

# **Regulation on medicines for children: frequently asked questions**

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## **Introductory questions**

### **What is the proposal on medicines for children, what is the objective?**

On 29 September 2004, the European Commission adopted a proposal for a regulation of the Council and the European Parliament on medicinal products for paediatric use. The overall objective is to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children. This will be achieved through: increasing the development of medicines for use in children, ensuring that medicines used to treat children are subject to high quality research, ensuring that medicines used to treat children are appropriately authorised for use in children, and, improving the information available on the use of medicines in children.

### **Where can I find an overview of the proposal?**

An overview and explanation of the proposal can be found [Here](#).

### **What did the Commission do to develop its proposal?**

A Council resolution in December 2000 invited the Commission to find solutions to the issue of inadequate medicines for children. The Commission has intensively researched the problem and potential solutions. Part of the research has included study of how other regions are tackling this issue and how regulation has dealt with similar but distinct problems such as how to stimulate the development and authorisation of medicines for rare diseases (orphan medicines).

Because of the complexity of healthcare delivery and the pharmaceutical sector, the Commission has conducted a detailed assessment of the social, economic and environmental impacts of its proposal on the different stakeholders involved (e.g. children and their families, healthcare workers, the pharmaceutical industry and those that pay for medicines). The results of the 'Extended Impact Assessment' show that the proposal will lead to the availability of more and better medicines for children and that the pharmaceutical industry will benefit through increased innovation (see [HERE](#)).

### **When will this become law?**

The proposal has been delivered to the Council and the European Parliament where it will go through the co-decision procedure. The earliest that the proposal is likely to become law is late 2006.

### **Where can I find the proposed regulation?**

The text of the proposal in all 20 official EU languages can be found [HERE](#).

### **Why does action need to be taken at a European level?**

The problem of the lack of authorised medicinal products for paediatric use is in part due to the small number of patients concerned (c.f. adults) 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 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 trial 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.

## **The issues to be addressed**

### **Why do we need a proposal?**

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 for use in children and are not authorised for use in children. Why should this matter? The answer is clear: the health of the children of Europe is suffering 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 can not be sure the medicine will be effective, can not be sure what dose is appropriate and can not predict what adverse reactions (side effects) 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. Innovative medicines can and do save lives and the children of Europe deserve at least the same access to such innovation as that enjoyed by adults.

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 leaves no alternative to the prescriber than to use 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. This is particularly ironic considering that our modern system of medicines regulation, that ensures the high standards of safety, quality and efficacy necessary for the authorisation of medicinal products for use in adults, was developed primarily in response to therapeutic disasters, such as the thalidomide tragedy of the 1950s and 60s, that occurred in children. Yet today children continue to be exposed to risks, and at the same time miss out on therapeutic advances.

### **How has this situation arisen?**

Industry has a free choice on what medicines to develop, and if successful, 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 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 into 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.

### **What are typical diseases for which there are no children specific medicines available?**

Almost all areas of paediatric medicine lack products that have been researched and authorised. In the case of newborns, there are almost no products authorised and the situation is the most serious.

To give a few examples, major needs exist in :

- infectious diseases (meningitis, tuberculosis, AIDS),
- rheumatology (arthritis),
- cardiac diseases (cardiac insufficiency and rhythm disorders),
- vascular diseases (hypertension, renal diseases),
- diabetes,
- asthma,
- gastroenterology (reflux disease, inflammatory bowel diseases),
- dermatology (allergic disorders),
- neurology (epilepsy, migraine, mental retardation),
- psychiatry (autism, psychosis, depression),
- metabolic diseases (hyperlipidaemia),
- ophthalmology (glaucoma),
- anaesthetics, and
- malaria.

### **What is the experience gained in the United States?**

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.

## Key measures

### What are the key measures proposed?

The key measures included in the draft paediatric regulation are:

#### *Newer medicines*

- 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;

#### *Older medicines*

- a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (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 initiative, of an EU paediatric study program Medicines Investigation for the Children of Europe (MICE) to fund research leading to the development and authorisation of off-patent medicine for children;

#### *Old and new medicines*

- the establishment of an expert committee, the Paediatric Committee within the EMEA;
- measures to increase the robustness of pharmacovigilance (safety monitoring) for medicines marketed for children;
- a requirement for industry to submit to the authorities study reports they already hold on use of their medicines 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 research and development on medicines for children;
- a system of free scientific advice for the industry, provided by the European Medicines Agency (EMA);
- a database of paediatric studies;

### What is 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 EMEA. 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 may 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.

### **What is a Paediatric Investigation Plan?**

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.

### **What are the Marketing authorisation requirements?**

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 [HERE](#)).

Simple procedures are proposed for agreeing paediatric investigation plans, as well as, requests for deferrals and waivers . 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 of children into studies and the implications of the results of one study to another cannot always be predicted in advance.

### **What are waivers?**

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.

### **What are deferrals?**

The 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.

### **How will companies be rewarded – non-orphan products?**

Companies complying fully with the requirements for new medicines (or line extensions of existing patented medicines) will be rewarded with a 6-month extension 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.

### **How will companies be rewarded – orphan products?**

Companies complying fully with the requirements for new orphan medicines will be rewarded with two-years extra market exclusivity. 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.

### **What is the 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 rules<sup>1</sup>.

An additional incentive applied to the PUMA that may prove particularly powerful at attracting small and medium-sized enterprises (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.

### **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

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<sup>1</sup> Case C-106/01, Novartis Pharmaceuticals UK, judgment of 29 April 2004, not yet reviewed.

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, but 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 Committee on Human Medicinal Product'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.

#### **What about 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. This free scientific advice might focus on more detailed questions on the design of specific studies.

#### **What will the effect be on 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.

### **Explain the Optional centralised procedure (Article 30 of the proposal)?**

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, the ‘optional centralised procedure’ is proposed. For line extensions including paediatric data of nationally authorised products (including those authorised via the Mutual Recognition procedure) 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.

### **What are the marketing requirements?**

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.

### **What about post-authorisation requirements?**

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.

**Will paediatric medicines be eligible for other 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.

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.

**Will there be an inventory of incentives?**

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.

**Will information on clinical trials be collated?**

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.

**What are the 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.

**What is the 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, should benefit the paediatric clinical trial population and act as a resource for industry.

**Will companies have to submit the 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.

**Will this proposal require funding from the European Community?**

The proposals presented will place demands on competent authorities and particularly on the EMEA. It is proposed that a Community subsidy 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 (HERE).



## **Justification of policy choices**

### **Why have a system of requirements and rewards?**

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.

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.

### **Why extend the supplementary protection certificate and why by 6-months?**

Extension of the supplementary protection certificate (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.

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 the far simpler system based on the existing EU-wide instrument: the supplementary protection certificate.

### **Why have a different reward for orphan medicines?**

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 an additional two years of the market exclusivity foreseen in Regulation (EC) No 141/2000 on orphan medicinal products (HERE for details). 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.

### **Why data protection rather than market exclusivity 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, 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.

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. 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 rules<sup>2</sup>. 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 a separate initiative.

### **What are the checks and balances in the proposal?**

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

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<sup>2</sup> Case C-106/01, Novartis Pharmaceuticals UK, judgment of 29 April 2004, not yet reviewed.

## **Extended Impact Assessment**

### **What is an Extended Impact Assessment?**

This proposal has been the subject of a Commission extended impact assessment of the proposal overall and the specific measures included. An extended impact assessment assesses the economic, social and environmental effects of the proposal on the key stakeholder groups. 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.

### **Where can I find a copy of the Extended Impact Assessment?**

The Extended Impact Assessment can be found at [HERE](#).

### **Overall, what will the impact be on stakeholders?**

The advantages of the 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 social and 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 paediatric regulation:

- the six-month Supplementary Protection Certificate (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 will lead to the creation of new companies within the EU.
- 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.

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. 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 profit across the entire generics sector of between 4 and 51 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.

### **What will be the costs to industry?**

There are obviously costs associated with the proposal. The requirements for phase III clinical trials in children will cost industry an average of 4 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.

### **What is the economic benefit to companies of getting the 6 months extension to their patent protection?**

The proposal provides major benefits and incentives for the industry. The six-month extension of the Supplementary Protection Certificate (in effect 6-months patent extension) will allow the industry to make a profit (i.e. after the costs of conducting studies have been deducted) estimated at between 0.8 and 9.1 million Euros per product, which will provide an incentive for further research. In addition, the data generated to satisfy the EU requirements can be used to support marketing authorisation applications outside the EU.

### **Will the proposal also benefit small and medium sized pharmaceutical companies?**

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. Once adopted, the Regulation will not only improve the health of the children of Europe: it will also stimulate innovation for existing medicines for adults, boost pharmaceutical research and development in the EU and provide new business opportunities, both for multinationals and for small and medium-sized enterprises.

The proposal contains a number of measures that bring potential benefits for small and medium-sized enterprises and could even lead to the creation of new companies within the EU. In particular, the new Paediatric Use Marketing Authorisation provides incentives to further develop products which are no-longer protected by patents or supplementary protection certificates. In this sector, characterised by a high percentage of small and medium-sized enterprises, the new authorisation will allow companies to capitalise currently unexploited niche markets and provides promising business opportunities for these enterprises.

Additional support for small and medium sized companies includes free scientific advice from the European Medicines Agency (EMA), a network of experts to conduct studies and an inventory of therapeutic needs of children to identify market opportunities.

### **What will be the effect on the generics industry?**

The Extended Impact Assessment has estimated that the six-month extension of the SPC will lead to the producers of generic medicines (across the entire sector) incurring a one-time loss of between €36 million and €42 million, which represents the value of market opportunities lost during the transitional period. The assumptions and caveats to be applied to these figures are provided in the full Extended Impact Assessment (HERE). 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 (HERE) 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.

## Consultation of stakeholders

### How did the Commission conduct its consultations?

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 during the Extended Impact Assessment
- Public consultation

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. HERE provides a summary list of the workshops and bilateral meetings held.

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 (EMA)

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)

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 and sent by e-mail to key stakeholder organisations.

Many of the comments on details of the draft paediatric regulation have been taken on board for the final proposal.

### Where can I find the results of the 2002 consultation?

A summary of the results of the consultation conducted in 2002 is available at [HERE](#).

### **Where can I find the results of the 2004 consultation?**

A summary of the results of the consultation conducted in 2004 is available at [HERE](#).

### **Could the new rules lead to a delay in the availability of new medicines for adults?**

The proposal will improve the availability of medicines for children without delaying market access of pharmaceuticals for adults. Indeed, specific measures are included in the proposal to ensure that delays do not occur. In general, the company has to submit results of studies performed in children in accordance with the paediatric investigation plan, when it applies for a marketing authorisation. But at the same time, the proposal ensures that the requirement for data in children do not block or delay the authorisation of medicines for other populations. A company may ask that the initiation or completion of some or all of the measures set out in the paediatric investigation plan be deferred to a later point in time. Such a deferral might be justified on scientific and technical grounds as well as on grounds related to public health. The proposal states explicitly that such deferral shall be granted, for example, when studies in the paediatric population will take longer to conduct than studies in adults.

### **The proposed rules will mean a lot more clinical trials in children: will children be at risk?**

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. The same is not true for medicines used to treat children. Over 50% of the medicines used in children may not have been studied in this age group. In fact, for many areas of paediatric medicines, there are few products assessed and authorised. Although there may be concerns about conducting trials in the paediatric population, this has to be balanced by the concerns about giving medicines to a population in which they have not been tested.

The new EU Directive on clinical trials (the so-called “Clinical Trials Directive”) lays down specific requirements to protect children who take part in clinical trials in the EU. In other words, the public health threat from the daily use across the EU of untested medicines in children can be safely addressed through the study of medicines for children, and this study is carefully controlled and monitored through the existing EU Clinical Trials Directive. Furthermore, there is evidence that individuals treated in clinical trials have a positive benefit compared with individuals treated outside of a trial.

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 all the children of the EU than to allow daily “experiments on children” that today occur in every medical clinic, in every Member State of the EU because medicines for children have never been tested for such use.

### **Could this important initiative not have come sooner?**

A Council Resolution of December 2000 called on the Commission to make proposals to ensure that medicinal products for children are fully adapted to the specific needs of children. Parliamentarians have also been highlighting the need for regulation to improve the research, development and authorisation of medicines for children.

Indeed, the health of our children is of utmost importance to all of us. It is a highly sensitive and at the same time very complex issue. The Commission had the ambition to present a well balanced and carefully thought-out proposal, responding at the same time to both the public health challenges and to the need for a stimulating regulatory environment for research and



innovation. For this reason, The Commission engaged on extensive research and consultation. In addition, The Commission decided to run an Extended Impact Assessment to get a clear picture of the impact of the proposed measures on all the key stakeholders.

Through this work The Commission is confident that the measures included in the proposed regulation will lead to better medicines for children, better health for the children of Europe and at the same time, opportunities for the European pharmaceutical industry.

### **Why does the proposal not require drugs that are already authorised (but not subject to patent protection) to undergo children-specific research?**

When it comes to medicines already authorised and on the market but not protected by intellectual property rights (IPRs), multiple companies usually market the same medicine and many of these companies will be generics manufacturers. Which company then should be compelled to do studies in children? Furthermore, for these medicines the stick of a requirement for studies in children cannot easily be linked to the carrot of extended IPRs.

For this reason the proposal takes another route to stimulate the necessary paediatric research in this area: We have developed a new type of authorisation, the Paediatric Use Marketing Authorisation or, PUMA. PUMAs will be for off-patent medicines specifically developed for use in children. This type of authorisation will cover use in children only. By establishing PUMAs this will lead to the development of medicines specifically for children by allowing a specific incentive of 10-years data exclusivity (also known as data protection). This data exclusivity will cover the data from the studies conducted specifically to develop the medicines for children. To further incentivise these older medicines the PUMA will allow, for the first time, “generic-type” marketing authorisation applications to be combined with the submission of new studies in children. In addition, companies will be able to use the existing brand name to aid brand recognition.

### **Why does the proposal not contain specific details setting up a study program (fund) for off-patent medicines?**

As the measures contained in these present proposals are not directly dependent on the paediatric study program (Medicines Investigation for the Children of Europe - MICE), 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, but as soon as possible.

The Explanatory Memorandum of the proposal makes a clear reference to the intension of the Commission to develop an initiative to fund studies leading the authorisation of off-patent medicines. This initiative will be separate from the proposed regulation on medicinal products for paediatric use, as:

- The details of the funding and the operation of MICE will require further discussions with stakeholders.
- It is predicted that the funding of MICE will stimulate extensive debate in both the Council and the Parliament. This extensive debate could delay the other measures in the proposed regulation on medicinal products for paediatric use.
- A number of measures in the proposed regulation need to be in place before MICE can operate (e.g. the Paediatric Committee, the inventory of therapeutic needs of children, the network for the conduct of clinical trials etc.).

### **Will the proposals affect doctor’s freedom to prescribe?**

No: the proposal is to regulate the pharmaceutical industry and not doctors. Doctors will remain free to prescribe whatever available treatment they judge to be best for an individual child.