

Proposed regulation on medicinal products for paediatric use

Overview and explanation of the proposal

1. INTRODUCTION AND BACKGROUND

The public health concern and its causes

This proposal aims to improve the health of the children of Europe by stimulating the research, development and authorisation of medicines to treat children.

In the 25 Member States of the European Union (EU), the paediatric population represents 100 million people, i.e. over 20% of the total population. This is a vulnerable group with developmental, physiological and psychological differences from adults, which makes age and development related research of medicines particularly important.

Before any medicine is authorised for use in adults, the product must have undergone extensive testing including pre-clinical tests and clinical trials to ensure that it is safe, of high quality and effective. In contrast, it has been demonstrated that more than 50% of the medicines used to treat the children of Europe have not been tested and are not authorised for use in children: the health and therefore quality of life of the children of Europe may suffer from a lack of testing and authorisation of medicines for their use. In practical terms every time a doctor in Europe writes a prescription for a child for an untested, unauthorised product, that doctor can not be sure the medicine will be truly effective, can not be sure what dose is really appropriate and can not predict exactly what adverse reactions (side effects) the child may suffer.

Although there may be concerns voiced about conducting trials in the paediatric population, this has to be balanced by the ethical issues related to giving medicines to a population in which they have not been tested and therefore their effects, positive or negative, are unknown. In order to address the concerns about trials in children it has to be pointed out that the new EU Directive on clinical trials (the so-called “Clinical Trials Directive”¹) lays down specific requirements to protect children who take part in clinical trials in the EU. Furthermore, there is evidence that individuals treated in clinical trials have a positive benefit compared with individuals treated outside of a trial^{2,3}. In terms of both public health and ethics, it is clearly preferable to test medicines in children, in a safe and controlled clinical trial environment, where the individual child is protected and the studies generate data and information for the benefit of the rest of the children of the EU than to go on with the daily “experiments on children” that today occur because such medicines for children have never been designed and evaluated for this particular use.

Recent US paediatric studies conducted in response to US legislation have led to 64 labels containing new paediatric information for established medicines between July 1998 and February 2004. In 41 cases or about two thirds the new labels included important new information which had an impact on the safe and effective use of the medicine in the paediatric population. Without specific studies in the paediatric population this important information would not have been available⁴.

¹ OJ L 121, 1.5.2001, p. 34

² Braunholtz D., Edwards, S. & Lilford, R. Are randomised clinical trials good for us (in the short term)? Evidence of a ‘trial effect’. J. Clin. Epidemiol. 54, 217 – 224 (2001).

³ Lantos, J.D. The ‘inclusion benefit’ in clinical trials. J. Pediatr. 134, 130-131 (1999).

⁴ <http://www.fda.gov/cder/pediatric>

The paediatric population is not a homogeneous group; it ranges from pre-term newborns, through toddlers and children to adolescents. These are not miniature versions of adults. Due to age-related differences in drug handling or drug effects which may lead to different dose requirements to achieve efficacy or to avoid adverse reactions, specific clinical trials in paediatric populations are normally required. In addition, there may be practical problems of administration e.g. difficulties swallowing tablets if a syrup is not available or, more significantly, serious calculation errors when using adult formulations to obtain paediatric dosages.

All medicines can, in some individuals, cause adverse reactions. One study conducted in the United States⁵ 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^{6,7} and that children are growing, developing physiologically and mentally and are therefore particularly vulnerable to adverse drug reactions, the public health implications of not testing and authorising medicines for children is clear. Untested and unauthorised products are associated with increased risks and these may not be balanced by a substantial benefit of treatment.

The absence of suitable authorised medicinal products to treat conditions in children 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 leaves no alternative to the prescriber than to use adult products “off-label” and use unauthorised (unlicensed) products with the associated risks of inefficacy and/or adverse reactions. In addition, existing data which could provide useful and important information are frequently not made available to the health practitioner.

Industry has a free choice as to what medicines to develop, authorise and market. The main drivers of overall return on investment are the size of the target pharmaceutical market and the price achievable within this market-place. 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 have proved insufficient to stimulate adequate research into and authorisation of medicines for children and the industry has thus considered that for many childhood diseases the potential return is insufficient to justify such investment in research and development.

Related initiatives: EU Orphan Regulation and US legislation on medicines for children

The absence of research into treatments for rare diseases led the Commission to propose the Regulation on orphan medicinal products, subsequently adopted in December 1999. This Regulation has proved successful in stimulating research leading to the authorisation of medicines to treat rare diseases. There are many similarities between the problems confronted in this area and the problems of medicines for paediatric (child) use. Elements of this existing Regulation have been taken as a model for medicines for paediatric use.

⁵ 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

⁶ Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards : a prospective study. *Acta Paediatrica*, 1999; 88(9): 965-968

⁷ Horen B et. Al. Adverse drug reactions and off-label drug use in paediatric patients. *British J. Clin. Pharmacology*.2002;54 : 665-670

In the US, specific legislation to encourage the performance of clinical trials in children was 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” 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 led 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.

The “paediatric exclusivity” provision in the Food and Drug Administration (FDA) Modernisation Act 1997 provides an incentive (6 months 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. 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. The new Act also includes a requirement to develop a prioritised list of medicines for which paediatric studies are needed.

The combined measures of incentives and obligations have been extremely successful in the US in stimulating the development of medicinal products for paediatric use. Over the same period of time, some Member States have tried, within the current legal framework, to introduce measures to increase the availability of information on the use of medicines in the paediatric population and to increase the availability of authorised medicines that are specifically adapted for use in the paediatric population. Their efforts have been largely unsuccessful. Furthermore, 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. It is unlikely, therefore, that there will be any substantive progress in this area in the European Union until there is a specific legislative system in place.

This was recognised in 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. After long debates and extensive consultations, the present proposal is a legislative response to this Council Resolution.

2. JUSTIFICATION

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.

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 without subjecting children to unnecessary clinical trials and in full compliance with the EU Clinical Trials Directive⁸.

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

- products in development (not yet to be authorised)
- authorised products still covered by patents or supplementary protection certificates
- authorised products no longer covered by these instruments

The proposal contains a package of measures to achieve its objectives both in terms of procedural aspects and regulatory and technical requirements.

Scope

The proposed system covers medicinal products for human use within the meaning of Directive 2001/83/EC.

Legal basis and procedure

The proposal is based on Article 95 of the EC Treaty. Article 95, which prescribes the codecision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, which include the free movement of goods (Article 14(2)), in this case human medicinal products. While taking account of the fact that any regulations on the manufacture and distribution of medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the manufacture and free movement of medicinal products within the Community. Since the Amsterdam treaty came into force, all legislative provisions adopted by the European Parliament and the Council, except for directives adopted on the basis of executive powers vested in the Commission, and aimed at aligning the provision on medicinal products have been adopted on the basis of that Article, since the differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. Any action to promote the development and authorisation of medicinal products for paediatric use is therefore justified with a view to preventing or eliminating these obstacles. More precisely it has to be stressed that Regulation (EC) No 141/2000 of the European Parliament and the

⁸ OJ L 121, 1.5.2001, p. 34

Council of 16 December 1999 on orphan medicinal products⁹, comparable to a large extent to the present proposal, was adopted on the basis of Article 95.

This proposal directly interfaces with five existing Community legislative texts. These are: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001¹⁰ which sets the framework for the regulation of medicinal products; Regulation (EC) No 726/04 of the European Parliament and of the Council of 31 March 2004¹¹ which establishes the EMEA and created the centralised authorisation procedure for medicinal products; Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001¹² which provides a framework for the regulation and conduct of clinical trials in the Community; Regulation (EC) No 141/2000 of the European Parliament and of the Council which establishes a Community system for the designation of medicinal products as orphan medicinal products and incentives to stimulate their development and authorisation, and; Council Regulation (EEC) No 1768/92 of 18 June 1992¹³ which created the Supplementary Protection Certificate.

This proposal utilises the existing Community framework for the regulation of medicines including the EMEA, committee structures, marketing authorisation procedures, protection of clinical trial subjects, and databases. As will be seen later, this proposal includes various key measures that are directly built on the existing regulatory framework. Member States acting independently cannot introduce these measures as such provisions would be contrary to existing Community legislation. Equally, if such measures were to be adopted in an uncoordinated manner by the Member States this would create obstacles to intra-Community trade, distort competition and impede the achievement of a single market.

Subsidiarity and proportionality

The proposal builds on the experience gained with the existing regulatory framework for medicines in Europe and learns from the 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. On the basis of the available evidence it is concluded that it is 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.

Council Resolution of 14 December 2000 on medicinal products for paediatric use states that “all Member States face” ...[the problem of inadequate development of medicinal products for paediatric use].... “and that a European approach offers advantages from the epidemiological, public health and economic points of view”. The problem of the lack of authorised medicinal products for paediatric use is in part due to the small number of patients concerned and the low commercial returns on the medicinal products developed to treat them. A common and concerted Community approach is clearly more likely to help solve this problem than isolated national initiatives. Community action allows the best possible use of the instruments set up in the pharmaceutical sector to complete the internal market, in particular the European Agency for the Evaluation of Medicinal Products and the centralised procedure for authorising the marketing of medicinal products. In addition, a European

⁹ OJ L 18, 22.1.2000, p. 1

¹⁰ OJ L 311, 28.11.2001 p. 67 - 128

¹¹ OJ L 136, 30.4.2004 p. 1 - 33

¹² OJ L 121, 1.5.2001, p. 34

¹³ OJ L 182, 2.7.1992, p. 1

solution to this public health challenge is warranted because 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 show that 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.

However, Member States will have an important role in the fulfilment of the objectives of the proposal. The proposal invites them to introduce National incentives for research and development of medicinal products for paediatric use and for placing such products on the market, within the framework of their own powers and responsibilities. Member States will wish to consider the training of doctors and other healthcare professionals needed to conduct clinical trials in children, the investment in infrastructure, such as clinical trials centres, needed for clinical trials and funding for clinical trials, particularly where industry is unlikely to invest. Member States may also wish to consider whether the increased supply of robustly tested, authorised medicinal products for children should be complimented by national actions to encourage the prescription and use of these medicines in preference to off-label and unlicensed use.

Legislative and administrative simplification

All the key measures in the proposal build on or strengthen the existing framework for the regulation of medicinal products: the Paediatric Committee is established, and the procedures for agreeing paediatric investigation plans, waivers and deferrals will operate, within the existing EMEA; the requirement for data in children applies to the current procedures for marketing authorisation applications; the reward for compliance with the requirement is an extension to the existing supplementary protection certificate; for orphan medicinal products the reward for compliance with the requirement is two years added to the existing market exclusivity; the new type of marketing authorisation, the PUMA, utilises the current marketing authorisation procedures; measures are put in place to increase the robustness of the current pharmacovigilance system for children; an EU inventory of the therapeutic needs of children and an EU network of trial investigators will be coordinated by the EMEA which will also be responsible for the provision of free scientific advice for the industry; the database set up to support the existing EU Clinical Trials Directive will provide the database of paediatric clinical trials.

This proposal for a regulation establishes a precise legal framework. However, where more detailed implementing provisions are required, a Commission regulation is foreseen and it is proposed that further provisions be adopted by the Commission as guidelines, in consultation with the Member States, the Agency and the parties concerned. This has been the normal way of proceeding in the pharmaceutical sector since the adoption of the very first texts and this approach has proven its efficiency, particularly as this domain sees technical / scientific evolution occurring frequently and at a rapid pace.

Outside consultation

Interested parties have been widely consulted on this proposal. The lack of available treatments for the paediatric population led the European Commission to organise a round table in 1997 and subsequently to participate in international discussions to develop and agree an international guideline on how best to perform clinical trials in children. In December 2000, the European Council of Ministers adopted a resolution on paediatric medicinal products calling on the Commission to make proposals on medicines for children. In November 2001, the European Commission organised a “brainstorming” meeting with representatives of Member States and research-based industry. This was followed by the release of a public consultation paper in February 2002. Over sixty sets of comments were

received from interested parties and these were taken into account when drafting this proposal. An ad-hoc working group of the Pharmaceutical Committee was set up in 2003 to help develop the proposal and workshops and bilateral meetings were also held. In March 2004 the Commission launched a continuation of its public consultation on the proposals. Sixty-nine responses were received (including responses from European and national patient organisations, industry associations, societies of doctors and pharmacists, insurance organisations and ethics groups). Overall the responses were very supportive of the proposal. Detail on the consultation conducted by the Commission is included in the Extended Impact Assessment that accompanies this proposal. The most debated issues during consultation are addressed below.

Incentives and rewards for patented 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 characteristics of the target market before the product is even 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: 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 substance, generic competition will be delayed for the entire product range based on that active substance 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 returns from the market for the innovator company that may significantly outweigh the costs incurred as a result of the requirements laid down by the proposal. 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. In this way, the SPC extension can be viewed as a mixed reward and incentive. Based on the 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 incentive for the innovative industry and a clear win for child health, which is the primary objective of this proposal.

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.

Some sectors of the industry have argued for incentives without requirements. Providing an incentive in the form of intellectual or industrial property rights (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 IPRs awarded. This would mean that some therapeutic needs of children would come second or be disregarded in favour of more valuable markets. As important public health needs would remain unmet, the objective of improving the health of the children of Europe would only be partially met.

The proposal aims to remedy the situation for children but it must not compromise the access of other populations to new medicines. The proposal 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 proposal 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). Therefore it has to be ensured that the requirements do not delay, in any way, the authorisation of medicines for adults. The proposal contains specific measures to deal with this. The Paediatric Committee 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.

Orphan medicinal products

A number of responses to the 2004 public consultation 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, this proposal excludes orphan medicines from the SPC extension and, instead, rewards them for compliance with additional two years of the market exclusivity foreseen in Regulation (EC) No 141/2000 on orphan medicinal products. Two years have 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.

Off-patent medicinal products

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. 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.

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, if not the majority of all 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.

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. Furthermore, the data protection period associated with the PUMA may prove more valuable in light of the recent case law of the European Court of Justice concerning the interpretation of data protection rules¹⁴. 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 proposed 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 initiative.

Evaluation of the proposal

A detailed discussion of the implementation and evaluation of the proposal is provided in the Extended Impact Assessment that accompanies this proposal. Prospective collection of data is foreseen, focussing particularly on the impact of the proposals on: clinical trials conducted, marketing authorisations applied for and granted, and amendments to existing marketing authorisations. The proposal also provides that the Commission will assess the application of the system six years after it has been introduced and will, within this period, publish a report on the experience acquired, including a detailed inventory of all medicinal products authorised for paediatric use since the introduction of the proposals.

Checks and balances are built into the proposals to ensure that the objectives are met while stakeholders' interests are protected. First and foremost, the paediatric regulation is built on the public health foundation provided by the EU Clinical Trials Directive. The well-being and interests of children in clinical trials are therefore protected. The role of the proposed Paediatric Committee is also central to the checks and balances. For example, all paediatric investigation plans will have to be agreed by the Paediatric Committee who will always have to consider the potential therapeutic benefit of studies to the paediatric population. The Paediatric Committee will consider waivers from the requirement for data from studies in children to ensure unnecessary, unsafe or duplicative studies are prevented. The Paediatric Committee will also be responsible for granting deferrals of the timing of studies in children to ensure studies are only conducted when it is safe to do so and, just as importantly, to ensure that the requirements in the proposal do not delay the authorisation of medicines for other populations. With regard to the extension of the period of the SPC and, for orphan medicines market exclusivity, to avoid abuse of such rewards/incentives, safeguards have been introduced to ensure that they will only be granted if, firstly, the agreed paediatric investigation plan has been completed according to an agreed paediatric investigation plan

¹⁴ Case C-106/01, Novartis Pharmaceuticals UK, judgment of 29 April 2004, not yet reviewed.

and, secondly, appropriate information on the use of products is included in the product information for healthcare professional and the public.

2.1. Summary of extended impact assessment

This proposal has been the subject of a Commission extended impact assessment of the proposal overall and the specific measures included. The Commission's extended impact assessment is principally based on an independent, externally contracted study, specifically designed to estimate the economic, social and environmental impacts of the proposal. The extended impact assessment 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, the published literature and other available data.

The extended impact assessment accompanies this proposal, however, the key findings are presented in the subsequent paragraphs. At the time the study was conducted 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. Based on the results and the 2004 part of the public consultation these measures have been amended in this final proposal.

Extended Impact Assessment findings

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 authorised medicines for children.

Ineffective treatment of children, incorrect dosing of children and adverse drug reactions in children will be minimised. This should lead, as far as children are concerned, to a reduced number of hospital days, fewer deaths, increased quality of life 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 could also benefit children outside the EU, including those in less developed countries.

Industry will benefit from the paediatric regulation in different ways:

- 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 marketed, 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 as this has been the case in the US¹⁵;
- New business opportunities will be created: through the PUMA with 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

¹⁵ C-P Milne, Exploring the frontiers of Law and Science : The FDA Modernization Act's Paediatric Studies Incentive Food & Drug Law Journal, Volume 57, Number 3, 2002 (in press)

medium-sized enterprises (SMEs) and could even lead to the creation of new companies or subsidiaries within the EU.

There are obviously 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 real costs associated with 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, a large proportion of off-patent products are produced by innovator manufacturers, so the estimated loss represents a maximum.

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 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 put pressure on the currently limited 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.

It is difficult to judge the balance the benefits and costs of the paediatric regulation. 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. When adopted the Regulation should not only improve the health of the children of Europe but may also stimulate innovation for existing

medicines for adults, should boost 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 vis a vis the objectives and is to be shared between those paying for medicines and industry.

3. PRESENTATION

Key measures included in the proposal

The Paediatric Committee

A committee with expertise in all aspects of the research, development, authorisation and use of medicines for children is central to the proposal and its operation. The proposed Paediatric Committee will be within the European Medicines Agency (EMA) in order to profit from its existing infrastructure and to allow effective coordination with the other EU committees on medicines, already operating within the EMA. These other committees include the Committee on Human Medicinal Products (CHMP) and its working groups including the Scientific Advice Working Group and the Committee on Orphan Medicinal Products (COMP). A new committee is required as none of the existing committees have sufficient specific paediatric expertise required to conduct the tasks required. The Paediatric Committee will be responsible primarily for the assessment and agreement of paediatric investigation plans and requests for waivers and deferrals described below. In addition the Paediatric Committee may assess compliance with paediatric investigation plans and be asked to assess the results of studies. This latter task will be only at the request of the CHMP or national Competent Authorities who will remain responsible for the assessment of safety, quality and efficacy required for marketing authorisation. Finally, the Paediatric Committee will be central to the various support measures proposed including the EU inventory of therapeutic needs in children and the EU network for the performance of clinical trials in children. The Paediatric Committee will comprise 31 members, of which five will also be members of the CHMP (to ensure effective coordination between the two committees). National competent authorities whose CHMP member is not on the Paediatric Committee will be able to nominate a member and the Commission will appoint six members from patient/family and healthcare professional groups based on a public call for expressions of interest. Because of the commercially sensitive work of the Paediatric Committee, a strict conflict of interest policy is proposed. In all its work the Paediatric Committee will consider the potential significant therapeutic benefits of studies in children including the need to avoid unnecessary studies, it will follow existing Community requirements including ICH guideline E11 on the development of medicines for children and will avoid any delay in the authorisation of medicines for other populations as a result of the requirements for studies in children.

Marketing authorisation requirements

The paediatric investigation plan will be the document upon which the studies in children are based and will have to be agreed by the Paediatric Committee. The paediatric investigation plan is defined as a research and development programme aimed at ensuring the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population. The basic concept is that development of medicines for children should be an integral part of the development of medicinal products, integrated into the development program for adults. Because the “paediatric population” is in fact made up of a number of subpopulations, the paediatric investigation plan will need to specify which subpopulations need to be studied, by what means and by when. It is proposed that paediatric investigation plans are submitted early during product development before the start of phase II studies, in time for studies to be conducted in children before marketing authorisation applications are submitted. When assessing paediatric investigation plans the Paediatric

Committee will have to take into consideration two overarching principles: firstly, that studies should only be performed if there is a potential therapeutic benefit to children (and avoiding duplication of studies) and, secondly, that the requirements for studies in children should not delay the authorisation of medicines for other populations.

The timing of studies will be particularly important as a core measure is a new requirement for the results of all studies performed in accordance with a completed, agreed paediatric investigation plan to be presented at the time of applications, unless a waiver or a deferral has been granted. This requirement will apply to marketing authorisation applications for new medicines other than generics, similar biological medicinal products (“biological generics”) and products authorised through the well-established medicinal use procedure. The requirement will also apply to products covered by a patent or a supplementary protection certificate at the time of applications for new indications, new pharmaceutical forms and new routes of administration. This core requirement has been included to ensure that medicines are developed for children based on the therapeutic needs of children rather than just on the basis of when the paediatric market may be profitable or incentives might be financially attractive. The paediatric investigation plan will be the basis upon which compliance with this requirement is judged. As such, the paediatric investigation plan will need to specify which studies in which paediatric sub-populations must have been completed at the time of a marketing authorisation application and which should be presented to the Competent Authorities at a later date. To reinforce this and particularly to avoid any ambiguity when checking the compliance with paediatric investigation plans, studies that are required but the start or finalisation is delayed beyond marketing authorisation application will be the subject of a deferral (see below).

Simple procedures are proposed for agreeing paediatric investigation plans, as well as, requests for deferrals and waivers (see below). A procedure for modifying the paediatric investigation plan after it has been agreed, including modifying deferrals and waivers is also proposed. The ability to modify paediatric investigation plans is important as the speed of recruitment into studies and the implications of the results of one study on another cannot always be predicted in advance.

Waivers from the requirements

Not all medicines being developed for adults will be suitable for children or will be needed to treat children and unnecessary studies in children should be avoided. To deal with such situations a system of waivers from the requirements described above is proposed. Such waivers might be issued, in particular, if there is evidence showing that the specific medicinal product or class of medicinal product is likely to be ineffective or unsafe in the paediatric population (or part of the paediatric population), or that the disease or condition for which the medicinal product is intended occurs only in adult populations.

To simplify the system for agreeing paediatric investigation plans and issuing waivers it is proposed that the Paediatric Committee will start work as soon as it is set up, on lists of waivers of medicinal products, classes of medicinal product and parts of classes of medicinal product. It is proposed that these lists of waivers will be published by the EMEA so that industry will know in advance for which products the requirements for studies in children will be waived and studies in children should not be conducted. However, it will not be possible for the Paediatric Committee to foresee all medicinal products that might be developed and therefore, for products not included in the published lists, a simple procedure is proposed for companies to request waivers. As knowledge on science and medicine evolves over time it is likely that the need for medicines in children will change. For example, at the time of entry into force of the regulation it may be judged that a particular class of medicinal product is

likely to be ineffective in children and a class waiver may be published. Later, however, new scientific evidence may emerge suggesting that that class of medicinal product could be of significant therapeutic benefit to children. In this situation, the class waiver would be removed from the published list. This dynamic feature of the published list of waivers will not complicate the requirements for studies in children at the time of marketing authorisation application as, if a waiver is removed from the published list, the requirement will not apply for 36 months, allowing time for at least a paediatric investigation plan to be agreed and studies in children to be initiated (although possibly not completed) prior to marketing authorisation application.

Deferrals from the timing of initiation or completion of studies in children

This proposal aims to improve the health of the children of Europe by increasing the availability of tested, developed and authorised medicines for children and one of the core measures for achieving this is a requirement at marketing authorisation application for adults for the data in children. However, sometimes studies in children will be more appropriate when there exists some initial experience on use of a product in adults or studies in children might take longer than studies in adults. This might apply to the entire paediatric population or just a subset, such as neonates. Therefore, to deal with this situation, a system of deferrals is proposed together with a procedure for agreeing them with the Paediatric Committee. The procedure will work hand in hand with the procedure for agreeing paediatric investigation plans (indeed the deferral can be viewed as an integral part of the paediatric investigation plan). It is also proposed that, once a marketing authorisation is granted, companies will submit annual reports to the Paediatric Committee on their compliance in progressing with the deferred studies. It should be noted that it is proposed that the Paediatric Committee can impose deferrals if it considers studies should be delayed even if a deferral is not requested by a company. Deferrals will ensure that studies in children only occur when it is safe to do them and that the proposed requirements do not delay the authorisation of medicines for adults.

Free scientific advice

The dialogue between companies and the Paediatric Committee on paediatric investigation plans and the necessity for their agreement will ensure that the development of medicines is driven by the therapeutic needs of children and that studies will be informative and useful to children. In addition, free scientific advice from the EMEA to sponsors developing medicines for children is proposed on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population and on pharmacovigilance and risk management systems post-authorisation. This free scientific advice might focus on more detailed questions on the design of specific studies.

EMEA Coordination

The interface between the CHMP, Scientific Advice Working Group of the CHMP and the Paediatric Committee will be important and will be managed by the EMEA. The EMEA is also ideally placed to coordinate the interaction between the other Community committees and working groups on medicines and the Paediatric Committee and it is proposed to specifically task the EMEA with this coordination.

Marketing authorisation procedures

The procedures set out in existing pharmaceutical legislation are not altered by the proposals. Indeed the proposals use these procedures as their foundation. The requirements set out above will require the Competent Authorities to check compliance with the agreed paediatric investigation plan (including waivers and deferrals) at the existing validation step for marketing authorisation applications. The assessment of safety, quality and efficacy of medicines for children and the granting of marketing authorisations remain the remit of the

Competent Authorities. The Paediatric Committee is likely to be asked for an opinion on compliance and may also be asked for a recommendation on the safety, quality and efficacy in children and this is foreseen in the proposals.

To increase the availability of medicines for children across the Community, because the requirements in the proposals are linked to Community-wide rewards and to prevent the distortion of free trade within the Community, it is proposed that an application for a marketing authorisation including at least one paediatric indication based on the results of an agreed paediatric investigation plan will have access to the centralised Community procedure. To provide healthcare professionals and patients with important information on the safe and effective use of medicines in children and as a transparency measure, it is proposed that information regarding the results of studies in children (whether positive or negative – negative information having an important public health impact), as well as, information on the status of the paediatric investigation plans, waivers and deferrals be included in product information. It is also proposed that when all the measures in the paediatric investigation plan have been complied with, this fact is recorded in the marketing authorisation. This will then be the basis upon which companies can obtain the rewards/incentives for compliance described below. Medicines authorised for children following an agreed paediatric investigation plan will include a superscript of the letter “P” after the name. This is proposed to aid recognition of medicines specifically developed for children and therefore to facilitate prescribing of such medicines.

The Paediatric Use Marketing Authorisation (PUMA)

In order to establish a vehicle for providing incentives for off-patent medicines, a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA) is proposed. A PUMA will utilise existing marketing authorisation procedures but is specifically for medicinal products developed exclusively for use in children. The name of the medicinal product granted a PUMA can utilise the existing brand name of the corresponding product authorised for adults but the product names of all medicines granted a PUMA will include a superscript of the letter “P” (to aid recognition and prescribing). By allowing retention of the existing brand name, pharmaceutical companies will be able to capitalise on existing brand recognition while benefiting from the data protection associated with a new marketing authorisation (10 years). The data protection period associated with the PUMA may prove more valuable in light of the recent case law of the European Court of Justice concerning the interpretation of data protection rules¹⁶.

An 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 refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community (according to the conditions specified in Article 14(11) of Regulation (EC) 726/2004 and in Article 10 of Directive 2001/83/EC). For the first time, therefore, it will be possible to submit new data in an otherwise generic-type application.

Optional centralised procedure (Article 30 of the procedure)

¹⁶ Case C-106/01, Novartis Pharmaceuticals UK, judgment of 29 April 2004, not yet reviewed.

In order to allow the straightforward and rapid introduction of information relevant to the use of a medicinal product in the paediatric population into the national summary of product characteristics, it is proposed that an applicant may use the existing procedure set out on Article 32, 33 and 34 of Directive 2001/83/EC. This will lead to an opinion of the CHMP specifically on use of the medicine in children leading to a Community Decision harmonising a priori – national marketing authorisations and allowing the introduction of relevant information in all national product information. In that case no decentralised procedure will then be necessary prior to this intervention of CHMP.

Placing a medicinal product on the market

When an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other indications, it is proposed that the marketing authorisation holder be obliged to place the product on the market taking into account the paediatric information within two years following the date of approval of the indication. This measure will increase access of the Community population to new medicinal products tested and adapted for paediatric use, and minimise the chance of community-wide rewards being granted without the paediatric population benefiting from the availability of a newly authorised medicine. It should be noted that this requirement only relates to products already authorised and therefore does not apply to medicines authorised via a PUMA. As a PUMA is linked to an incentive that is only realised if the product is marketed, such a requirement to market is not necessary in terms of providing a check on the awarding of the incentive and could actually prove to be a disincentive.

Robust pharmacovigilance, risk management systems, long-term efficacy and post-authorisation studies

Pharmacovigilance involves the monitoring of the safety of marketed medicines and taking action to minimise risks from medicines and maximise benefits. It is essential to ensure that pharmacovigilance mechanisms are adapted, in specific cases, to meet the challenges of collecting robust safety data in children, including data on possible long-term effects. In addition, there may be situations where information on the efficacy, particularly long-term efficacy of a medicine is needed post authorisation. Therefore, an additional requirement is proposed for applying for a marketing authorisation that includes the results of an agreed paediatric investigation plan: an obligation for the applicant to indicate how he/she proposes to ensure the long-term follow-up of efficacy and possible adverse reactions to the use of the medicinal product in the paediatric population. Additionally, where there is particular cause for concern, the applicant may be required to submit and implement a risk management system and/or perform specific post-marketing studies as a condition of the marketing authorisation. It is proposed that the EMEA draw up detailed guidance relating to paediatric pharmacovigilance to support these important public health measures.

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

This proposed measure will share the burden of the costs of the requirements between the industry and society at large, will minimise non-compliance with the requirements by the industry, will stimulate innovation in medicines development and will stimulate the development of the EU-based pharmaceutical industry.

The SPC is an EU wide instrument that compensates the pharmaceutical industry for the extensive and time consuming research, development and authorisation required before a patented medicinal product can be placed on the market. These existing requirements are clearly necessary to protect public health but mean that patents may have run out or be of only limited duration by the time a product reaches the market. The SPC can be viewed as a method of EU-wide patent extension to prevent the public health requirements from blocking

innovation. Extension of the SPC is therefore a logical, EU-wide mechanism by which the requirements for studies in children can be rewarded and incentivised.

For products covered by a patent or a SPC, if all the measures included in the agreed paediatric investigation plan are complied with, if the product is authorised in all Member States and if relevant information on the results of studies is included in product information, the six-month SPC extension will be granted. The mechanism for this will be the inclusion of a statement in the marketing authorisation that these measures have been met. Companies will then be able to present the marketing authorisation to patent offices that will then award the SPC extension.

The need to have a marketing authorisation in all Member States is to prevent a Community-wide reward without Community-wide benefits to child-health. Because the reward is for conducting studies in children and not for demonstrating that a product is safe and effective in children, the reward will be granted even when a paediatric indication is not granted. However, relevant information on use in paediatric populations will have to be included in authorised product information, to improve the information available on the use of medicines in the paediatric populations and to better protect public health.

Extended market exclusivity for orphan medicinal products

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 it is proposed 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. By the time these proposals come into force, all orphan designated medicinal products will have to go through the centralised procedure.

Paediatric study program: Medicines Investigation for the Children of Europe (MICE)

An additional tool for promoting high quality, ethical research that may lead to the development and authorisation of medicines for children 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. Funding is considered necessary as the return from investment for off-patent medicines is more limited than for patent-protected medicines and the data protection associated with the PUMA, although a valuable IPR, does not guarantee market exclusivity. A reference is included in the proposal to creating a paediatric study program: Medicines Investigation for the Children of Europe (MICE). The setting up of the program and its operation will be included in separate initiative. As the measures contained in these present proposals are not directly dependent on the paediatric study program, the children of Europe will gain most through the rapid introduction of the measures in this proposal, with the paediatric study program being added later, as soon as possible. Furthermore, a number of the measures included in this proposal, including the inventory of therapeutic needs of children (by identifying research priorities) and the creation of a network for the performance of clinical trials (to facilitate the conduct of studies) will lay the foundation for the operation of the paediatric study program. The CHMP's existing ad-hoc Paediatric Expert Group has drawn up a provisional list of paediatric priorities for off-patent medicines. This provisional list contains 65 active substances and provides a measure of the scale of research that needs priority funding and the scope of products to be targeted.

Eligibility for other incentives and inventory of incentives

The proposals do not preclude access of medicines being developed for children to other incentives or rewards not contained in this proposal. It will be up to the Community and the Member States, within their respective spheres of competence, to provide other incentives for developing medicinal products for paediatric use.

It is proposed that the Commission will draw up a detailed list of all the incentives available, on the basis of information provided by the Member States.

The measures set out in this regulation, including the agreement of paediatric investigation plans will not be grounds for obtaining any other Community incentives to support research, such as the funding of research projects under the multi-annual Community Framework Programs for Research, Technological Development and Demonstration Activities.

Information on clinical trials

One of the objectives of these proposals is to increase the information available on the use of medicines for children. Through increased availability of information, the safe and effective use of medicines for children can be increased so promoting public health. In addition, availability of this information will help prevent the duplication of studies in children and the conduct of unnecessary studies in children. One of the measures proposed to meet this objective is to build on the public health work of the Clinical Trials Directive. The Clinical Trials Directive establishes a Community database of clinical trials (EudraCT). It is proposed to build onto this database an information resource of all ongoing and terminated paediatric studies conducted both in the Community and in third countries. It is proposed that the Commission draw up detailed guidance on the nature of the information to be included in the database.

Survey of existing uses and inventory of therapeutic needs

An additional public health information resource is proposed. Based on a survey of existing use of medicines in Europe, conducted by the Member States and coordinated by the EMEA and Paediatric Committee, an inventory of therapeutic needs of children will be adopted by the Paediatric Committee. This inventory will be regularly updated and should include information on paediatric formulations (for which input from pharmacists will be needed). The inventory will identify the existing medicines used by children, highlight the therapeutic needs of children and the priorities for the research and development of medicines for children. In this way, companies will be able to easily identify opportunities for business development, the Paediatric Committee will be able to better judge the need for medicines and studies when assessing draft paediatric investigation plans, waivers and deferrals, and healthcare professionals and patients will have an information source available to support their decisions on which medicines to choose.

Community network for the performance of clinical trials

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. It is proposed to create a Community network to link together existing national networks and clinical trial centres in order to build up the necessary competences at a European level and to facilitate the conduct of studies including clinical trials, to increase co-operation and avoid duplication of studies. The EMEA and Paediatric Committee will be charged with adopting an implementing strategy to establish this network. This will contribute to the work of strengthening the foundations of the European Research Area and should benefit the paediatric clinical trial population and act as a resource for industry.

Submission of results from existing studies

Pharmaceutical companies have, in some cases, already conducted clinical trials in children. However, frequently, the results of these studies have not been submitted to Competent Authorities and have not resulted in updates to product information that would have benefited public health through the increased availability of information on the use of medicines in children. It is particularly unfortunate that companies have not submitted data in the EU generated as a result of the requirements and incentives already in place in the US. To deal with this issue, it is proposed that any studies completed before this proposed legislation is adopted will not be eligible for the rewards and incentives proposed for the EU. These studies will, however, be taken into account for the requirements contained in the proposals and it will be mandatory for companies to submit the studies to the competent authorities once this proposed legislation is adopted. The studies can then be assessed by the competent authorities and, when appropriate, product information can be updated (for example with new dosing instructions for children) to the benefit of public health.

EMEA Community subsidy

The proposals presented will place demands on competent authorities and particularly on the EMEA. It is proposed that a new specific Community subsidy, distinct from that allocated through existing legislation be allocated to the EMEA. Such subsidy will cover all aspects of the operation of this legislative proposal including the operation of the Paediatric Committee and the experts that support it, the assessment of paediatric investigation plans, fee waivers foreseen for scientific advice and the information and transparency measures (including the database of paediatric studies and the network) proposed. A financial statement accompanies this proposal.