric market share of 15% and an additional 10% for the increase in the development of paediatric medicines, the market value at patent-protected prices that is denied to generic manufacturers for six-months amounts to $479 million (€428 million).

Generic manufacturers generally offer their products at prices between 20% and 80% below those of the original patented product. Depending on the price cut, Rand estimate the *maximum* potential six-month loss of revenues of generic manufacturers at between $96 million (€86 million) and $383 million (€342 million).

Rand state that profitability is lower among generic manufacturers than originator companies. Rand therefore assume a profit margin of between 5% and 15%, the *maximum* potential six-month loss of profit amounts to between €4 million (5% of €86 million) and €51 million (15% of €342 million). Rand consider that these figures can be considered the cost of adjusting to new market conditions resulting from the six-month delay of market access for a

[18] At the official discount rate of 4%.

selection of products. Rand point out that this cost is not incurred overnight as: generic manufacturers are already anticipated in the paediatric regulation; SPC extensions will not be granted for perhaps another 4 years (due to the legislative process and the staggered introduction of the requirements); SPC extensions will be published publicly and generic companies will therefore be forewarned for individual products. Therefore, by the time the draft paediatric regulation enters into force, generic drug manufactiurers will have had several years to adjust to new market conditions and they will not be faced with a sudden six-month market blockade. In the future, they will be given several years advance notice of extensions to specific SPCs. The costs of adjusting to new market conditions will therefore be absorbed by the generics industry over a period of 2 to 5 years.

This loss would not go at the expense of generic products already on the market. It would represent a decline in annual market opportunities (and therefore impact on competitiveness). In addition, not all off-patent products are produced by generic drug manufacturers, so the estimated loss represents a maximum. And it will be *a one-time loss*: after the transitional period generic manufacturers will simply continue with business as usual even though they will have lost part of their market share.

The Rand study estimates of the impact on healthcare costs

Based on the information and assumptions used to estimate the loss of revenues for generic manufactures, the Rand study has estimated the impact of the six-month extension of the SPC on the expenditure of households and health insurers. The six-month extension of the SPC could result in consumers paying €428 million where they would have paid between €86 million and €342 million. The difference amounts to between 0.01% and 0.04% of total European health care expenditure and to between 0.06% and 0.25% of annual European pharmaceutical expenditure.

Once again, a number of assumptions are included in these figures. Importantly, the effects will note take place for many years and they will be gradual (as described above). In addition, the figures do not take account of the current move to greater generic prescribing which could more than offset these increases. Finally, these estimated increases in pharmaceutical and healthcare costs may be more than offset by savings resulting from: more effective treatment; fewer adverse drug reactions; and, wastage of medicines due to the current use of high dose adult formulations to treat children (the excess being discarded). As has already been discussed, the Rand study has not been able to accurately estimate these potential savings. For all of these reasons, overall, the Commission concludes that these figures should be regarded as a worst-case scenario.

Impact of the Paediatric Use Marketing Authorisation (PUMA)

Operationalisation

In the draft paediatric regulation, the Paediatric Study Program (see later) and the PUMA are proposed to incentivise development and authorised for children of off-patent medicines. Sections 1 and 3 of this report have provided some explanation of the difficulties in dealing with the issue of stimulating research and authorisation for off-patent medicines and the pros and cons of data-protection vs. market exclusivity have been explored. This section, based principally on the Rand study explores the likely impact of the PUMA with its associated data-protection.

To have access to the PUMA, the application will have to be specifically for use in children and the studies will have to be the result of an agreed paediatric investigation plan. In contrast

to the SPC extension, the incentive of data protection (applied to the studies in children supporting that application) can only be realised if the PUMA application is successful, i.e. the product is demonstrated to be safe and effective in children. Furthermore, the data protection will apply only to the new data generated to support the application, whereas the SPC-extension applies to the patented drug substance and therefore sales in adults are included.

The Paediatric Board will assess the draft paediatric investigation plans; the CPMP or the national competent authorities will assess the results of these plans, consulting the Paediatric Board if they wish. Healthcare professionals will cooperate in the conduct of clinical trials. Children need to be enrolled to do the studies, and parents need to give their consent.

Producers of patented products usually continue to produce the branded product after its patent expires. After the patent has expired, either the company that held the patent or competitors including generics companies can then apply for a PUMA. Companies can use their brand image to maintain market share, possibly increase it by lowering prices, and thus use the PUMA as an after-patent competitive instrument. More off-patent products will be tested for use in children. The PUMA gives companies the opportunity to buy market access and capture a niche of the paediatric market. A PUMA may be more attractive for SMEs rather than for the big players in the pharmaceutical sector.

The Rand study has concluded that the incentive of 10-years data protection attached to the PUMA is “most likely relatively weak” and the incentive will “most likely be less valuable to manufacturers of off-patent medicines” than the SPC extension for patent protected medicines, as: (i) data protection extends only to paediatric use, while the extension of the SPC also applies to adult use, (ii) the incentive derives its economic value from a highly specific and generally small niche in the medicinal market, and (iii) it does not involve market exclusivity and competitors can consequently compete for the same market niche. The Rand study points out that the advantage may go to the first mover. New entrants into the market will have to perform their own tests and the Paediatric Board may decide not to allow trials when there is no clear therapeutic or clinical value added or if double-testing is likely. The PUMA will not *necessarily* result in higher sales. The authorisation applies to products already on the market that will now be tested for use in children. Healthcare professionals can either switch to the tested medicine or use an off-label alternative in an appropriate way by applying the information gathered as a result of paediatric testing. Healthcare professionals are, however, likely to switch prescribing if the product represents a child-friendly formulation or dosage form where none previously existed. In addition, those responsible for healthcare delivery may selectively reimburse or include in formularies, authorised medicines for children over off-label products and such measures would support and reinforce the effectiveness of the PUMA.

The Rand study has raised the theoretical possibility of the incentive leading to more research in the most profitable areas rather than to meet the unmet medical need of children. The existence of the proposed inventory of the therapeutic needs of children, the central role of the Paediatric Board in agreeing Paediatric Investigation Plans and focussing the Paediatric Study Programme towards niche markets will offset this.

Despite these reservations, the Commission considers that data-protection remains the best and most practical incentive for off-patent products. The PUMA is most likely to be effective where a child specific formulation or dosage form is required as this will likely lead to

preferential prescribing over non child-adapted products. Furthermore, the fact that the Paediatric Board is likely to block repeat testing in children unless a significant therapeutic benefit for children is foreseen means that the PUMA with its data-protection may, for some products, result in market exclusivity (although this cannot be garunteed). It is acknowledged, however, that it will not, on its own, provide sufficient incentive to ensure that all the off-patent medicines needed by children are tested and authorised for children. To effectively deal with the off-patent market, other measures, including the Paediatric Study Program, as well as, the inventory of paediatric therapeutic needs, will also need to be in place. As will be seen in section 7, the Commission is also proposing altered data requirements for PUMA applications which are likely to prove particularly attractive to generics companies and SMEs.

Impacts of additional requirements

The additional requirements concern labelling, placing on the market, post-marketing requirements, and submission of pre-existing studies.

Operationalisation

Pharmaceutical companies will have to adjust the labels of their medicines (which involves a small cost). For an already authorised medicine, after a marketing authorisation has been extended for use in children, the company has to ensure that the product is marketed, taking into consideration the new paediatric indication, within 12 months (extended to two-years in the final proposal – see section 7). Companies will, in selected cases, have to submit a plan on how to ensure follow-up particularly to monitor for adverse reactions related to the use of the medicinal product in the paediatric indication. CPMP or a national competent authority will decide when a risk management system should be set up and specific post-marketing studies should be performed. If the submission of the results of paediatric testing was deferred, the marketing authorisation holder has to report annually to the Paediatric Board to provide an update on the progress with the realisation of the paediatric investigation plan. For deferred studies, the Paediatric Board needs to inform CPMP or competent national authorities if the marketing authorisation holder does not comply with the agreed paediatric investigation plan.

In the case of pre-existing studies, companies must submit the results of completed paediatric studies to the competent authorities within a year of the entry into force of the Regulation. The authorities need to assess the results of pre-existing studies and update the summary of product characteristics and patient information leaflets, as required.

In general, government authorities must monitor and enforce compliance with the additional requirements.

Short-term effects

Existing medicines, newly tested in children and authorised will be made available. Health care professionals will gain better knowledge of the safety of paediatric medicines and, as a result, children will receive safer treatment. If companies comply adequately, the additional requirements will generate considerable benefits to the European paediatric population and prevent the misallocation of resources at comparatively low marginal costs to pharmaceutical companies and government authorities. Both can build on currently existing (mandatory) systems for pharmacovigilance (specific estimates of these additional costs are not available).

Pharmaceutical companies will have to pay fixed costs to design plans for follow-up and progress reporting and variable costs to maintain pharmacovigilance and write annual reports. The level of costs is unknown. Pharmacovigilance is, however, already a requirement and it is

safe to assume that pharmaceutical companies will have acquired the necessary expertise to adapt efficiently to the requirements of the draft paediatric regulation. Competent authorities will, however, be faced with an increased workload and a need for more experts as follow-up plans have to be assessed and compliance has to be monitored and enforced. The same applies to the requirement concerning pre-existing studies (see the accompanying financial statement). Competent authorities should set up a system to monitoring and check if applicants have already performed studies.

Long-term effects

Appropriate labelling of tested paediatric drugs will create a sharper definition of paediatric and other segments of the market for off-patent drugs. The higher objectives of the proposed Regulation are served by a clear distinction in the market between tested paediatric medicines and untested medicines for use in adults and by the gradual eradication of unlicensed and off-label prescription. Health care professionals benefit from increased transparency in the choice between tested and untested off-patent medicines: it will be easier to see whether a drug is tested for use in children or not.

The post-marketing requirement will force companies to develop an improved understanding of the safety, efficacy and quality of their paediatric medicines, which may result in the development of better medicines for children. Children can be treated more effectively and there will most likely be fewer cases of adverse drug reaction or suboptimal treatment. The impact of this requirement can only really be fully ascertained at a later date, because the long-term effects of a medicine in children cannot necessarily be assessed until much later in a child's development.

Risks and uncertainties

The Rand study draws a number of conclusions about the weaknesses of the current pharmacovigilance systems, particularly with regard to the spontaneous reporting of suspected adverse drug reactions. The draft paediatric regulation contains proposed measures to specifically address these weaknesses in the form of post-marketing pharmacovigilance plans, post-marketing study requirements and risk management systems.

Impacts of the facilitating measures

Three measures have been included to make it easier for companies to fulfil the requirements of the proposed Regulation. They concern the waiver of the requirement for data in children, deferral to initiating or completing studies in the paediatric investigation plan, and optional access to a centralised assessment via the existing Community referral procedure for nationally authorised products.

Operationalisation

Regarding the centralised assessment via the existing Community referral procedure, pharmaceutical companies will be gaining an opinion of the CPMP on use of the nationally authorised product in children, which will lead to a Commission Decision, which will direct the Member States to implement specific wording in product information. In the case of deferrals, companies have to report regularly on ongoing studies and take into account the need to avoid delaying the availability of new medicines for use in adults. The Paediatric Board has to assess requests for waivers and deferrals. EMEA will maintain a list of waivers and publish this list on its website. All requests for waivers and deferrals will be processed by the EMEA and judged by the Paediatric Board.

Long-term effects

The optional centralised assessment via the existing Community referral procedure provides a streamlined route to gain a harmonised EU-wide opinion on paediatric use of already authorised products. The centralised assessment will also facilitate access to more Member State markets.

Paediatric testing will only be done when necessary, that is, when there is a potential benefit for children. The possibility of deferral allows the pharmaceutical industry to adjust to new requirements or when paediatric testing takes longer than adult testing to complete, and will ensure that the requirements do not obstruct the availability of medicines for use in adults.

Waivers will help identify medicinal products that are not suitable for use in children, which acts as a support for health care professionals in their choice between different available medicinal products. They will also prevent unnecessary testing when a new medicine adds no apparent therapeutic / clinical value.

Risks and uncertainties

For some medicinal products a waiver will be clearly appropriate or inappropriate. However, the Rand Study highlights that there will be a grey area where decisions are difficult and it is uncertain how many medicinal products inhabit this grey area.

The Rand study suggests that deferral could become an automatic resort when standard investigation plans are submitted but resources are not (immediately) allocated to put them into action. According to the Rand study, in the worst case, the product may never be labelled for children. No time limit has been set for the deferral of paediatric investigations in the draft paediatric regulation. However, because the SPC extension will prove attractive to industry (as a mixed reward and incentive), the Commission considers that industry is likely to be keen to meet the requirements in the draft paediatric regulation and therefore to deliver on paediatric studies even when a deferral has been granted. In addition, enforcement measures are included in the draft paediatric regulation in the form of: annual deferral progress reports; recording of the fact that a deferral has been granted in the product information (for the general public to see); fines, and; a naming and shaming policy.

The impacts of the support measures

The objectives of the proposed Regulation are reinforced by three support measures, namely the provision of free scientific advice, a number of initiatives involving communication and coordination, and the establishment of a paediatric study programme or Medicines Investigation for the Children of Europe (MICE). As the paediatric study programme is only referenced in the Explanatory Memorandum of the draft paediatric regulation and will be the subject of a separate prposal it is dealt with separately in the subsequent section.

Operationalisation

The EU knowledge base will depend crucially on the contribution of companies, academic researchers, and healthcare professionals. They can give input, provide feedback, and supply experts for the creation of new knowledge (e.g. for the inventory of existing medicinal products). Specific healthcare experts may be asked to become advisors to the Paediatric Board, they may become members of the network, and they can provide information on all existing uses of medicinal products in paediatric indications.

The EMEA and the Paediatric Board have to establish a network with specific expertise in the performance of trials in the paediatric population. In addition, the EMEA will have to adapt the database set up by the Clinical Trials Directive and online facilities as well as hire in-house experts.

Companies can request scientific advice to support and improve paediatric testing. The EMEA gives advice on the design and conduct of various tests and studies necessary to demonstrate the quality, safety and efficacy of the product in the paediatric population. Such advice is already available for a fee that varies between €6,000 and €70,000 depending on the nature and extent of the questions. The Rand Study has estimated the direct value of free scientific advice. The additional applications that the EMEA expects to have to handle when the draft paediatric regulation enters into force, may all be accompanied by a request for free scientific advice. If that advice is valued against current fees, then the total value of this particular measure can be estimated. In the first year the expected costs would amount to €840,000 for minor requests and €9.8 million for major requests. After the first year the costs would decline to between €240,000 and €540,000 for minor requests, and between €2.8 and €6.3 million for major requests.

Short-term effects

Access to knowledge about paediatric medicines, clinical trials involving children, and related issues will be improved. Pharmaceutical companies can achieve efficiency gains by obtaining prior information on the Paediatric Board's assessment of the paediatric investigation plan as well as by improving the design of clinical trials. Free advice can help to contain the costs of developing a paediatric investigation plan.

The competent authorities' interests will be served by the higher average quality of submitted paediatric investigation plans and a shorter average period of assessment. Providing free scientific advice will, however, cost time (increased workload for EMEA, the Paediatric Board and its experts). Public money will be required for fixed costs for establishing a network, extending the Clinical Trials Directive database, and a survey. Healthcare professionals will benefit in that better clinical trials will lead to better evidence on the use of paediatric medicines, which can in turn result in better treatment.

The inventory of existing medicinal products will help to create a good picture of the products that are currently available for the use in children and to centrally collect the information that is available on each medicine in different countries. In addition, the inventory will help prevent the duplication of clinical trials in children.

Long-term effects

In the long run free scientific advice, communication and coordination (and the study fund) will generate economies of scale and scope in pharmaceutical R&D and paediatric testing. Together, they are generally considered a highly valuable measure that will provide a strong stimulus to paediatric research in Europe. The inventory of existing medicines will provide companies with an overview of the market for paediatric medicinal products and help to identify opportunities (e.g. therapeutic gaps). Knowledge will spill over from large companies to SMEs that have a narrower knowledge base. SMEs are most likely to use the opportunity to acquire free advice, because they may lack in-house expertise on trial designs, pre-clinical and clinical trials, and on the centralised procedures. Larger companies generally employ experts in each area, but even they may not have sufficient expertise in the area of paediatric medicines.

The period between trials, approval, and placing on the market will become shorter. Improvements in knowledge transfers may also result in more cost-effective study designs and industrial savings and will prevent the duplication of tests. In this fashion the government contributes to a more homogeneous basis to the performance of tests.

The instruments of communication and coordination create greater transparency in the market and provide support for the self-regulating behaviour of companies (which products to select) and health care professionals (which medicines to prescribe). For example, health care professionals as well as children, parents and guardians may use the inventory of existing medicinal products to choose between medicines (prescription or OTC; tested and untested). The network of experts can create an economy of scale considering that there are relatively few experts and they are scattered across Europe.

Risks and uncertainties

The Rand study has highlighted some theoretical risks and uncertainties. Pharmaceutical companies, as well as, researchers may be reluctant to share proprietary information on medicinal R&D, testing, and marketing, particularly if such information is publicly disseminated. The guidelines on the transparency measures, already foreseen in the draft paediatric regulation, will need to take careful consideration of this. If the regulators provide free advice, this could theoretically act as a disincentive to hire experts (an effect on employment) or on the creation of knowledge within companies and institutions (an effect on the overall knowledge base). The quality of the information can also pose a problem, especially when parties with an interest in the market supply it. Therefore, the conflict of interest measures already included in the draft paediatric regulation will be important. As a consequence of the current lack of knowledge in the field, it is uncertain whether a working group of the CPMP, which will be responsible for providing scientific advice, has sufficient expertise in the field of paediatric testing. As has already been highlighted, resources, including expert human resources will need to be secured by the EMEA and National competent authorities to support the operation of the draft paediatric regulation and, specifically the delivery of scientific advice.

The Rand Study has also suggested that companies may become dependent, to a degree, on the expertise and speed of the authorities. Delays in the response to scientific advice questions could affect the development and marketing process. However, the scientific advice process has fixed time frames meaning that there is a maximum time within which the advice has to be given. In addition, the benefits of scientific advice appear to be very real. In its annual report the EMEA states that “42% of the medicinal products that received a positive opinion in 2002 had previously benefited from scientific advice, whereas 90% of applications that were withdrawn had not requested scientific advice.”

Impacts of the Paediatric Study Program

The Explanatory Memorandum of the draft paediatric regulation makes a reference to the creation of a paediatric study program: Medicines Investigation for the Children of Europe (MICE). The creation of the funding and its operation will be included in a separate proposal. A detailed assessment of the impacts of the program will accompany that separate proposal. However, given the interface between a paediatric study program and the draft paediatric regulation assessed here, some consideration is required. The difficulties of incentivising the off-patent medicines sector have already been described, as have the potential weaknesses of the PUMA. An EU paediatric study program, focussed on funding or part funding studies on off-patent medicines will be important if research and authorisation for children of off-patent

products are to occur for the majority of products needed by children. It is envisaged that the paediatric study program could be funded from the Community budget. The paediatric study program will also need to take account of other relevant Community funding, including the 6th and 7th framework programs operated by the Commission Directorate General Research. Community funding for studies into off-patent medicines for children (which may lead to the authorisation of an off-patent medicine for children) may only be partial e.g. 50% funding: the remainder of the funding may need to come industry, Member State governments or medical charities.

The impact of the referenced paediatric study program will critically depend on its funding, size and awarding rules. A fund, set up under the United States Best Pharmaceuticals for Children Act 2002, is of $200,000,000 for fiscal year 2000 and such sums as are necessary for each of the succeeding five years for the study of the use in the paediatric population of medicinal products for which there is no patent protection or market exclusivity. The CPMP Paediatric Expert Group has produced a preliminary list of sixty-five off-patent active substances considered to be priorities for research and development for children in the EU. The number and type of studies required to develop these sixty-five active substances for children is variable, however, this provisional list gives an idea of the scope of application of a future paediatric study fund.

An EU paediatric study program has the potential to stimulate research and development of off-patent medicines for children and could have a major beneficial impact on EU pharmaceutical companies, including SMEs, and a major impact on clinical trials conducted in the EU including strengthening pharmaceutical R&D in Europe.

Environmental impacts

The measures proposed in the Regulation have no substantial environmental impacts. However, the development and manufacturing of medicinal products requires natural resources and generates waste. In addition, households, GPs and hospitals regularly dispose of unused medicinal products. The pharmaceutical industry currently operates in a framework of environmental regulation, both at EU and national level. As a consequence, the industry tries to minimise its impact on the environment by adopting the waste minimisation hierarchy of elimination, re-use, recycling, recovery and disposal. The revised pharmaceutical legislation includes a new requirement for an environmental assessment at the time of marketing authorisation application of medicines and this is likely to further minimise the environmental impact of medicines development and use. Finally, considering that at present, adult preparations of medicines are usually used to treat children with the clear wastage that that incurs (high dose preparations of adult medicines being opened, small quantities being used to treat children and the excess discarded), the draft paediatric regulation may actually reduce the environmental impact of use of medicines by children. The minimal environmental impact was confirmed by the interviews conducted for the Rand study.

Impacts on sustainability

Sustainability relates to three issues: (1) protection and renewal of the stock of natural, human, and other resources; (2) the technical efficiency with which resources are used to produce goods and services; and (3) equity within and between generations. The impact on sustainable development of the draft paediatric regulation as a whole is considered because a discussion of the way in which each of the individual key provisions affects sustainability is neither feasible nor useful.

Protection and renewal of stocks of resources: The impact of the draft paediatric regulation is limited. The draft paediatric regulation is mainly aimed at encouraging clinical trials in the paediatric population. However, it is most unlikely that an increase in the number of trials in the paediatric population will have serious consequences for the stock of resources. Furthermore, as the draft paediatric regulation should reduce the amount of wastage of adult medicines currently being used to treat children, overall wastage of stocks of resources should be reduced.

Technical efficiency of resource use: Innovation in paediatric medicines will be increased. The efficiency of paediatric research will increase through increased expertise in the EU, the Paediatric Board, scientific advice, the inventory of paediatric therapeutic needs and the EU network of paediatric trialists. The effect on innovation for adults is less predictable: innovation for existing products is likely to be increased as industry tries to access the SPC-extension. However, if industry has fixed resources (both financial and human) for all research and development of medicines, for both adults and children, then an increase in investment in child medicines might divert some investment from adults. Given that, after the first year, the draft paediatric regulation is predicted to increase the expenditure on phase III clinical trials by between 7% and 16% but that phase III clinical trials only make up about 15% of total drug development costs, this effect is likely to be modest. This possible diversion of investment also needs to be considered in the context of decades of underinvestment in children and neglect of the therapeutic needs of children.

Equity within and between generations: With respect to intergenerational equity, future generations of children are more likely to be enrolled in clinical trials, but in return they will be provided with better medicines, more effective and safer treatment, and a higher quality of life. Furthermore, the transparency measures in the draft paediatric regulation mean that data, information and knowledge generated from research into medicines for children will not be lost and will be of benefit to generations to come.

4.2 Additional analysis of impact on specific groups

Section 4.1 has estimated the social and economic impacts of the draft paediatric regulation on different sections of the industry and other stakeholders. Therefore this section is limited to bringing together the key points.

Impacts on the innovative pharmaceutical industry

The draft paediatric regulation will create work for the innovative industry by requiring the development and authorisation of medicines for children. Across the entire innovative sector there will be an increase in the costs of phase III clinical trials of about 160 – 360 million Euros after the first year (an increase in total European expenditure on drug development of 1% - 2.5%). This corresponds to about 4 million Euros per medicinal product. The Rand study has estimated that the six-month SPC extension (proposed as a mixed reward / incentive in response to the requirements for paediatric testing) will allow the innovative industry to recover the costs of testing and make a profit of between 0.8 and 9.1 million Euros per product and between 63 and 205 million Euros (profit minus the discounted costs of testing) over the entire sector (i.e. for all medicines added together). The assumptions and caveats to be applied to these figures were provided in section 4.1. The requirements for paediatric testing and authorisation of medicines in the EU should stimulate EU industry innovation as companies will want to develop new formulations, dosage forms and indications for their existing products in order to access the six-month SPC extension. Furthermore, data generated

from paediatric testing for the EU market can be used to support marketing authorisation application in other regions of the world. This should increase the global competitiveness of the EU pharmaceutical industry.

The PUMA is a pure incentive that will provide the option for innovative companies to secure additional IPRs (in the form of data protection) and therefore sales for their products when the patent and SPC have expired. The referenced paediatric study program is likely to provide public funds to support research and therefore innovation in off-patent products and will be open to all sectors of the industry. This should further stimulate innovation and competitiveness.

The various support and facilitating measures in the draft paediatric regulation, including the paediatric board, free scientific advice, an inventory of paediatric therapeutic needs and an EU network of paediatric clinical trial centres / trialists will all act to make the conduct of high quality research in children easier, more efficient and cheaper.

Impacts on the generic pharmaceutical industry

The Rand study has estimated that the six-month extension of the SPC will lead to the producers of generic medicines incurring a one-time loss of between €86 million and €342 million, which represents the value of market opportunities lost during the transitional period. The assumptions and caveats to be applied to these figures were provided in section 4.1. After that period business will be as usual, although producers of generic medicines will have lost some of their market share.

Some generics companies have expressed interest in exploiting the PUMA for off-patent medicines, with its associated data protection. The PUMA therefore offers a business opportunity to the generics sector.

The various support and facilitating measures in the draft paediatric regulation should be particularly helpful to smaller companies including generics companies. The referenced paediatric study program will also be open to generics companies, providing them with further support for research and development.

Impacts on small and medium-sized enterprises (SMEs)

The Rand study considers that the requirement to submit results from studies in children may result in the rise of a market for specialised services in developing paediatric investigation plans and in conducting studies in children. This, therefore, provides an important opportunity for SMEs to develop new business and this opportunity is likely to benefit particularly EU based companies, including companies in the new Member States.

The Rand study has suggested that the requirement for studies in children for new products may be a challenge for smaller companies with limited resource and expertise. It is possible that such companies will need to rely heavily on the free scientific advice provided by the EMEA and may need to work with industrial partners including contract research organisations. In contrast, feedback on the draft paediatric regulation from stakeholders, notably the generic industry association, has revealed that a number of generic companies are very interested in the opportunity to capitalise on niche markets with niche paediatric products including new formulations of established off-patent drugs via the PUMA (which is linked to data protection). Here, therefore, is another opportunity for SMEs to develop new business

and this opportunity is once again, likely to benefit particularly EU based companies, including companies in the new Member States.

Impacts on regulators of medicines

The draft paediatric regulation will lead to an important increase in work load for EU regulators, particularly early after its introduction and particularly for the EMEA. A European Paediatric Board will need to be set up, together with experts to support it. The Paediatric Board will need to assess draft paediatric Investigation Plans, requests for waivers and deferrals and data generated from studies in children. Scientific advice will need to be provided and compliance with the draft paediatric regulation will need to be monitored and enforced. The EMEA has estimated than following the initial introduction of the regulation, its costs will increase by about five million Euros per year.

Impacts on governments, the children of Europe and society in general

The Rand study has estimated that, overall, paediatric testing may increase the price of individual medicines by less than 0.5% while the shift in market share from off-patent medicines towards patented medicines may increase European pharmaceutical expenditure by 0.06% - 0.25% and total healthcare expenditure by 0.01% - 0.04%. However, these estimates do not include the savings from the supply of better medicines for children.

The children of Europe will have access to innovation in medicines, they will be treated with effective medicines at the appropriate dosage and they will avoid some of the risk of adverse drug reactions. This should translate into more effective treatment of childhood disease and reduced suffering and deaths from drug toxicity. Thus, children should spend less-time sick, deaths will be avoided and this should translate into significant reductions in child-health expenditure and overall savings to society from reduced child morbidity and mortality. This includes the economic loss to society of a child death (the value of a life saved is greatest for children due to their long potential future working lives) and the economic loss to society associated with the long term sickness of a child (for example, parents need to take time off work to care for the child). Finally, an important injustice, that children do not enjoy medicines of the same quality, effectiveness and safety as adults, will be remedied.

In economic terms, this extended impact assessment is fundamentally imbalanced. The costs to industry and society of the draft paediatric regulation can be estimated, whereas the benefits, in terms of improved child heath can not. This results from the inadequacies of the available data and must be borne in mind when judging the draft paediatric regulation.

Impacts on the EU research community

The draft paediatric regulation will lead to a major increase in paediatric research in the EU. This provides a major opportunity, including an employment opportunity, for highly skilled EU workers and it is likely that this will reduce, or possibly reverse the widely discussed drain of such workers to the US. There is no doubt that the draft paediatric regulation will also put pressure on academics and researchers, particularly in the early years after its introduction while additional trialists are trained. This pressure can, in the first years after introduction of the draft paediatric regulation, be released through the existing capacity for research in the US.

4.3 Impacts outside the EU

Research in the EU and the authorisation and availability of medicines for children in the EU are likely to have a benefit for the health of children of less developed countries. Many less developed countries use EU authorisation of medicines to guide their own judgements on allowing market access to products and the manufacture of medicines for the EU market provides economies of scale in the production of the same medicines for other markets. Some of the medicines destined for the EU market may be tested or manufactured outside the EU, bringing economic benefits to non-EU countries.

A final consideration relates to the US market. As the US already has requirements and incentives for research, development and authorisation of medicines for children, measures in the EU will be complimentary, allowing companies to satisfy the legislation in both regions with the same studies. This will require the EU and US authorities and expert committees to closely collaborate and attempt to reach consensus on the required development of individual medicines for children. Such collaboration can only be of benefit to the regulators, industry and children.

4.4 Changes in impact over time

Section 4.1 has explored the possible impacts of the different elements of the draft paediatric regulation on the different stakeholders and this included consideration of the change in effects over time. This section brings together the key temporal aspects of the economic and social impacts.

Because of the impact of the draft paediatric regulation on industry, regulators and research in the EU, the draft paediatric regulation proposes to stagger the introduction of the various requirements. First the Paediatric Board will be established together with the procedures to support assessment of draft paediatric investigation plans and requests for waivers and deferrals. Work will also begin on the support and facilitation measures including the development of lists of class waivers, the inventory of the therapeutic needs of the children of Europe and the establishment of an EU network of trial investigators. Only later will the requirements for new products to present the results of studies in children come into force and only later still will the requirements for patent-protected, authorised products come into force. In this way, introduction of the draft paediatric regulation will be controlled to ensure that requirements do not pre-date the facilities necessary for their operation.

In the first year following the introduction of the requirements, the economic impacts of the draft paediatric regulation on the innovative industry will be greatest. The costs to the entire innovative industry of paediatric clinical testing are estimated at 560 million Euros in the first year falling to 160 – 360 million Euros in subsequent years. The increase in the costs of medicines from paediatric testing (estimated at about 0.2%) will occur gradually over time and the impact on the costs of medicines of the SPC extension (estimated at between 0.06 and 0.25% of European pharmaceutical expenditure) will also be gradual. A one-time loss of market opportunities to the generics sector will occur.

New innovative medicines for children and established medicines newly developed for children should start to enter the EU market as soon as the requirements for new products and incentives (PUMA) for off-patent medicines are established. However, the full social savings resulting from the draft paediatric regulation will take time to realise. It is likely to take approximately five to ten years before medicines for children are available to meet the

majority of children's therapeutic needs and nearer twenty years before the majority of products are tested and authorised for children. The social benefits, in terms of lives saved, adverse reactions avoided, improved quality of life and, overall, improved child-health in the EU will therefore take time to realise.

5. HOW TO MONITOR AND EVALUATE THE RESULTS AND IMPACTS OF THE PROPOSAL AFTER IMPLEMENTATION

Appendix one of the report of the Rand Study presents a discussion on evaluating the implementation and outcomes of the draft paediatric regulation. The sections below bring together the key points.

5.1 Policy implementation

Section 4.4 has already summarised the staggered nature of introduction of the measures in the draft paediatric regulation. The draft paediatric regulation also proposes the development and adoption of various guidelines to support its operation. The paediatric study program will be the subject of a separate proposal. It will therefore only come into operation after the draft paediatric regulation. Given that aspects of the draft paediatric regulation, such as the inventory of therapeutic needs, will help support the proposed paediatric study program, this order of introduction is logical.

5.2 Monitoring the policy

Many of the effects of the draft paediatric legislation lend themselves to measurement and some of these can be directly related to the objectives set out in section 2. Others, including the overall objective of improved child health will be more difficult to measure due to a lack of robust EU-wide data. Collection of the following data is possible:

- The dates on which the Paediatric Board and EU network of clinical trialists are established and guidelines and first inventory of therapeutic needs are adopted.
- The date on which the database of paediatric studies becomes operational.
- The number of clinical trials in children initiated and completed (broken down by country and type of trial).
- The number of children enrolled into clinical trials.
- The number of draft paediatric investigation plans submitted for assessment and the number of paediatric investigation plans agreed by the Paediatric Board.
- The number of requests for waivers and the number of waivers granted by the Paediatric Board
- The number of requests for deferrals and the number of deferrals granted by the Paediatric Board
- The number of requests for scientific advice
- The numbers of marketing authorisation applications made and granted for adults and children including applications for new formulations, dosage forms and routes of administration: these data can be broken down by marketing authorisation procedure used (centralised, mutual recognition, optional centralised procedure). Data could also be broken down on the basis of whether data in children were part of the initial application, presented later (through a deferral) or not presented (e.g. following a waiver).
- The number of PUMA applications made and PUMAs (with their associated data protection) granted.

- The number of requests for post-marketing studies, pharmacovigilance plans and risk management systems and the delivery against those plans.
- The number of existing studies in children submitted and the number of marketing authorisations updated as a result.
- The number of times marketing authorisations record that a paediatric investigation plan has been complied with. This provides a measure of the number of supplementary protection certificates that can be extended.
- Impact on the budget of the EMEA.

These data would provide a robust measure of the impact of the draft paediatric regulation in terms of stimulating research, development and authorisation of medicines for children and any collateral effect on the authorisation of medicines for other populations. They would also provide some measure of the financial impacts on the EMEA.

Prospective measurement of the costs to industry and on the price of medicines is not proposed as such measurement lends itself better to a post-hoc study (see section 5.3).

Section 4 of this extended impact assessment pointed out that the impact, both financial and social, of improved health of the children of Europe is very difficult to measure (and hence is not accurately, quantitatively assessed in section 4). Unless there is major investment in the central collection of indices of EU child-health, this difficulty will remain when attempting to measure, in the future, the impact of the draft paediatric regulation.

5.3 Arrangements for ex-post evaluation of the proposals

The draft paediatric regulation includes proposals for: a database of paediatric studies; annual reports from the Member States to the Commission on problems encountered with the implementation of the draft paediatric regulation; annual publication of lists of companies that have benefits from the rewards / incentives or companies that have failed to comply with the obligations, and; within six years of entry into force, a general report on experienced acquired as a result of the application of the draft paediatric regulation, including in particular a detailed inventory of all medicinal products authorised for paediatric use since it came into force.

Through these measures, specifically proposed in the draft paediatric regulation, ex-post evaluation is already planned. The general report will likely be based on the indices listed in section 5.2. Furthermore the need for a designated independent study to support the general report should be considered. Such an independent study could include within its scope the financial and social impacts for which prospective data collection is problematic.

6. STAKEHOLDER CONSULTATION

6.1 Consultation process

The Commission has consulted extensively on the issue of medicines for children and on its proposals for a draft paediatric regulation. This consultation has included:

- Workshops and roundtable meetings
- Stakeholder interviews by Rand Europe
- Public consultation

Workshops and roundtable meetings

The Commission has held a series of workshops and bilateral meeting with stakeholders on the issue of medicines for children and on its proposals for a draft paediatric regulation. Annex 2 provides a summary list of the workshops and bilateral meetings held.

Stakeholder interviews by Rand Europe

In the course of conducting the Rand Study interviews took place with representatives of the following organisations:
Association of the British Pharmaceutical Industry (ABPI, United Kingdom)
Aventis Pharma
AOK Health Insurance (AOK Krankenkassenverband, Germany)
BLISS (United Kingdom)
British Medical Association, General Practitioners Committee (BMA, United Kingdom)
Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen (CBG), The Netherlands)
Dutch Health Care Insurance Board (College voor Zorgverzekeringen (CVZ), The Netherlands)
Confederation of European Specialist in Paediatrics (CESP)
Direzione Generale dei Farmaci e dei Dispositivi Medici (Italy)
European Agency for the Evaluation of Medicinal Products (EMEA)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
European Generic Medicines Association (EGA)
European Network for Drug Investigation in Children (ENDIC)
European Organisation for Rare Diseases (Eurordis)
European Society of Clinical Pharmacy (ESCP)
Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom)
National Perinatal Epidemiology Unit (United Kingdom)

Public consultation

The Commission's public consultation was split into two halves. Between 28 February 2002 and 30 April 2002, the public consultation focussed on the key elements to be included in a regulation. Between 8 March 2004 and 9 April 2004 the public consultation was based on the draft legislative text. For the latter part of the consultation the consultation document was placed prominently on the Commission website (http://pharmacos.eudra.org) and sent by e-mail to the following organisations:
Member States via the Pharmaceutical Committee (an its ad-hoc group on paediatrics)
EMEA
CPMP
CPMP Paediatric Expert Group
COMP
EFPIA
EGA
AESGP
I'AIM
CESP
ITCC European Consortium
ESPGHAN

PENTA
ENDIC/ESDP
EFGCP
ESPR
SSIEM
ESPE
ESPN
Eurordis
French rare diseases
German cystic fibrosis
Genethon
Standing Committee of European Doctors
European Union of General Practitioners (UEMO)
Union of national European paediatric Societies and Associations (UNEPSA) –
European Society for Clinical Pharmacy (ESCP)
International Pharmaceutical Federation
European Patient Forum
EPPOSI
Comite Europeen des Assurances (CEA)

The 2004 part of the public consultation was limited in duration because: 1. it was the second time the public had been consulted by the Commission on this issue, and, 2, it was considered that the public health issues of insufficient medicines for children needed to be dealt with in a timely manner.

6.2 Consultation results

A summary of the results of the 2002 part of the consultation is provided at Annex 3 and of the 2004 part of the consultation at Annex 4.

In the 2004 part of the public consultation the Commission received 69 contributions. Many of them, in particular the ones from regulators, patients associations, or the industry, were the result of wider consultation by specific stakeholder organisations. A full listing of all parties providing comments is provided at Annex 4. The vast majority of the comments welcomed the Commission's draft legislative proposal and explicitly supported the outlined objectives. As already revealed by the 2002 part of the consultation, all respondents recognised the need to take specific regulatory measures in order to achieve the objectives. Broadly speaking, most of the contributors agree with the key principles and concepts underlying the Commission's proposal.

Many of the comments on details of the draft paediatric regulation have been taken on board for the final proposal. Two key issues that were amended as a result of the consultation response (and the extended impact assessment) were rewards/ incentives for orphan medicines and the strength of the incentive for off-patent medicines, and these are briefly explored below.

A number of responses were concerned about the interface between the proposal and the EU orphan regulation. There was some concern that, if SPC extension was the only reward offered for compliance with the requirement, the requirement would not be rewarded for a significant proportion of orphan medicines as many such medicines are not patent-protected at

the time of authorisation. Others were concerned that, for orphan medicines covered by a patent, a double incentive would be granted (SPC extension from this proposal and ten-year market exclusivity from the orphan regulation). To meet these concerns, the final Commission proposal excludes orphan medicines from the SPC extension and, instead, rewards them for compliance with an additional two-years of market exclusivity. Two-years has been chosen rather than six-months as the market exclusivity only covers the medicinal product in the orphan indication. In contrast, the SPC extension covers the active substance and therefore relates to all products containing it. Consequently, for the same time period, SPC extension is more valuable.

Both this Extended Impact Assessment and the 2004 part of the public consultation conclude that the incentive attached to the PUMA (ten-years data protection was proposed at the time consultation and the Rand Study were conducted) might prove weak. To address this, the final proposal includes a provision for an additional incentive for the development of off-patent medicines in the form of amended data requirements for marketing authorisation applications. Ten years data protection is considered sufficient to provide an incentive, particularly where a specific formulation is required or where the market in children is potentially quite large. The ten-years of data protection will also prove a stronger incentive if Member States introduce measures to support the draft paediatric regulation that lead to preferential prescribing of PUMA medicines. The additional incentive applied to the PUMA that may prove particularly powerful at attracting SMEs, including generic companies to develop off-patent medicines for children is an amendment to the data requirements for PUMA applications. An application for a PUMA will require the submission of data necessary to establish safety, quality and efficacy specifically in children, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration of the product, collected in accordance with an agreed paediatric investigation plan. These data might be derived from the published literature or new studies in children. However, an application for a PUMA may additionally refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community. In other words, for the first time, the Community will have a new type of marketing authorisation that allows a data protection period to be applied to new data in a marketing authorisation application dossier that is partly composed to meet the ‘generic’ requirements.

7. COMMISSION DRAFT PROPOSAL AND JUSTIFICATION

Between 50 and 90 % of the medicines prescribed for children in Europe have not been tested or authorised (licensed) for use in children. The health and therefore quality of life of the children of Europe may be suffering from this lack of testing and authorisation of medicines for their use. Every time a doctor in Europe writes a prescription for a child for an untested or unauthorised product, that doctor may not be sure the medicine will be effective, may not be sure what dose is appropriate and may not be able to predict what adverse reactions the child may suffer. Furthermore, new innovative products developed by the pharmaceutical industry to meet the therapeutic challenges we face today are frequently denied to children.

The objective of the draft paediatric regulation is to improve the health of the children of Europe by increasing high quality research, development and authorisation of medicines for children and by improving the information available on the use of medicines for children.

The draft paediatric regulation builds on the experience gained with the existing regulatory framework for medicines in Europe, requirements and incentives for paediatric medicines in

the US, and the EU orphan regulation. These have shown that market forces alone cannot deliver the medicines needed to treat childhood diseases and that a balanced package of measures including requirements, rewards and incentives and support measures are required to stimulate the pharmaceutical industry into researching, developing and authorising medicines for children. Action is required now as child health in Europe continues to suffer and further delays mean more innovation denied, more ineffective treatment, more incorrect-dosing and more adverse drug reactions. A European regulation is warranted as this public health issue is EU-wide and the existing framework for the regulation of medicines is based in EU law leaving little scope for the Member States to act on there own.

The key measures included in the draft paediatric regulation are:

- the establishment of an expert committee, the Paediatric Board within the EMEA;
- a requirement at the time of marketing authorisation applications for new medicines and line-extensions for existing patent-protected medicines for data on the use of the medicine in children resulting from an agreed paediatric investigation plan;
- a system of waivers from the requirement for medicines unlikely to benefit children;
- a system of deferrals of the requirement to ensure medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;
- excluding orphan medicines, a mixed reward and incentive for compliance with the requirement in the form of six-months extension to the supplementary protection certificate (in effect, six-month patent extension on the active moiety);
- for orphan medicines, a mixed reward and incentive for compliance with the requirement in the form of an additional two-years of market exclusivity added to the existing ten-years awarded under the EU orphan regulation;
- a new type of marketing authorisation, the PUMA, which allows ten-years of data protection for innovation (new studies) on off-patent products;
- amended data requirements for PUMA applications to attract SMEs including generics companies;
- a reference in the explanatory memorandum to the establishment, via a separate proposal of an EU paediatric study program to fund research leading to the development and authorisation of off-patent medicine for children;
- access to an optional centralised procedure via the community referral procedure for existing nationally authorised medicines to gain an EU-wide Commission Decision on use in children;
- measures to increase the robustness of pharmacovigilance for medicines for children;
- a requirement for industry to submit to the authorities study reports they already hold on use of their medicine in children, to maximise the utility of existing data and knowledge;
- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines;
- an EU network of investigators and trial centres to conduct the research and development required;
- a system of free scientific advice for the industry, provided by the EMEA;
- a database of paediatric studies;
- Community funding for the EMEA to support the implementation and operation of the draft paediatric regulation.

The advantages of the draft paediatric regulation are many. First and foremost, over time, it should lead to an improvement in the health of the children of Europe, through:

- ensuring the generation of robust, evidence based information on the use of medicines for children;
- the greater availability of this information, and;
- the greater availability of high quality, effective and safe medicines for children.

Ineffective treatment of children, incorrect dosing of children and adverse drug reactions in children should be minimised. This should lead to a reduced number of hospitalisations of children, fewer child deaths, increased quality of life for children and therefore bring the economic benefits to our society associated with these savings and benefits. It should also be noted that research, development and authorisation of medicines in the EU will also benefit children outside the EU, including those in less developed countries.

Industry will also benefit from the draft paediatric regulation:

- the six-month SPC extension will allow the industry to recover the costs of paediatric testing of new products and make a profit estimated at between 0.8 and 9.1 million Euros per product, which will provide an incentive for further research;
- the data generated to satisfy the EU requirements can be used to support marketing authorisation applications outside the EU;
- increased research and development on paediatric medicines in the EU could help generate high quality, skilled jobs, as well as, investment in the EU;
- New business opportunities will be created: through the PUMA (capitalisation of niche markets that are currently unexploited); through the need for clinical trials and support services and for consultancy services. All of these may particularly benefit small and medium-sized enterprises (SMEs) and could lead to the creation of new companies within the EU.

There are costs associated with the proposal. The requirements for phase III clinical trials in children will cost industry an average of four million Euros per product, representing a total across the entire industry of 160 – 360 million Euros after the first year. This corresponds to a 1 – 2.5% increase in total European expenditure on drug development after the first year. If the innovative industry allocates a fixed amount of revenue to all research and development then the resource allocated to meet the requirement for paediatric testing will likely be cut from other research and development projects, however, the effect is inevitably modest due to the modest cost of the requirements. Because the industry is likely to want to access the rewards/incentives of SPC extension (or extended market exclusivity for orphan medicines), the proposal is likely to stimulate innovation, particularly for products already authorised. This innovation may also benefit adults. Other costs to the innovative industry include administrative costs incurred to meet the regulatory requirements, manufacturing costs if a specific child formulation is required and marketing costs.

Overall, the costs of clinical trials in children, if added to the costs of medicines would add less than 0.5% to the price of individual medicines. In addition, six-month extension of SPCs,

leading to delayed generic entry onto the market, could add over time, between 0.06 and 0.25% to European expenditure on pharmaceuticals. However this is likely to be balanced by reduced healthcare costs from the supply of safer and more effective medicines for children.

Six-months SPC extension could also cost the generics sector a one-time loss of between 86 and 342 million Euros in lost-opportunity costs. This loss would not go at the expense of generic products already on the market. It would represent a decline in market opportunities.

In addition, not all off-patent products are produced by generic drug manufacturers, so the estimated loss represents a maximum. And it will be *a one-time loss*: after the transitional period generic manufacturers will simply continue with business as usual even though they will have lost part of their market share.

It should be noted that these estimates are based a number assumptions. It should also be noted that the first SPC extensions will not occur for many years (considering the time to entry into force of the draft paediatric regulation and the fact that the extension is at the end of the patent / SPC life). Finally, SPC extensions will occur gradually over time as the requirements in the draft paediatric regulation are met and subsequently rewarded.

The use of deferrals from the requirements in the proposal will prevent the requirements from delaying the authorisation of medicines for adults. In the first few years after coming into force, the proposal will lead to a significant increase in work for regulators (and this will need to be resourced) and put pressure on the currently limited EU resources for conducting clinical trials in children. This initial pressure in conducting clinical trials will be released through the increased capacity for paediatric research already available in the US. There are no significant environmental or sustainability impacts from the proposal.

The extended impact assessment is inherently unbalanced. This results from the fact that it is possible to make an estimate of the costs resulting from the proposal but robust data are not available to allow estimation of the value, both economic and social, of the lives of children that will be saved and the improvements in the quality of life of the children of Europe.

The proposal aims to meet its objective of improved EU child health through stimulating research, development and authorisation of medicines for children and to provide as many wins as possible to the various stakeholders. If adopted into EU law the proposal should not only improve the health of the children of Europe but may also stimulate innovation for existing medicines for adults, should increase pharmaceutical research and development in the EU and provide new business opportunities for SMEs. The proposal comes at a price but this price can be said to be modest and is shared between those paying for medicines and industry.

European Commission
DG Enterprise

September 2004

ANNEXES

1. Rand Europe Study Report
2. Consultation: summary list of the workshops and meetings held
3. Summary of the results of the 2002 consultation
4. Summary of the results of the 2004 consultation

ANNEX 1
Rand Study Report

Available on request by e-mailing peter.arlett@cec.eu.int

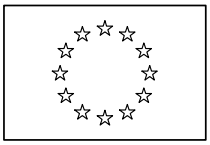
ANNEX 2

Consultation: summary list of workshops and meetings held

1997	DG III organises round table discussion with participation of Member States, CPMP, Commission, Paediatricians and Industry to explore problem and identify potential solutions
1998	DG III supports international discussion on the performance of clinical trials in children within the ICH (International Conference on Harmonisation) framework.
July 2000	Adoption of ICH guideline.
June 2000	Discussions on a Council resolution under French presidency begin.
December 2000	Council resolution invites Commission to make appropriate proposals as soon as possible in the form of incentives, regulatory measures or other supporting measures 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.
Jan – June 2001	Informal discussion with industry, attendance at workshops, conferences
July 2001	EMEA adopts mandate for a CPMP Paediatric Expert Group to obtain information on currently used medicines in children, advise on global paediatric development and on the provision of information to the public
21 September 2001	First meeting of EMEA Paediatric Expert Group
7 November 2001	Meeting with Industry/Paediatricians (IFIP, Paris)
15 November 2001	Brainstorming meeting with Member States
2nd December 2001	Discussion with European Group of Paediatricians (CESP)
5 April 2002	Workshop in France with all interested parties
November 2002	Circulation of reflection paper to Member States
15 May 2003	Discussion with Member States in the Pharmaceutical Committee
22 July 2003	First meeting of ad-hoc group of the Pharmaceutical Committee on paediatric medicines.

27 November 2003	2nd meeting of ad-hoc group of the Pharmaceutical Committee on paediatric medicines. Comments on detail but all broadly supportive.
8 January 2004	Commission Workshop with interested parties.
2 February 2004	Meeting with EGA
3 February 2004	Meeting with EFPIA
1 April 2004	Public meeting organised by CESP (European organisation of Paediatricians and national paediatric societies) and EFGCP (European Forum on Good Clinical Practice). Co-chaired by the Commission.

ANNEX 3
Consultation 2002: summary of responses



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels, June 2002
DG ENTR F2/EC/gm D(2002)

Overview of comments on consultation paper "Better Medicines for Children"

As of end May 2002 over **sixty sets of comments** were received by the Commission, DG Enterprise on its consultation document launched by Commissioner Liikanen on 28th February. The vast majority of these come from associations of health care professionals and academia, followed by patient associations, industry associations, NGOs and individual Member States. Separate comments from three EMEA committees/groups were received as well as comments from the EMEA executive director. One set of comments from a Health insurance provider and several comments from individuals and individual companies were also received. Comments from DG Research, DG Competition and DG Internal Market have also been provided. A full listing of all parties providing comments is provided at the end of this document.

It should be noted that there is a strong bias in terms of numbers of responses from professional associations in the UK, possibly reflecting the fact that the UK Medicines Control Agency appears to have distributed its request for comments rather widely.

All of the comments **welcome the Commission's consultation paper** and indicate support for most of the ideas expressed therein. Several of the comments provide ideas on how to expand on the suggestions in a practical manner.

In view of the number and diversity of the comments, it is difficult to provide a comprehensive overview. Nonetheless the following trends can be observed:
All responders recognise the **need to take specific regulatory measures** to improve the availability of suitable adapted medicines for children.
An overarching concern expressed throughout the comments was the **urgency** of this matter and the need to ensure that any framework put in place was underpinned by **adequate resources and funding** to meet its objectives.
While there is considerable support for the idea of **incentives** to encourage the development of new products, a number of concerns that this would result in medicines **being developed for financial gain**, rather than for the benefit of children were expressed. All parties who expressed views on the duration of any market exclusivity provision recommended a timing **of 12 months**.
The idea of a **"kid marketing authorisation"** was supported in principle. However whether this would be sufficient to generate the necessary studies was questioned. Putting in place mechanisms to avoid two companies embarking on the same set of studies was seen as essential. The prefix/suffixes were not considered appropriate.

The need for **multidisciplinary involvement** in any expert group or paediatric network to include patient support groups, pharmacists, nurses, parents etc. was stressed by several respondents.
Patient or health professional associations with a particular interest in a specific therapeutic area tended to stress the specific needs of children suffering from these diseases e.g. eczema, diabetes. **Childhood cancers** were indicated as priority areas by several respondents.
The need to **improve and disseminate information** on medicines authorised in one of more countries but not in others and feedback on empirical success or failures from treatment with unauthorised medicinal products and/or medicinal products used off-label was strongly stated by most respondents. There was significant support for the **development of a central database.** The need for **negative as well as positive** results of trials to be made available was also highlighted as well as the need to avoid unnecessary trials;
The need for **specific and adapted pharmacovigilance systems** was stressed by most parties, although the high cost and disincentives for industry were noted. Industry respondents tended to recommend targeting these studies carefully.
With some notable exceptions there was support for establishing a **paediatric expert group or committee** within the European Medicines Evaluation Agency. However the importance of clearly defining the role and mandate of this group and to allocate **sufficient resources** to its operation was highlighted.
The idea of a **network of excellence** for the performance of paediatric studies, which could vary from non-clinical, to dose ranging, to observational to pharmacovigilance was strongly supported. Several organisations indicated examples of existing networks which could be integrated or used as models. It was also suggested that such a network could be used to develop specific methodologies. **Training** needs should also be met. The idea of a Steering Committee to manage this was proposed. There was also significant support for the idea of **creating a register** of paediatric studies.
The challenge of generating information for **paediatric sub-populations**, in particular **neonates** was also mentioned by several parties.

List of providers of comments on "Better medicines for Children"

Patients organisations

EU Patients Voice – Erik Wendel
Eurordis
British Epilepsy Association (UK)
The National Council of Women of GB
Diabetes UK
National Eczema Society
UK Coalition of People Living with HIV & AIDS

Health Care Professionals and associations

European Respiratory Society
International Society of Paediatric Oncology (SIOP) – Michael Stevens
Sultan Qaboos University Hospital – Sultanate of Oman – Elizabeth Worthing
Special Interest group of the ESCP
Queens University Belfast, Clinical and practice research group
ISDB- International Society of Drug Bulletins
Paediatric Rheumatology International Trials Organisation PRINTO Alberto Martini – University of Genova
Children's Hospital – Infectious Diseases Unit (University of Geneva) (Italian association for Paediatric Haematology and Oncology
Independent Consultant in Pharmaceutical Medicine - Robert Smith

European Forum for Good Clinical Practice (EFGCP) – Francis Crawley
ECCH (Homeopathy) – Stephen Gordon
Pharmaceutical Society of Northern Ireland
The Royal Society for the Promotion of Health
Royal College of Physicians
Institut Gustave Roussy, Innovative therapies in paediatric oncology
The Royal College of Pathologists
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal Pharmaceutical Society of Great Britain
Royal College of General Practitioners
Cancer Research UK Children's Cancer Group (Prof. Vaskar Saha)
Academic Division of Child Health (University of Nottingham) - Pr Imti Choonara
LBL (Expertisecentrum)
University of Nottingham – Derbyshire Children's Hospital - Sharon Conroy
Cancer Research UK
Sheffield Children's Hospital
Royal Liverpool Children's NHS Trust - Tony Nunn
University of Wales College of Medicine
Chairman of the Medical Research Ethics – Gisela Dahlquist
European Society for Development, Perinatal and Paediatric Pharmacology (ESDP) Anders Rane – labtek
Pr of Paediatrics and Clinical Pharmacology –Philipps University
Schaper & Brümmer GmbH - Dr Zepelin
Finnish Paediatric Society (Kalle Hoppu)
Prof. Ramet (AZ VUB)
Univ. Klinik für Kinder - Dr Ronald Kurz
Klinikum - Maria Wagenhofer
The Standing Committee of European Doctors (CPME)

Member States

France
Denmark
Sweden
Netherlands
Belgium
UK
Germany

Pharmaceutical associations and individual companies

GlaxoSmithKline
BAH (Bundesverband der Arzneimittel-Hersteller)
BIA (BioIndustry Association)
EFPIA (European Federation of Pharmaceutical Industries and Associations
Sanofi
Association of the British Pharmaceutical Industry (ABPI)
AESGP (OTC association)
EGA (European Generics Association
Micromedex (database provider)

Health Insurance

Maison européenne de la Protection sociale

NGOs

BUKO Pharma: German Federal Congress of Development action groups
Association of Medical Research Charities
Action Research UK – Medical Research charity

Individuals

RadcliffesLeBrasseur (lawyer)

European Commission and Agency (EMEA)

European Commission (DG RTD : Dir. E)
European Commission (DG RTD : Dir. F)
European Commission (DG COMP)
European Commission (DG MARKT)
EMEA – Paediatric Expert Group
EMEA- CPMP
EMEA-COMP
EMEA- Executive Director

ANNEX 4

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels, April 2004
DG ENTR F2/paediatrics/consultation 04

Overview of comments on the Commission's 2004 public consultation on a draft proposal for a European Parliament and Council Regulation (EC) on medicinal products for paediatric use

In March 2004 the Commission launched a continuation of its public consultation on the legislative proposals on a draft proposal for a European Parliament and Council Regulation (EC) on medicinal products for paediatric use. The comments received during this 2004 public consultation are summarised in this document. The Commissions response to the issues raised and justification for the final Commission proposal are in the discussions included in the Commission's Extended Impact Assessment and in the Explanatory Memorandum that forms part of the final Commission legislative proposal.

Contributors

The Commission received 69 contributions. Many of them, in particular the ones from regulators, patients associations, or the industry, were the result of wider consultation by specific stakeholder organisations. A full listing of all parties providing comments is provided at the end of this document.

The participants can be subdivided into six groups:
-Patients associations (3 contributions)
-Healthcare professionals (27 contributions)
-Insurance bodies (3 contributions)
-Regulators (15 contributions)
-Industry (18 contributions)
-Others (3 contributions)

Healthcare professionals' responses were received from 20 associations (societies, consortia, networks, foundations, committees, federations and organisations), 1 Hospital, 1 University, and 5 individuals.

Regulators sent 15 contributions: 7 from Regulatory Agencies (1 EU, 5 European National, 1 non-EU National), 3 from EU Committees or Expert Groups, 2 from EU National Ministries, and 3 from individual regulators.

Industry sent 18 contributions: 10 from industrial associations, and 8 from individual companies involved in the pharmaceutical or biotechnology sector. Industrial associations represented the innovative and generics industry, as well as other sectors.

All contributions received provide valuable information for the Commission's further action in this field.

Summary of contributions

The vast majority of the comments welcome the Commission's draft legislative proposal, the opportunity to submit contributions, and explicitly support the outlined objectives.

A minority (7) of contributions suggest that more emphasis on **avoiding unnecessary studies in children** should be included in the proposal.

As already revealed by the 2002 part of the consultation, all respondents recognise the need to take **specific regulatory measures** in order to achieve these objectives.

Broadly speaking, most of the contributors agree with the **key principles and concepts** underlying the Commission's proposal.

The creation of the **Paediatric Board (PB)** within the EMEA is welcomed by almost all the contributors. 39 contributions suggest 'minor' changes related to the **composition of the PB** (so as to ensure better representation of all stakeholders), to the size of the committee, and to the assigned tasks.

Some respondents (mainly industry) cast doubts over the suggested procedure for the **re-examination of the opinions** adopted by the PB. A separate appeal committee is requested by a majority of the respondents who expressed their views on this matter.

The concept of a **paediatric investigation plan (PIP)** was agreed upon by most of the respondents. Specific points raised included:

- Thirteen contributions, mostly from the 'Regulators' and 'HealthCare Professionals' subgroups, suggest to define a specific timeline for the submission of a PIP, so as to make sure that results from paediatric studies are readily available by the time the marketing authorisation application is filed.
- A few respondents from the 'Industry' subgroup consider that PIP-data should be provided on a voluntary basis, and should not constitute a mandatory requirement. Seven respondents (notably from the 'Industry' subgroup) were of the opinion that the requirements may impact negatively on the pharmaceutical research and development in Europe. This was usually proposed as support for the argument for 'voluntary requirements'.

The **waiver and deferral** systems are well accepted as tools to ensure that research in children is only conducted to meet the therapeutic needs of the paediatric population. A number of responses stress the importance of the deferral system being retained in the final proposal to ensure that the PIP and requirements for data do not delay the authorisation of medicines for other populations. Many stakeholders provide technical suggestions for criteria to define waiver categories, depending on the nature of the concerned medicinal products.

The requirement to **market the paediatric product within 12 months** of the date of approval of the paediatric indication is considered to be unachievable. Respondents from the 'Industry' subgroup argue that negotiations and/or administrative procedures at a national level (*e.g.* regarding pricing) can last longer than 12 months.

The **incentives** for patented medicinal products raise a lot of comments. 8 contributions, all coming from the 'Industry' subgroup, suggest **extending the SPC extension from 6 months to 12 months**. A few other responses, from 'Regulators' and 'HealthCare Professionals', are also of the opinion that a longer period would be a greater incentive. Various respondents from all the subgroups consider that the exact duration should be informed by the estimated financial impact that such an incentive may entail, in particular *vis-à-vis* national health-insurance systems (see section 4 of the Extended Impact Assessment).

A number of responses were concerned about the **interface between the SPC extension and the EU orphan regulation**. There was some concern that, if SPC extension was the only reward offered for compliance with the requirement, the requirement would not be rewarded for a significant proportion of orphan medicines as many such medicines are not patent-protected at the time of authorisation. Others were concerned that, for orphan medicines covered by a patent, a double incentive would be granted (SPC extension from the paediatric proposal and ten-year market exclusivity from the orphan regulation).

The **Paediatric Use Marketing Authorisation (PUMA)** and the '8+2+1' data protection scheme it confers was considered an inadequate incentive for off-patent medicines in 18 contributions, which represent a large majority of the stakeholders who expressed views on this subject. 12 respondents, including 'Patients associations' 'Healthcare professionals', 'Industry', and 'Regulators' subgroups, favour stronger incentives for off-patent medicines and many suggest **market exclusivity** instead (similar to the incentive for orphan medicinal products).

The **PUMA labelling** (a "P" in blue lettering surrounded by the outline of a star, also in blue) raises questions related to public perception. New medicinal products (*i.e.* patented products), with a paediatric indication, but for which a PUMA is not granted do not have access to the 'P' labelling: as a result, they may be perceived as products less-suitable for the paediatric population.

Almost all respondents who commented on the **Medicines Investigation for the Children of Europe (MICE)** express concern over the current lack of explicit funding for this study program (21 contributions). Responders point out that without appropriate financial support, the 'incentive' effect of MICE in the Commission's proposal appears to be seriously weakened.

Free scientific advice is welcomed, in particular, by the Industry. Such a provision seems to be viewed as a real incentive, both by the innovative and by the generics pharmaceutical industry.

Suggested measures to **increase the robustness of pharmacovigilance** on medicines for children, as well as the requirements for industry to **submit existing study reports**, are welcomed by most of the stakeholders. Similarly to the 2002 part of the consultation, contributions from the 'Industry' subgroup stress the costs and administrative burden that such studies might entail.

Patients associations and healthcare professionals strongly support the proposal for an **inventory of the therapeutic needs** for children, which in their opinion should help to prioritise research areas in paediatrics. Along the same line, the establishment of a **European network** with specific expertise in the performance of trials in the paediatric population is, in

principle, welcomed. 7 contributions (mostly from 'Regulators') ask for clarification as regards the detailed implementation, funding and maintenance of such a network. The use of already-existing networks is also emphasised by healthcare professionals.

Finally, the concept of a **central database** of the studies conducted according to agreed paediatric investigation plans, although being supported by a large majority of stakeholders, raises two concerns:

- The set of information which is to be accessible to the public should be clearly defined, in order to avoid confidentiality issues (response from industry).
- The interaction with the database set up in the framework of Directive 2001/20/EC requires more clarification.

EUROPEAN COMMISSION
DG ENTERPRISE F2
APRIL 2004

List of respondents

Patients Organisations

Pool of Patients organisations (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP), Genetic Interest Groups (GIG), Heart, Europe, Hoofddorp, the Netherlands, the European Cholesterol Patient Foundation, RERetina Europe (RE), Central and East European Genetic Network (CEE-GN), European Gaucher Alliance (EGA), World Alliance Neuromuscular Disorder Associations (WANDA/Europea), Fighting Blindness)

EFA (European Federation of Allergy and Airways Diseases Patients' Associations)

Eurordis (European Organisation for Rare Diseases)

HealthCare Professionals

Consortium (ITCC, ICCCPO, UKCCSG, SFCE, DCOG, AIEOP, GPOH)

ACP/CSB (Italian Cultural Paediatric Association and Centre for Child Health)

ANME (Association of Natural Medicine in Europe)

CACP (Children's and Adolescent Cancer Partnership)

ECH (European Committee for Homeopathy)

ECPM (European Council of Doctors for Plurality in Medicines)

ERS (European Respiratory Society)

ESDP (European Society for Developmental, Perinatal and Paediatric Pharmacology)

ESPR/ESN (European Society for Paediatric Research)

FPS (Finnish Paediatric Society)

Gio.I.A. Foundation

GSPAM (German Society for Paediatric and Adolescent Medicine)

Marionegri (Italian Pharmacological Research Institute)

NPPG (Neonatal and Paediatric Pharmacists Group)

NPPG/RCPCH (Royal College of Paediatrics and Child Health)

PAED-Net (Paediatric Network, Germany)

PRINTO (Paediatric Rheumatology International Trials Organisation)

Royal Liverpool Children's NHS Trust

SIOP Europe (European Society of Paediatric Oncologists)

TEDDY (Task force in Europe for Drug Development for Young)

UKCCSG (UK Children's Cancer Study Group)

Université Catholique de Louvain, Belgium

G. Benzi (Università degli Studi di Pavia)

Jane Lamprill, freelance consultant

A. Loizzo (Istituto Superiore di Sanita', Roma), F. Franconi (Society of Pharmacology, Gio.i.a Foundation), G. Biggio (University of Cagliari)

T. Nunn, Royal Liverpool Children's NHS Trust

Kalle Hoppu (Finnish Paediatric Society)

Insurance Bodies

AIM (Association internationale de la Mutualité)

CNAMTS (Caisse Nationale de l'Assurance Maladie Française des Travailleurs Salariés)

MEDEV (subcommittee of the European Social Health Forum)

Regulators

AFIGP, Belgium

BMGS,Germany

Dkma, Denmark

IMB, Ireland

MEB, Netherlands

MHRA, UK

Ministère de la Santé, France

Swissmedic, Switzerland

COMP, EMEA

CPMP, EMEA

Paediatric Expert Group, EMEA

EMEA

Priya Bahri, EMEA

X. Kurz, AFIGP, Belgium

M Toivonen & P Kurki, CPMP members, Finland

Industry

ABPI (Association of the British Pharmaceutical Industry)

AESGP (Association of the European Self-Medication Industry)

BIA (BioIndustry Association)

BPI (German Pharmaceutical Industry Association)

ECHAMP (European Coalition of homeopathic and anthroposophic medicinal products)

EFPIA (The European Federation of Pharmaceutical Industries and Associations)

EGA (European Generic Medicines Association)

Pharma.be (Belgian General Association of the Pharmaceutical Industry)

PhRMA (Pharmaceutical Research and Manufacturers of America)

VFA (German Association of Research-based Pharmaceutical Companies)

Amgen ltd

Aventis Pharma

Genzyme

Millenium

Novartis

Schering-Plough

Servier

Yamanouchi

Others

EFGCP (European Forum for Good Clinical Practice)

Revue Prescrire

Joanne Shaw, Task Force on Medicines Partnership