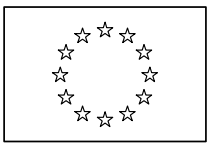

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 29.9.2004
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2004/0217 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004

(presented by the Commission)

{SEC(2004) 1144}

EXPLANATORY MEMORANDUM

1. INTRODUCTION AND BACKGROUND

The public health concern and its causes

The paediatric population is a vulnerable group with developmental, physiological and psychological differences from adults, which makes age and development related research of medicines particularly important. In contrast to the situation in adults, 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.

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, the EU Directive on clinical trials[1] lays down specific requirements to protect children who take part in clinical trials in the EU.

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.

In the US, specific legislation to encourage the performance of clinical trials in children has been introduced, containing combined measures of incentives and obligations which have proven successful in stimulating the development of medicinal products for paediatric use.

Council Resolution

The Council Resolution of 14 December 2000 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.

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; to ensure that medicines used to treat children are subject to high quality research; to ensure that medicines used to treat children are appropriately authorised for use in children; to improve

[1] OJ L 121, 1.5.2001, p. 34.

the information available on the use of medicines in children, and; to achieve these objectives without subjecting children to unnecessary clinical trials and in full compliance with the EU Clinical Trials Directive.

Scope, legal basis and procedure

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

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 includes 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 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 in this field 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 justified at a European level with a view to preventing or eliminating these obstacles.

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. 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.

Community action allows the best possible use of the instruments set up in the pharmaceutical sector to complete the internal market. In addition, authorisation of medicines for children is a Europe-wide issue. However, Member States will have an important role in the fulfilment of the objectives of the proposal.

Legislative and administrative simplification

All the key measures in the proposal build on or strengthen the existing framework for the regulation of medicinal products. This proposal directly interfaces with five existing Community legislative texts: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001[2] which sets the framework for the regulation of medicinal products; Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004[3] which establishes the European Medicines Agency (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 2001 which provides a framework for the regulation and conduct of clinical trials in the Community; Regulation (EC) No 141/2000 of

[2] OJ L 311, 28.11.2001 p. 67.
[3] OJ L 136, 30.4.2004 p. 1.

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[4] and; Council Regulation (EEC) No 1768/92 of 18 June 1992[5] which created the Supplementary Protection Certificate.

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 EMEA and the parties concerned.

Consistency with other Community policies

Consistency will be sought with activities in the areas of research and development and health and consumer protection.

Outside consultation

Interested parties have been widely consulted on this proposal. Detail on the consultation conducted by the Commission is included in the Extended Impact Assessment that accompanies this proposal.

Evaluation of the proposal: Extended impact assessment

This proposal has been the subject of a Commission extended impact assessment, attached to this proposal, which is based on data collected by an independent contracted study.

3. PRESENTATION

A brief description of the main elements of the proposal is hereby provided. For a more detailed description, we refer to the Commission's explanatory document attached to this proposal.

Key measures included in the proposal

The Paediatric Committee

A committee with expertise in all aspects related to medicines for children is central to the proposal and its operation. 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 it may assess compliance with paediatric investigation plans and be asked to assess the results of studies. In all its work it will consider the potential significant therapeutic benefits of studies in children including the need to avoid unnecessary studies, it will follow existing Community requirements and will avoid any delay in the authorisation of medicines for other populations as a result of the requirements for studies in children.

[4] OJ L 18, 22.1.2000, p. 1.
[5] OJ L 182, 2.7.1992, p. 1.

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

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 core requirement has been included to ensure that medicines are developed for children based on their therapeutic needs. The paediatric investigation plan will be the basis upon which compliance with this requirement is judged.

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. The Paediatric Committee will start work as soon as it is set up, on lists of waivers of specific medicinal products and classes of medicinal product. For products not included in the published lists, a simple procedure is proposed for companies to request waivers.

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

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. Therefore, to deal with this situation, a system of deferrals is proposed together with a procedure for agreeing them with the Paediatric Committee.

Marketing authorisation procedures

The procedures set out in existing pharmaceutical legislation are not altered by the proposals. The requirements above will require the Competent Authorities to check compliance with the agreed paediatric investigation plan 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. 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.

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. Thus, pharmaceutical companies will be able to capitalise on existing brand recognition while benefiting from the data protection associated with a new marketing authorisation. 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[6].

An application for a PUMA will require the submission of data necessary to establish safety, quality and efficacy specifically in children, collected in accordance with an agreed paediatric investigation plan. 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.

Extension of the duration of the supplementary protection certificate

For new medicines and for products covered by a patent or a Supplementary Protection Certificate (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.

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.

Paediatric study programme: 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 into the paediatric use of medicines not covered by a patent or a supplementary protection certificate. The Commission intends to examine the possibility of setting up a

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

paediatric study programme: Medicines Investigation for the Children of Europe, taking into consideration existing Community Programmes.

Information on the use of medicines for children

One of the objectives of this proposal 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 with help prevent the duplication of studies in children and the conduct of unnecessary studies in children.

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.

In addition, based on a survey of existing use of medicines in Europe, an inventory of therapeutic needs of children will be established by the Paediatric Committee.

It is also proposed to create a Community network to link together 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, to increase co-operation and avoid duplication of 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. 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. They 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.

Other measures

The interface between the Committee for Medicinal Products for Human Use, its Scientific Advice Working Group and other Community committees and working groups on medicines and the Paediatric Committee will be managed by the EMEA. In addition, free scientific advice from the EMEA to sponsors developing medicines for children is proposed.

The proposals presented will place demands on competent authorities and particularly on the EMEA. It is proposed to increase the Community subsidy, to be allocated to the EMEA to take account of the new tasks. A financial statement accompanies this proposal.

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(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission[1],

Having regard to the Opinion of the European Economic and Social Committee[2],

Having regard to the Opinion of the Committee of the Regions[3],

In accordance with the procedure referred to in Article 251 of the Treaty[4],

Whereas:

(1) Before a medicinal product for human use is placed on the market of one or more Member States, it generally has to have undergone extensive studies, including pre-clinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population.

(2) Such studies may not have been done for use in children and many of the medicines currently used to treat children have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research, development and authorisation of medicines for children.

(3) Problems resulting from the absence of suitably adapted medicines for children include inadequate dosing information leading to increased risks of adverse reactions including death, ineffective treatment through under-dosing, non-availability to children of therapeutic advances, as well as the use of extemporaneous formulations to treat children which may be of poor quality.

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1 OJ C […], […], p. […].
2 OJ C […], […], p. […].
3 OJ C […], […], p. […].
4 OJ C […], […], p. […].

(4) The aim of this Regulation is to increase the development of medicines for use in children, to ensure that medicines used to treat children are subject to high quality, ethical research and are appropriately authorised for use in children, and to improve the information available on the use of medicines in the various paediatric populations. These objectives should be achieved without subjecting children to unnecessary clinical trials and without delaying the authorisation of medicinal products for other populations.

(5) While taking into account the fact that any regulations on medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the free movement of medicinal products within the Community. 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. Article 95 of the Treaty is therefore the proper legal basis.

(6) The establishment of a system of both obligations and rewards and incentives has proved necessary to achieve these objectives. The precise nature of the obligations and rewards and incentives should take account of the status of the particular medicinal product concerned. This Regulation should apply to all the medicines required by children and therefore its scope should cover products in development and yet to be authorised, authorised products still covered by intellectual property rights and authorised products no longer covered by intellectual property rights.

(7) Any concerns about conducting trials in the paediatric population should be balanced by the ethical concerns about giving medicines to a population in which they have not been tested. The public health threat from the use of untested medicines in children can be safely addressed through the study of medicines for children, which should be carefully controlled and monitored through the specific requirements for the protection of children who take part in clinical trials in the Community laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[5].

(8) It is appropriate to create a scientific committee, the Paediatric Committee, within the European Medicines Agency, hereinafter 'the Agency', with expertise and competence in the development and assessment of all aspects of medicinal products to treat paediatric populations. The Paediatric Committee should be primarily responsible for the assessment and agreement of paediatric investigation plans and for the system of waivers and deferrals thereof, and it should also be central to various support measures contained in this Regulation. In all its work the Paediatric Committee should consider the potential significant therapeutic benefits of studies in children including the need to avoid unnecessary studies. It should follow existing Community requirements, including Directive 2001/20/EC, as well as International Conference on Harmonisation (ICH) guideline E11 on the development of medicines for children, and

[5] OJ L 121, 1.5.2001, p. 34.

it should avoid any delay in the authorisation of medicines for other populations as a result of the requirements for studies in children.

(9) Procedures should be established for the Agency to agree and modify a paediatric investigation plan, the document upon which the development and authorisation of medicines for children should be based. The paediatric investigation plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. Because the paediatric population is in fact made up of a number of subpopulations, the paediatric investigation plan should specify which subpopulations need to be studied, by what means and by when.

(10) The introduction of the paediatric investigation plan in the legal framework concerning medicinal products for human use aims at ensuring that development of medicines for children becomes an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during product development, in time for studies to be conducted in children before marketing authorisation applications are submitted.

(11) It is necessary to introduce a requirement for new medicinal products and for authorised medicinal products covered by a patent or a supplementary protection certificate to present the results of studies in children in accordance with an agreed paediatric investigation plan in order to obtain validation of a marketing authorisation application or an application for a new indication, new pharmaceutical form or new route of administration. The paediatric investigation plan should be the basis upon which compliance with that requirement is judged. However, that requirement should not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established medicinal use procedure, or to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[6].

(12) In order to ensure that research in children is only conducted to meet their therapeutic needs, there is a need to establish procedures for the Agency to waive that requirement for specific products or for classes or part of classes of medicinal products, to be then published by the Agency. As knowledge on science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, the requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in children to be initiated prior to marketing authorisation application.

(13) In certain cases, the Agency should defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan, with a view to ensuring that research is done only when it is safe and ethical to do so and that the requirement for study data in children does not block or delay the authorisation of medicines for other populations.

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[6] OJ L 311, 28.11.2001, p. 67. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34.)

(14) Free scientific advice should be provided by the Agency as an incentive to sponsors developing medicines for children. To ensure scientific consistency, the Agency should manage the interface between the Paediatric Committee and the Scientific Advice Working Group of the Committee for Medicinal Products for Human Use , as well as the interaction between the Paediatric Committee and the other Community committees and working groups concerning medicinal products.

(15) The existing procedures for the marketing authorisation of medicinal products for human use should not be changed. However, it follows from the requirement for the results of studies in children to be presented in accordance with an agreed paediatric investigation plan that competent authorities should check compliance with the agreed paediatric investigation plan and any 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 should remain the remit of the competent authorities. Provision should be made for the possibility of asking the Paediatric Committee for an opinion on compliance and for an opinion on the safety, quality and efficacy of a medicine in children.

(16) To provide healthcare professionals and patients with information on the safe and effective use of medicines in children and as a transparency measure, information regarding the results of studies in children, as well as on the status of the paediatric investigation plans, waivers and deferrals, should be included in product information. When all the measures in the paediatric investigation plan have been complied with, that fact should be recorded in the marketing authorisation, and should then be the basis upon which companies can obtain the rewards for compliance.

(17) To distinguish medicines authorised for use in children following completion of an agreed paediatric investigation plan and enable their prescription , provision should be made for the name of medicinal products granted an indication for use in children following an agreed paediatric investigation plan to include the letter “P” in blue lettering surrounded by the outline of a star, also in blue.

(18) In order to establish incentives for authorised products no longer covered by intellectual property rights, it is necessary to establish a new type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in children. It should be possible for the name of the medicinal product granted a Paediatric Use Marketing Authorisation to utilise the existing brand name of the corresponding product authorised for adults, in order to capitalise on existing brand recognition while benefiting from the data exclusivity associated with a new marketing authorisation.

(19) An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community. That is intended to provide an additional incentive to attract small and

medium sized enterprises, including generic companies, to develop off-patent medicines for children.

(20) This Regulation should include measures to maximise access of the Community population to new medicinal products tested and adapted for paediatric use, and minimise the chance of Community-wide rewards and incentives being granted without sections of the Community paediatric population benefiting from the availability of a newly authorised medicine. An application for a marketing authorisation, including an application for a Paediatric Use Marketing Authorisation, which contains the results of studies conducted in compliance with an agreed paediatric investigation plan should be eligible for the Community centralised procedure set out in Articles 5 to 15 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[7].

(21) When an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other indications, the marketing authorisation holder should 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. That requirement should relate only to products already authorised, but not to medicines authorised via a Paediatric Use Marketing Authorisation.

(22) An optional procedure should be established to make it possible to obtain a single Community-wide opinion for a nationally authorised medicinal product when data on children following an agreed paediatric investigation plan form part of the marketing authorisation application. To achieve this, the procedure set out in Articles 32 to 34 of Directive 2001/83/EC may be used. This will allow the adoption of a Community harmonised Decision on use of the medicinal product in children and its introduction in all national product information.

(23) It is essential to ensure that pharmacovigilance mechanisms are adapted to meet the specific challenges of collecting safety data in children, including data on possible long-term effects. Efficacy in children may also need additional study following authorisation. Therefore, an additional requirement for applying for a marketing authorisation that includes the results of studies conducted in compliance with an agreed paediatric investigation plan should be an obligation for the applicant to indicate how he proposes to ensure the long-term follow-up of possible adverse reactions to the use of the medicinal product and efficacy in the paediatric population. Additionally, where there is a particular cause for concern, provision is made for the possibility of requiring the applicant to submit and implement a risk management system and/or perform specific post-marketing studies as a condition of the marketing authorisation.

(24) For products falling within the scope of the requirement to submit paediatric data, 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

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[7] OJ L 136, 30.4.2004, p. 1.

results of studies is included in product information, a reward should be granted in the form of a 6-month extension of the Supplementary Protection Certificate created by Council Regulation (EEC) No 1768/92[8].

(25) Because the reward is for conducting studies in children and not for demonstrating that a product is safe and effective in children, the reward should be granted even when a paediatric indication is not authorised. However, to improve the information available on the use of medicines in the paediatric population, relevant information on use in paediatric populations should be included in authorised product information.

(26) Under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products[9], medicinal products designated as orphan medicinal products gain ten years of market exclusivity on the granting of a marketing authorisation for the orphan indication. As such products are frequently not patent-protected, the reward of Supplementary Protection Certificate extension cannot be applied and when they are patent-protected, such an extension would provide a double incentive. Therefore, for orphan medicinal products, instead of extension of the Supplementary Protection Certificate, the ten-year period of orphan market exclusivity should be extended to twelve years if the requirement for data on use in children is fully met.

(27) The measures provided for in this Regulation should not preclude the operation of other incentives or rewards. To ensure transparency on the different measures available at Community and Member State levels, the Commission should 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, should 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 Programmes for Research, Technological Development and Demonstration Activities.

(28) In order to increase the availability of information on the use of medicines in children, and to avoid the repetition of studies in children which do not add to the collective knowledge, the European database provided for in Article 11 of Directive 2001/20/EC should include an information resource of all ongoing, prematurely terminated, and completed paediatric studies conducted both in the Community and in third countries.

(29) An inventory of therapeutic needs of children should be adopted by the Paediatric Committee after consultation with the Commission, the Member States and interested parties, and regularly updated. The inventory should identify the existing medicines used by children and highlight the therapeutic needs of children and the priorities for research and development. In this way, companies should be able to identify easily opportunities for business development; the Paediatric Committee should 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 should have an information source available to support their decisions as to which medicines to choose.

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8 OJ L 182, 2.7.1992, p. 1. Regulation as last amended by the Act of Accession 2003.

9 OJ L 18, 22.1.2000, p. 1.

(30) 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. A network linking together existing national and European initiatives and study centres in order to build up the necessary competences at a European level, would help facilitating co-operation and avoiding duplication of studies. This network should contribute to the work of strengthening the foundations of the European Research Area in the context of Community Framework Programmes for Research, Technological Development and Demonstration Activities, benefit the paediatric population and provide a source of information and expertise for industry.

(31) For certain authorised products, pharmaceutical companies may already hold data on safety or efficacy in children. To improve the information available on the use of medicines in the paediatric populations, companies holding such data should be required to submit them to all competent authorities where the product is authorised. In this way the data can be assessed and, if appropriate, information should be included in the authorised product information aimed at healthcare professionals and patients.

(32) Community funding should be envisaged to cover all aspects of the work of the Paediatric Committee and of the Agency resulting from the implementation of this Regulation, such as the assessment of paediatric investigation plans, fee waivers for scientific advice, and information and transparency measures, including the database of paediatric studies and the network.

(33) The measures necessary for the implementation of this Regulation should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission[10].

(34) Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004 should therefore be amended accordingly,

HAVE ADOPTED THIS REGULATION:

TITLE I
Introductory provisions

CHAPTER 1
SUBJECT-MATTER AND DEFINITIONS

Article 1

This Regulation lays down rules concerning the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population, without subjecting children to unnecessary clinical trials and in compliance with Directive 2001/20/EC.

[10] OJ L 184, 17.7.1999, p. 23.

Article 2

In addition to the definitions laid down in Article 1 of Directive 2001/83/EC, the following definitions shall apply for the purposes of this Regulation:

(1) *paediatric population* means that part of the population aged between birth and 18 years;

(2) *paediatric investigation plan* means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population.

(3) *medicinal product authorised for a paediatric indication* means a medicinal product which is authorised for use in part or all of the paediatric population and in respect of which the details of the authorised indication are specified in the summary of the product characteristics drawn up in accordance with Article 11 of Directive 2001/83/EC.

CHAPTER 2
PAEDIATRIC COMMITTEE

Article 3

1. A Paediatric Committee is established within the European Medicines Agency set up under Regulation (EC) No 726/2004, hereinafter "the Agency".

   The Agency shall act as the secretariat of the Paediatric Committee and shall provide it with technical and scientific support.

2. Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply to the Paediatric Committee.

3. The Executive Director of the Agency shall ensure appropriate co-ordination between the Paediatric Committee and the Committee for Medicinal Products for Human Use, the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.

   The Agency shall draw up specific procedures for possible consultations between them.

Article 4

1. The Paediatric Committee shall be composed of the following members:

   (a) five members of the Committee for Medicinal Products for Human Use, appointed by the latter;

(b) one person appointed by each Member State whose national competent authority is not represented through the members appointed by the Committee for Medicinal Products for Human Use;

(c) six persons appointed by the Commission, on the basis of a public call for expressions of interest, in order to represent paediatricians and the interests of patient associations.

For the purposes of point (b), the Member States shall cooperate, under the coordination of the Executive Director of the Agency, in order to ensure that the final composition of the Paediatric Committee covers the scientific areas relevant to paediatric medicinal products, and including at least: pharmaceutical development, paediatric medicine, paediatric pharmacy, paediatric pharmacology, paediatric research, pharmacovigilance and ethics.

2. The members of the Paediatric Committee shall be appointed for a renewable period of three years. At meetings of the Paediatric Committee, they may be accompanied by experts.

3. The Paediatric Committee shall elect its Chairman from among its members for a term of three years renewable once.

4. The names and scientific qualifications of the members shall be published by the Agency.

Article 5

1. When preparing its opinions, the Paediatric Committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.

2. The Paediatric Committee shall draw up its own rules of procedure for the implementation of its tasks. The rules of procedure shall enter into force after receiving a favourable opinion from the Management Board of the Agency and, subsequently, from the Commission.

3. All meetings of the Paediatric Committee may be attended by representatives of the Commission, the Executive Director of the Agency or his representatives.

Article 6

Members of the Paediatric Committee and its experts shall undertake to act in the public interest and in an independent manner. They shall not have financial or other interests in the pharmaceutical industry that could affect their impartiality.

All indirect interests that could relate to the pharmaceutical industry shall be entered in a register held by the Agency which the public may consult. The register shall be updated annually.

Members of the Paediatric Committee and its experts shall declare at each meeting any specific interests which could be considered to be prejudicial to their independence with respect to the points on the agenda.

Members of the Paediatric Committee and its experts shall be required, even after their duties have ceased, not to disclose any information of the kind covered by the obligation of professional secrecy.

Article 7

1. The tasks of the Paediatric Committee shall include the following:

   (a) to assess the content of any paediatric investigation plan for a medicinal product submitted to it in accordance with this Regulation and formulate an opinion thereon;

   (b) to assess waivers and deferrals and formulate an opinion thereon;

   (c) at the request of the Committee for Medicinal Products for Human Use, a competent authority or the applicant, to assess compliance of the application for a Marketing Authorisation with the concerned agreed paediatric investigation plan and formulate an opinion thereon;

   (d) at the request of the Committee for Medicinal Products for Human Use or a competent authority, to assess any data generated in accordance with an agreed paediatric investigation plan and formulate an opinion on the quality, safety or efficacy of the medicinal product for use in the paediatric population;

   (e) to advise on the content and format of data to be collected for the survey referred to in Article 41 and to adopt an inventory of therapeutic needs as referred to in Article 42;

   (f) to support and advise the Agency on establishing the European network referred to in Article 43;

   (g) to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation;

   (h) to provide advice on any question related to medicinal products for paediatric use, at the request of the Executive Director of the Agency or the Commission.

2. When carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to the paediatric population.

TITLE II
Marketing authorisation requirements

CHAPTER 1
GENERAL AUTHORISATION REQUIREMENTS

Article 8

1. An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

   (a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

   (b) a decision of the Agency granting a product-specific waiver;

   (c) a decision of the Agency granting a class waiver;

   (d) a decision of the Agency granting a deferral.

   For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.

2. The documents submitted pursuant to paragraph 1 shall, cumulatively, cover all subsets of the paediatric population.

Article 9

In the case of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 8 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.

Article 10

Articles 8 and 9 shall not apply to products authorised under Articles 10, 10a, 13 to 16 or 16a to 16i of Directive 2001/83/EC.

Article 11

In consultation with the Member States, the Agency and other interested parties, the Commission shall draw up the modalities concerning the format and content which applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals must follow in order to be considered valid.

CHAPTER 2
WAIVERS

Article 12

1. Production of the information referred to in point (a) of Article 8(1) shall be waived for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:

   (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

   (b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;

   (c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. The waiver provided for in paragraph 1 may be issued with reference only to one or more specified subsets of the paediatric population, with reference only to one or more specified therapeutic indications, or with reference to a combination of both.

Article 13

The Paediatric Committee may of its own motion adopt an opinion, on the grounds set out in Article 12(1), to the effect that a class or a product-specific waiver, as referred to in Article 12(1), should be granted.

As soon as the Paediatric Committee adopts an opinion, the procedure laid down in Chapter 4 shall apply. In the case of a class waiver, only Article 26(4) shall apply.

Article 14

1. The applicant may, on the grounds set out in Article 12(1), apply to the Agency for a product-specific waiver.

2. Within 60 days of receipt of the application, the Paediatric Committee shall adopt an opinion as to whether or not a product-specific waiver should be granted.

Either the applicant or the Paediatric Committee may request a meeting during that 60-day period.

Whenever appropriate, the Paediatric Committee may request the applicant to supplement the particulars and documents submitted. Where the Paediatric Committee avails itself of this option, the 60-day time-limit shall be suspended until such time as the supplementary information requested has been provided.

3. As soon as the Paediatric Committee adopts an opinion, the procedure laid down in Chapter 4 shall apply. The Agency shall inform the applicant accordingly without delay. The applicant shall be informed of the reasons for the conclusion reached.

Article 15

1. The Agency shall maintain a list of all waivers.

2. The Paediatric Committee may, at any time, adopt an opinion advocating the review of a granted waiver.

In the case of a change affecting a product-specific waiver, the procedure laid down in Chapter 4 shall apply.

In the case of a change affecting a class waiver, Article 26(5) shall apply.

3. If a particular product-specific or class waiver is revoked, the requirement set out in Articles 8 and 9 shall not apply for 36 months from the date of its removal from the list of waivers.

CHAPTER 3
PAEDIATRIC INVESTIGATION PLAN

SECTION 1
REQUESTS FOR AGREEMENT

Article 16

1. Where the intention is to apply in accordance with points (a) or (d) of Article 8(1), a paediatric investigation plan shall be drawn up and submitted to the Agency with a request for agreement.

2. The paediatric investigation plan shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

Article 17

1. In the case of applications as referred to in Articles 8 and 9, the paediatric investigation plan shall be submitted with a request for agreement, unless otherwise justified, not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC, so as to ensure that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of the assessment of the marketing authorisation or other application concerned.

2. Within 30 days of receiving the request referred to in paragraph 1, the Agency shall verify the validity of the request and shall prepare a summary report for the Paediatric Committee.

3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until such time as the supplementary information requested has been provided.

Article 18

1. Within 60 days of receiving a proposed paediatric investigation plan which is valid, the Paediatric Committee shall adopt an opinion as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits justify the studies proposed.

   Within the same period, either the applicant or the Paediatric Committee may request a meeting.

2. Within the 60-day period referred to in paragraph 1, the Paediatric Committee may request the applicant to propose modifications to the plan, in which case the time-limit referred to in paragraph 1 for the adoption of the final opinion shall be extended for a maximum of 60 days. In such cases, the applicant or the Paediatric Committee may request an additional meeting during this period. The time-limit shall be suspended until such time as the supplementary information requested has been provided.

Article 19

As soon as the Paediatric Committee adopts an opinion, whether positive or negative, the procedure laid down in Chapter 4 shall apply.

Article 20

If, having considered a paediatric investigation plan, the Paediatric Committee concludes that Article 12(1)(a), (b) or (c) applies to the medicinal product concerned, it shall adopt a negative opinion under Article 18(1).

In such cases, the Paediatric Committee shall adopt an opinion in favour of a waiver under Article 13, whereupon the procedure laid down in Chapter 4 shall apply.

SECTION 2
DEFERRALS

Article 21

1. At the same time as the paediatric investigation plan is submitted under Article 17(1), a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan. Such deferral shall be justified on scientific and technical grounds or on grounds related to public health.

   In any case, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

2. On the basis of the experience acquired as a result of the operation of this Article, the Commission may adopt provisions in accordance with the procedure referred to in Article 51(2) to define further the grounds for granting a deferral.

Article 22

1. At the same time as the Paediatric Committee adopts a positive opinion under Article 18(1), it shall, of its own motion or following a request submitted by the applicant under Article 21, adopt an opinion, if the conditions specified in Article 21 are met, in favour of deferring the initiation or completion of some or all of the measures in the paediatric investigation plan.

   An opinion in favour of a deferral shall specify the time-limits for initiating or completing the measures concerned.

2. As soon as the Paediatric Committee adopts an opinion in favour of deferral, as referred to in paragraph 1, the procedure laid down in Chapter 4 shall apply.

SECTION 3
MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN

Article 23

If, after the decision agreeing the paediatric investigation plan, the applicant encounters difficulties with its implementation such as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee. The Paediatric Committee shall review these changes and adopt an opinion proposing their refusal or acceptance. As soon as the Paediatric Committee adopts an opinion, whether positive or negative, the procedure laid down in Chapter 4 shall apply.

SECTION 4
COMPLIANCE WITH THE PAEDIATRIC INVESTIGATION PLAN

Article 24

The Paediatric Committee may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan:

(a) by the applicant, prior to submitting an application for marketing authorisation or variation as referred to in Articles 8 and 9, respectively;

(b) by the Agency, or the competent authority, when validating an application, as referred to in point (a), which does not include an opinion concerning compliance adopted following a request under point (a);

(c) by the Committee for Medicinal Products for Human Use, or the competent authority, when assessing an application, as referred to in point (a), where there is doubt concerning compliance and an opinion has not been given already following a request under points (a) or (b).

Member States shall take account of such an opinion.

If the Paediatric Committee is asked to give an opinion under the first paragraph, it must do so within 60 days of receiving the request.

Article 25

If, when conducting the scientific assessment of a valid application, the competent authority concludes that the studies are not compliant with the agreed paediatric investigation plan, the product shall not be eligible for the rewards provided for in Articles 36 and 37.

CHAPTER 4
PROCEDURE

Article 26

1. Within 30 days of receiving the opinion of the Paediatric Committee, the applicant may submit to the Agency a written request, on detailed grounds, for a re-examination of the opinion.

2. Within 30 days of receiving a request for re-examination pursuant to paragraph 1, the Paediatric Committee, having appointed a new rapporteur, shall issue a new opinion confirming or revising its previous opinion. The opinion shall be duly reasoned and a statement of reasons for the conclusion reached shall be annexed to the new opinion, which shall become definitive.

3. If, within the 30-day period referred to in paragraph 1, the applicant does not request re-examination, the opinion of the Paediatric Committee shall become definitive.

4. The Agency shall adopt a decision without delay. This decision shall be communicated to the applicant.

5. In the case of a class waiver as referred to in Article 13, the Agency shall adopt a decision, which shall be published.

CHAPTER 5
MISCELLANEOUS PROVISIONS

Article 27

The sponsor of a medicinal product intended for paediatric use may, prior to the submission of a paediatric investigation plan and during its implementation, request advice from the Agency 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 in accordance with Article 57(1)(n) of Regulation (EC) No 726/2004.

In addition, the sponsor may request advice on the design and conduct of pharmacovigilance and risk management systems as referred to in Article 35.

The Agency shall provide advice under this Article free of charge.

TITLE III

Marketing authorisation procedures

Article 28

Save where otherwise provided in this Title, marketing authorisation procedures for the marketing authorisations covered by this Title shall be governed by the provisions laid down in Regulation (EC) No 726/2004 or in Directive 2001/83/EC.

CHAPTER 1
MARKETING AUTHORISATION PROCEDURES FOR APPLICATIONS FALLING WITHIN THE SCOPE OF ARTICLES 8 AND 9

Article 29

1. Applications may be submitted in accordance with the procedure laid down in Articles 5 to 15 of Regulation (EC) No 726/2004 for a marketing authorisation as referred to in Article 8(1) of this Regulation which includes one or more paediatric

indications selected on the basis of studies conducted in compliance with an agreed paediatric investigation plan.

Where authorisation is granted, the results of those studies shall be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product, whether or not all the paediatric indications concerned were approved.

2. Where a marketing authorisation is granted or varied, any waiver or deferral which has been granted pursuant to this Regulation shall be recorded in the summary of product characteristics and if appropriate, the package leaflet of the medicinal product concerned.

3. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the competent authority shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan.

Article 30

In the case of medicinal products authorised under Directive 2001/83/EC, an application as referred to in Article 9 of this Regulation may be submitted, in accordance with the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC, for authorisation of a new indication, including the extension of an authorisation for use in the paediatric population, a new pharmaceutical form or a new route of administration.

That application shall comply with the requirement laid down in point (a) of Article 8(1).

The procedure shall be limited to the assessment of the specific sections of the summary of product characteristics to be varied.

CHAPTER 2
PAEDIATRIC USE MARKETING AUTHORISATION

Article 31

1. For the purposes of this Regulation, a paediatric use marketing authorisation shall mean a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

2. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other indications.

3. An application for a paediatric use marketing authorisation shall be accompanied by the particulars and documents necessary to establish safety, quality and efficacy in children, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration of the product, in accordance with an agreed paediatric investigation plan.

   The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned.

4. Where a medicinal product is or has been authorised in a Member State or in the Community, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or Article 10 of Directive 2001/83/EC, in an application for a paediatric use marketing authorisation.

5. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same holder has been granted authorisation for use in adults.

Article 32

Without prejudice to Article 3(2) of Regulation (EC) No 726/2004, an application for a paediatric use marketing authorisation may be made in accordance with the procedure laid down in Articles 5 to 15 of Regulation (EC) No 726/2004.

CHAPTER 3
IDENTIFICATION

Article 33

Where a medicinal product is granted a marketing authorisation for a paediatric indication based on the results of studies conducted in compliance with an agreed paediatric investigation plan, the label shall display the name of the medicinal product followed by a superscript of the letter “P” in blue lettering surrounded by the outline of a star, also in blue, for any paediatric presentation.

The first paragraph shall apply whether the name of the medicinal product is an invented name or a common name as referred to in Article 1(20) and (21), respectively, of Directive 2001/83/EC.

TITLE IV

Post-authorisation requirements

Article 34

Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those products have already been marketed with other indications, the marketing authorisation holder shall, within two years of the date on which the paediatric indication is authorised, place the product on the market taking into account the paediatric indication.

Article 35

1. In the following cases, the applicant shall detail, in addition to the normal requirements for post-marketing monitoring, the measures to ensure the follow-up of efficacy and of possible adverse reactions to the paediatric use of the medicinal product:

   (a) applications for a marketing authorisation that includes a paediatric indication;

   (b) applications to include a paediatric indication in an existing marketing authorisation;

   (c) applications for a paediatric use marketing authorisation.

2. Where there is particular cause for concern, the competent authority may require, as a condition for granting marketing authorisation, that a risk management system be set up or that specific post-marketing studies be performed and submitted for review. The risk management system shall comprise a set of activities and interventions designed to prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

   Assessment of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 104(6) of Directive 2001/83/EC and Article 24(3) of Regulation (EC) No 726/2004.

   In addition, the competent authority may request submission of additional reports assessing the effectiveness of any risk minimisation system and the results of any such studies performed.

3. In the case of a deferral, the marketing authorisation holder shall submit an annual report to the Agency providing an update on progress with paediatric studies in accordance with the decision of Agency agreeing the paediatric investigation plan and granting a deferral.

The Agency shall inform the competent authority if it is found that the marketing authorisation holder has failed to comply with the decision of Agency agreeing the paediatric investigation plan and granting a deferral.

4. The Agency shall draw up detailed guidelines relating to the application of this Article.

TITLE V

Rewards and incentives

Article 36

1. Where an application under Articles 8 or 9 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92.

   The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics, and if appropriate, in the package leaflet of the medicinal product concerned.

2. The inclusion in a marketing authorisation of the statement referred to in Article 29(3) shall be used for the purposes of applying paragraph 1 of this Article.

3. Where the procedures laid down in Directive 2001/83/EC have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.

4. Paragraphs 1, 2 and 3 shall apply to products that are protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or under a patent which qualifies for the granting of the supplementary protection certificate.They shall not apply to medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

Article 37

Where an application for a marketing authorisation is submitted in respect of a medicinal product designated as an orphan medicinal product pursuant to Regulation (EC) No 141/2000 and that application includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, and the statement referred to in Article 29(3) of this Regulation is subsequently included in the marketing authorisation granted, the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be extended to twelve years.

The first paragraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics, and if appropriate, in the package leaflet of the medicinal product concerned.

Article 38

1. Where a paediatric use marketing authorisation is granted in accordance with Articles 5 to 15 of Regulation (EC) No 726/2004, the data and marketing protection periods referred to in Article 14(11) of that Regulation shall apply.

2. Where a paediatric use marketing authorisation is granted in accordance with the procedures laid down in Directive 2001/83/EC, the data and marketing protection periods referred to in Article 10(1) of that Directive shall apply.

Article 39

1. In addition to the rewards and incentives provided for in Articles 36, 37 and 38, medicinal products for paediatric use may be eligible for incentives provided by the Community or by the Member States to support research into, and the development and availability of, medicinal products for paediatric use.

2. Within one year of the entry into force of this Regulation, the Member States shall communicate to the Commission detailed information concerning any measures they have enacted to support research into, and the development and availability of, medicinal products for paediatric use. This information shall be updated regularly at the request of the Commission.

3. Within 18 months of the entry into force of this Regulation, the Commission shall publish a detailed inventory of all incentives provided by the Community and Member States to support research into, and the development and availability of, medicinal products for paediatric use. This inventory shall be updated regularly.

TITLE VI

Communication and coordination

Article 40

1. Appropriate details of trials that are contained within agreed paediatric investigation plans, including those that are carried out in third countries, shall be entered into the European database created by Article 11 of Directive 2001/20/EC.

2. The Commission shall, on a proposal by the Agency and in consultation with Member States and interested parties, draw up guidance on the nature of the information referred to in paragraph 1 to be entered in the European database created by Article 11 of Directive 2001/20/EC.

Article 41

Member States shall collect available data on all existing uses of medicinal products in the paediatric population and, within 2 years of the entry into force of this Regulation, shall communicate these data to the Agency.

The Paediatric Committee shall provide guidance on the content and the format of the data to be collected.

Article 42

1. The Agency shall assess the data referred to in Article 41, in particular with a view to identifying research priorities.

2. On the basis of the assessment under paragraph 1 and other information available, and following consultation with the Commission, the Member States and interested parties, the Paediatric Committee shall establish an inventory of therapeutic needs.

   The Agency shall publish the inventory within 3 years of the entry into force of this Regulation, and shall update it on a regular basis.

3. In establishing the inventory of therapeutic needs, account shall be taken of the prevalence of the conditions in the paediatric population, the seriousness of the conditions to be treated, the availability and suitability of alternative treatments for the conditions in the paediatric population, including the efficacy and the adverse reaction profile of those treatments, including any unique paediatric safety issues.

Article 43

1. The Agency shall, with the scientific support of the Paediatric Committee, develop a European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population.

2. The objectives of the European network shall be, *inter alia*, to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, and to avoid duplication of studies and testing in children.

3. Within one year of the entry into force of this Regulation, the Management Board of the Agency shall, on a proposal from the Executive Director and following consultation with the Commission, the Member States and interested parties, adopt an implementing strategy for the launching and operation of the European network. This network must, where appropriate, be compatible with the work of strengthening

the foundations of the European Research Area in the context of the Community Framework Programmes for Research, Technological Development and Demonstration Activities.

Article 44

1. Within one year of the entry into force of this Regulation, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted for assessment to the competent authority.

   The competent authority shall, as appropriate, update the summary of product characteristics and package leaflet, and shall vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and their implications for any marketing authorisations concerned.

   The Agency shall coordinate the exchange of information.

2. All existing paediatric studies, as referred to in paragraph 1, shall be taken into consideration by the Paediatric Committee when assessing applications for paediatric investigation plans, waivers and deferrals and by competent authorities when assessing applications submitted pursuant to Articles 8, 9 or 31.

3. No paediatric studies, as referred to in paragraph 1, which have at the date of entry into force of this Regulation already been submitted for assessment in a third country, shall be taken into consideration for the rewards and incentives provided for in Articles 36, 37 and 38.

Article 45

Any other marketing authorisation holder sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the competent authority within six months of the completion of the studies concerned.

The first paragraph shall apply whether or not the marketing authorisation holder intends to apply for a paediatric indication.

The competent authority shall, as appropriate, update the summary of product characteristics and package leaflet, and shall vary the marketing authorisation accordingly.

Competent authorities shall exchange information regarding the studies submitted and their implications for any marketing authorisations concerned.

The Agency shall coordinate the exchange of information.

TITLE VII

General and final provisions

CHAPTER 1
GENERAL

SECTION 1
FEES, COMMUNITY FUNDING, PENALTIES AND REPORTS

Article 46

1. Where an application for a paediatric use marketing authorisation is submitted in accordance with the procedure laid down in Regulation (EC) No 726/2004, the amount of the reduced fees for the examination of the application and the maintenance of the marketing authorisation shall be fixed in accordance with Article 70 of Regulation (EC) No 726/2004.

2. Council Regulation (EC) No 297/95[11] shall apply.

3. Assessments of the following by the Paediatric Committee shall be free of charge:

   (a) applications for waiver;

   (b) applications for deferral;

   (c) paediatric investigation plans;

   (d) compliance with the agreed paediatric investigation plan.

Article 47

The Community contribution provided for in Article 67 of Regulation (EC) No 726/2004 shall cover all aspects of the work of the Paediatric Committee, including scientific support provided by experts, and of the Agency, including the assessment of paediatric investigation plans, scientific advice and any fee waivers provided for in this Regulation, and shall support the Agency's activities under Articles 40 and 43 of this Regulation.

Article 48

1. Without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for

[11] OJ L 35, 15.2.1995, p. 1.

infringement of the provisions of this Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedures laid down in Directive 2001/83/EC and shall take all measures necessary for their implementation. The penalties shall be effective, proportionate and dissuasive.

Member States shall inform the Commission of these provisions no later than […]. They shall notify any subsequent alterations as soon as possible.

2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.

3. At the Agency's request, the Commission may impose financial penalties for infringement of the provisions of this Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedure laid down in Regulation (EC) No 726/2004. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down in accordance with the procedure referred to in Article 51(2) of this Regulation.

4. The Commission shall publish the names of the marketing authorisation holders involved and the amounts of and reasons for the financial penalties imposed.

Article 49

1. On the basis of a report from the Agency and at least on an annual basis, the Commission shall publish a list of the companies that have benefited from any of the rewards and incentives in this Regulation and the companies that have failed to comply with any of the obligations in this Regulation. The Member States shall provide this information to the Agency.

2. Within six years of entry into force of this Regulation, the Commission shall publish a general report on experience acquired as a result of its application, including in particular a detailed inventory of all medicinal products authorised for paediatric use since its entry into force.

SECTION 2
COMMITTEE

Article 50

The Commission shall, after consulting the Agency, adopt appropriate provisions for the performance of the tasks of the Paediatric Committee referred to in Article 7 in the form of a Regulation in accordance with the procedure referred to in Article 51(2).

Article 51

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121 of Directive 2001/83/EC.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

   The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

CHAPTER 2
AMENDMENTS

Article 52

Regulation (EEC) No 1768/92 is amended as follows:

(1) In Article 7, the following paragraph 3 is added:

"3. The application for an extension of the duration of a certificate already granted in application of Article 13(3) of this Regulation and of Article 36 of Regulation (EC) No […/… of the European Parliament and of the Council (Paediatric Regulation)*] shall be lodged not later than two years before the expiry of the certificate.

* OJ L […], […], p. […]."

(2) Article 8 shall be amended as follows:

(a) in paragraph 1, the following point (d) is added:

"(d) where the application for a certificate includes a request for an extended duration in application of Article 13(3) of this Regulation and Article 36 of Regulation (EC) No […/…(Paediatric Regulation)]:

(i) a copy of the statement indicating compliance with an agreed completed paediatric investigation plan as referred to in Article 36(3) of Regulation (EC) No […/…(Paediatric Regulation)];

(ii) where necessary, in addition to the copy of the authorisations to place the product on the market as referred to in point (b), copies of the authorisations to place the product on the market of all other Member States, as referred to in Article 36(4) of Regulation (EC) No […/… (Paediatric Regulation)] ."

(b) the following paragraph 1a is inserted:

"1a. The application for an extension of the duration of a certificate already granted shall contain:

(a) a copy of the certificate already granted;

(b) a copy of the statement indicating compliance with an agreed completed paediatric investigation plan as referred to in Article 36(3) of Regulation (EC) No […/… (Paediatric Regulation)];

(c) copies of the authorisations to place the product on the market of all Member States."

(c) paragraph 2 is replaced by the following:

"2. Member States may provide that a fee is to be payable upon application for a certificate and upon application for the extension of the duration of a certificate."

(3) Article 9 is amended as follows:

(a) in paragraph 1, the following subparagraph is added:

"The application for an extension of the duration of a certificate already granted shall be lodged with the competent industrial property office of the Member State which granted the certificate."

(b) the following paragraph 3 is added:

"3. Paragraph 2 shall apply to the notification of the application for an extension of the duration a certificate already granted. The notification shall additionally contain the request for an extended duration of the certificate in application of Article 36 of Regulation (EC) No […/… (Paediatric Regulation)]."

(4) In Article 11, the following paragraph 3 is added:

"3. Paragraphs 1 and 2 shall apply to the notification of the fact that an extension of the duration of a certificate already granted has been granted or rejected."

(5) In Article 13, the following paragraph 3 is added:

"3. The periods laid down in paragraphs 1 and 2 shall be extended by six months in the case of application of Article 36 of Regulation (EC) No […/… (Paediatric Regulation)]. In that case, the duration of the period laid down in paragraph 1 of this Article may be extended only once."

Article 53

In Article 6 of Directive 2001/83/EC, the first subparagraph of paragraph 1 is replaced by the following:

"No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No. 726/2004, read in conjunction with Regulation (EC) No […/of the European Parliament and of the Council (Paediatric Regulation)*].

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* OJ L […], […], p. […]."

Article 54

Regulation (EC) No.726/2004 is amended as follows:

(1) Article 56(1) is replaced by the following: :

"1. The Agency shall comprise:

(a) the Committee for Medicinal Products for Human Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;

(b) the Committee for Medicinal Products for Veterinary Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for veterinary use;

(c) the Committee on Orphan Medicinal Products;

(d) the Committee on Herbal Medicinal Products;

(e) the Paediatric Committee;

(f) a Secretariat, which shall provide technical, scientific and administrative support for the committees and ensure appropriate coordination between them;

(g) an Executive Director, who shall exercise the responsibilities set out in Article 64;

(h) a Management Board, which shall exercise the responsibilities set out in Articles 65, 66 and 67."

(2) The following Article 73a is inserted:

"Article 73a

Decisions taken by the Agency under Regulation (EC) No […/… of the European Parliament and of the Council (Paediatric Regulation)*] may form the subject of an action before the Court of Justice of the European Communities under the conditions laid down in Article 230 of the Treaty.

* OJ L […], […], p. […]."

CHAPTER 3
FINAL PROVISIONS

Article 55

The requirement laid down in Article 8(1) shall not apply to valid applications pending at the time of entry into force of this Regulation.

Article 56

1. This Regulation shall enter into force on the thirtieth day following that of its publication in the *Official Journal of the European Union*.

2. Article 8 shall apply from … [18 months following the entry into force].

   Article 9 shall apply from … [24 months following the entry into force].

   Articles 31 and 32 shall apply from … [6 months following the entry into force].

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, […]

For the European Parliament	*For the Council*
The President	*The President*
[…]	*[…]*

LEGISLATIVE FINANCIAL STATEMENT

Policy area(s): Internal market

Activities: The activities of the European Medicines Agency are included in the following policies:

- Support for the development of paediatric medicines ;
- Improvement in the protection of public health and for consumers across the Community
- Maintaining a reliable and independent source of scientific advice and information, and
- Support and achievement of the internal market for the pharmaceutical sector.

TITLE OF ACTION: REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE AND AMENDING REGULATION (EEC) NO 1768/92, DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

1. BUDGET LINE(S) + HEADING(S)

02.040201 – European Agency for the Evaluation of Medicinal Products — Subsidy under Titles 1 and 2

02.040202 – European Agency for the Evaluation of Medicinal Products — Subsidy under Title 3

2. OVERALL FIGURES

2.1. Total allocation for action (Part B): € million for commitment

EUR 21 282 million

2.2. Period of application:

2007 to 2012

2.3. Overall multiannual estimate of expenditure:

(a) Schedule of commitment appropriations/payment appropriations (financial intervention) *(see point 6.1.1)*

EUR million (*to three decimal places)*

	Year 2007	2008	2009	2010	2011	2012 and subs. Years	Total
Commitments	1,000	3,039	3,377	3,598	5,053	5,215	21,282
Payments	1,000	3,039	3,377	3,598	5,053	5,215	21,282

(b) Technical and administrative assistance and support expenditure *(see point 6.1.2)*

Commitments							
Payments							

Subtotal a+b							
Commitments	1,000	3,039	3,377	3,598	5,053	5,215	21,282
Payments	1,000	3,039	3,377	3,598	5,053	5,215	21,282

(c) Overall financial impact of human resources and other administrative expenditure *(see points 7.2 and 7.3)*

Commitments/ payments							

TOTAL a+b+c							
Commitments	1,000	3,039	3,377	3,598	5,053	5,215	21,282
Payments	1,000	3,039	3,377	3,598	5,053	5,215	21,282

2.4. Compatibility with financial programming and financial perspective

[X] Proposal will entail reprogramming of the relevant heading in the financial perspective. The proposal is compatible with the new financial framework (2007-2013) proposed by the Commission (Communication from the Commission to the Council and the European Parliament COM(2004) 101).

2.5. Financial impact on revenue[1]:

[X] Proposal has no financial implications (involves technical aspects regarding implementation of a measure)

3. BUDGET CHARACTERISTICS

Type of expenditure		**Budget line**	**New**	**EFTA contribution**	**Contributions from applicant countries**	**Heading in financial perspective**
Non-comp	Non-diff	02.040201	NO	YES	NO	1 a
Non-comp	Non-diff	02.040202	NO	YES	NO	1 a

[1] For further information, see separate explanatory note.

4. LEGAL BASIS

– Treaty establishing the European Community and notably article 235.

– Draft Regulation of the European Parliament and of the Council on medicinal products for paediatric use (to support the Agency's work required for the operation of the draft Regulation including all work of the Paediatric Committee, scientific advice and any fee waivers provided for by virtue of the draft Regulation).

– Regulation (EC) No 726/2004 of the European parliament and of the Council of 30 May 2004, establishing the community procedures for the authorisation and follow up of medicines for human and veterinary use, and establishing the European Agency for the Evaluation of Medicinal Products (OJ L 136, 30.4.2004, p. 1).

– Council Regulation (EC) No 297/95 of 10 February 1995 modified by Council Regulation (EC) No 2743/98 of 14 December 1998 concerning fees payable to the European Agency for the Evaluation of Medicinal Products (OJ L 345, 19.12.1998, p. 3).

5. DESCRIPTION AND GROUNDS

5.1. Need for Community intervention

5.1.1. Objectives pursued

It is estimated that between 50 and 90% of medicinal products used in the paediatric population have never been specifically studied or authorised (licensed) for use in that age group. This leaves no alternative to the prescriber than to use products "off-label" (i.e. use of product authorised for adults - products that have not been tested or authorised for paediatric use) or use of completely unauthorised products with the associated risks of inefficacy and/or adverse reactions (side effects).

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 Directive.

5.1.2. Measures taken in connection with ex ante *evaluation*

The draft Regulation of the European Parliament and of the Council on medicinal products for paediatric use was the subject of a Commission Extended Impact Assessment (EIA). The EIA accompanies this Financial Statement. The Commission's EIA is based on an independent, externally contracted study, specifically designed to estimate the economic, social and environmental impacts of the proposal. The EIA also draws on experience with the existing EU pharmaceutical market and regulatory framework, experience with legislation on paediatric medicines in the US, experience with orphan medicines in the EU, extensive consultation with stakeholders, and the published literature.

5.1.3. Measures taken following ex post *evaluation*

The draft Regulation of the European Parliament and of the Council on medicinal products for paediatric use is a new legislative proposal and no interim or ex post evaluation has been conducted.

5.2. Action envisaged and budget intervention arrangements

The key measures included in the draft paediatric regulation are:

- the establishment of an expert committee, the Paediatric Committee within the EMEA;
- a requirement at the time of marketing authorisation applications for new medicines and line-extensions for existing patent-protected medicines for data on the use of the medicine in children resulting from an agreed paediatric investigation plan;
- a system of waivers from the requirement for medicines unlikely to benefit children;
- a system of deferrals of the requirement to ensure medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;
- excluding orphan medicines, a mixed reward and incentive for compliance with the requirement in the form of a six-month extension to the supplementary protection certificate (in effect, a six-month patent extension on the active moiety);
- for orphan medicines, a mixed reward and incentive for compliance with the requirement in the form of an additional two-years of market exclusivity added to the existing ten years awarded under the EU orphan regulation;
- a new type of marketing authorisation, the PUMA, which allows ten years of data protection for innovation (new studies) on off-patent products;
- amended data requirements for PUMA applications to attract SMEs including generics companies;
- a reference in the explanatory memorandum to the establishment, via separate legislation of an EU paediatric study programme to fund research leading to the development and authorisation of off-patent medicine for children;

- access to an optional centralised procedure via the community referral procedure for existing nationally authorised medicines to gain an EU-wide Commission Decision on use in children;

- measures to increase the robustness of pharmacovigilance for medicines for children;

- a requirement for industry to submit to the authorities study reports they already hold on use of their medicine in children, to maximise the utility of existing data and knowledge;

- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines;

- an EU network of investigators and trial centres to conduct the research and development required;

- a system of free scientific advice for the industry, provided by the EMEA;

- a database of paediatric studies (based on the existing database set up by the EU Directive on clinical trials (OJ L 121, 1.5.2001, p. 34).

Populations affected by the activity:

- more than 100 million children in the newly enlarged EU stand to benefit from better medicines for children. Children will also be enrolled into clinical trials;

- healthcare professionals will benefit through the supply of medicines specifically developed for children and may take part in clinical research on medicines for children;

- all pharmaceutical companies seeking to access the EU market will be affected by the draft Regulation;

- the EMEA and all National competent authorities will have to change their working practices as a result of the draft Regulation;

Expense type

Article 47 of the draft Regulation on medicinal products for paediatric use foresees a contribution from the Community to cover the work resulting from the draft Regulation on medicinal products for paediatric use, incorporated into the contribution provided for in Article 67 of Regulation (EC) No 726/2004 and in Article 7 of Regulation (EC) No 141/2000 to be allocated to the European Medicines Agency. This contribution should cover all aspects of the work of the European Medicines Agency to implement and operate the draft Regulation, in particular: the operation of the Paediatric Committee including assessment of paediatric investigation plans, requests for waivers and deferrals, assessment of compliance with paediatric investigation plans and assessment of the safety, quality and efficacy of medicinal products for paediatric use; an EU inventory of the therapeutic needs of children; an EU network of investigators and trial centres to conduct the research; free scientific advice for the industry; a database of paediatric studies.

The explanatory memorandum of the draft paediatric regulation makes a reference to the possible creation of a paediatric study programme: Medicines Investigation for the Children

of Europe (MICE)[2]. The creation of the funding and its operation would be included in a separate Commission initiative. A detailed assessment of the impacts of the programme will accompany that separate initiative. However, given the interface between legislation on a paediatric study programme and the draft paediatric Regulation assessed here, some consideration is required. An EU paediatric study programme, focussed on funding or part funding studies on off-patent medicines will be important if research and authorisation for children of off-patent products are to occur for the majority of products needed by children. It is envisaged that the paediatric study programme may be funded, at least in part, from the Community budget. The paediatric study programme would also need to take account of other relevant Community funding, including the 6th and 7th Framework Programmes operated by the Commission Directorate General Research. Community funding for studies into off-patent medicines for children (which may lead to the authorisation of an off-patent medicine for children) may only be partial, e.g. 50% funding: the remainder of the funding may need to come from industry, Member State governments or medical charities.

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

Estimated resources and costs of the paediatric Regulation, based on the draft proposal released for consultation by the European Commission on 8 March 2004

The increased contribution will cover: increased administration costs of the European Medicines Agency relating to all tasks of the Paediatric Committee; the costs of free scientific advice and fee reductions for paediatric use marketing authorisations.

Justifications of the resources implications based on its coming into force in 2007

As of 2006, the EMEA would have to set up a task force to prepare for the work of the Paediatric Committee and the procedures as laid out in the Regulation. It is estimated that the task force would require 1 A grade full time and 1 C grade half time. This will be covered by an internal redeployment.

In 2007

Activities planned for the first year. All activities are based on the EMEA's experience of Committee activities, and in particular the experience gained in the last 3 years of activities on orphan medicinal products and the Committee for orphan medicinal products. Activities will start in full as soon as the Regulation is implemented due to the legal obligations created by it.

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[2] The impact of the referenced paediatric study programme will critically depend on its funding, size and awarding rules. A fund, set up under the United States Best Pharmaceuticals for Children Act 2002, is of $ 200 000 000 for fiscal year 2000 and such sums as are necessary for each of the succeeding five years for the study of the use in the paediatric population of medicinal products for which there is no patent protection or market exclusivity. The CHMP Paediatric Expert Group has produced a preliminary list of sixty-five off-patent active substances considered to be priorities for research and development for children in the EU.

A. Paediatric Committee

Functioning of the Paediatric Committee

- Meeting costs

A monthly meeting of 2-3 days is necessary. Eleven meetings a year with 31 members are envisaged, representing 682-1023 expert days. In addition, it is anticipated that additional experts will be needed on an ad-hoc basis by the Paediatric Committee.

- Meeting Management and Conference services

Eleven meetings a year of 31 members plus additional experts will have heavy implications on the Meeting Management & Conferences Sector of the EMEA which will have to organise travel and accommodation and meetings, as well as on the meeting room occupation.

- Secretariat costs

The secretariat of the Paediatric Committee represents a full time position all year round, therefore taking into consideration the need for a back-up, this represents 1.5 A grade and 1.5 C grade positions.

- Expert costs

Estimated at 5-10 experts per Paediatric Committee meeting, in addition to members of the Paediatric Committee (i.e. 55-110 experts per year).

Activities of the Paediatric Committee

– Paediatric Investigation Plans

– Deferrals

– Waiver of Paediatric Investigation Plans

– Paediatric needs

– Paediatric priorities

– Compliance

– Expert work

In the draft paediatric Regulation, there is an obligation to submit the results of studies performed according to an agreed Paediatric Investigation Plan for applications for marketing authorisations of new products (Marketing Authorisation Applications) and variations for patented products. The best estimate of the number of Paediatric Investigation Plans to be submitted per year to the Agency in the first years is about 235-285.

The activities related to the submission of Paediatric Investigation Plans are rather similar to the work done for orphan drug designation. However the level of scientific involvement to

judge the submitted plan is considered higher, more complex, and the number of procedures is 2.5 times more than the current number of orphan applications.

– Agreed Paediatric Investigation Plans revisions

– Procedures

It is not expected that applications for the revision of Paediatric Investigation Plans would occur in the first year. Only procedures would have to be established.

B. Other activities created by the Regulation

– **Paediatric scientific advice**

There will be an increase in scientific advice for paediatric development. It is expected that up to 60% of companies may seek advice (the current situation is about 30% for products submitted for Marketing Authorisation). This represents about three times the current number of Scientific Advice requests (currently 100 per year). See section 6.2 for details of the financial implications of fee waivers for paediatric scientific advice.

– **Information publication and management**

This has implications on the current development of the databases at the EMEA and on other forms of EMEA communication.

– **Survey of paediatric use and inventory of research priorities**

These activities will be performed by the staff in charge of other paediatric activities but will represent a significant part of the workload.

– **Establishment of a paediatric research network**

This is a new type of activity for the EMEA, which will require at least a full time position for an A and a C grade.

C. Impact on the Agency

In addition to involving specific staff all activities have direct implications on other sectors such as Meeting Management and Conference, IT and administration.

The activities will generate the need for regular training, workshops and will involve missions outside the Agency (for example for the establishment of a network of paediatric clinical research).

D. Need for Experts in Secondment

To strengthen the collaboration between EMEA and Member States in particular in relation to paediatric activities on national products, authorisations and pharmacovigilance, the EMEA will invite Experts in Secondment to join the Agency to facilitate the work. This will be done also at the stage of the preparatory work.

A typical stabilised year

It has been considered that year 2009 would represent a typical year, when the number of applications per year would be stable, and all activities provided for by the Regulation would be developed.

A. Paediatric Committee

Functioning of the Paediatric Committee

– Meeting costs

No major changes in activities are anticipated.

– Meeting Management and Conference services

No major changes in activities are anticipated.

– Secretariat costs

No major changes in activities are anticipated.

– Experts costs

Changes in activities may be needed. Estimates are however given for the same numbers.

Activities of the Paediatric Committee

Figures for new products (on patent) should remain stable. Variations capturing products that never included a Paediatric Investigation Plan should slightly decrease, as some products would have been captured at the stage of marketing authorisation applications. This would however not be the case of variation applications in a new indication (new therapeutic area) for which a new Paediatric Investigation Plan may have to be submitted.

There should not be any more products undergoing purely national procedures in respect of the obligation to submit a Paediatric Investigation Plan.

The 'stable' number of Paediatric Use Marketing Authorisation procedures cannot be estimated. It is judged that the initial figure of 15 per year should be kept.

Overall the level of activities should remain around 235-285 procedures per year.

The additional (fully developed) tasks will include in particular the Annual Reports on deferrals, and the revision of agreed Paediatric Investigation Plans. Once a Paediatric Investigation Plan is agreed, the draft Regulation offers the possibility to amend it as often as needed on request from the sponsor. It is estimated that 30% of the Paediatric Investigation Plans may need revision at some point in time. This may represent a minimum of 80 additional applications a year.

B. Activities created by the Regulation

– **Scientific Advice**

Paediatric Scientific Advice and follow up procedures would increase progressively over time.

– **Pharmacovigilance and risk management**

This activity will be fully developed.

– **Information publication and management**

Modifications or developments of the current structures will take place over several years.

– **Inventory of research priorities**

Regular updates are forecasted for in the Regulation.

– **Establishment of a paediatric research network**

The implementation and running of the network should be in place.

C. Impact on the Agency

In addition to involving specific staff all activities and their related increases have direct implications on other sectors.

5.3. Methods of implementation

The draft Regulation will be implemented and operated primarily by the existing European Medicines Agency. Certain aspects will also be operated by the National Competent Authorities. The Commission will be responsible for an implementing regulation and a number of supporting guidelines.

6. FINANCIAL IMPACT

6.1. Total financial impact on Part B - (over the entire programming period)

(The method of calculating the total amounts set out in the table below must be explained by the breakdown in Table 6.2.)

6.1.1. Financial intervention

Commitments (in EUR million to three decimal places)

Breakdown	2007	2008	2009	2010	2011	2012 and subs. Years	Total
02.040201 – European Agency for the Evaluation of Medicinal Products — Subsidy under Titles 1 and 2	0,800	2,397	2,688	2,881	4,280	4,409	17,455
02.040202 – European Agency for the Evaluation of Medicinal Products — Subsidy under Title 3	0,200	0,642	0,689	0,717	0,773	0,806	3,827
Action 2							
etc.							
TOTAL	1,000	3,039	3,377	3,598	5,053	5,215	21,282

6.1.2. Technical and administrative assistance, support expenditure and IT expenditure (commitment appropriations)

	2007	2008	2009	2010	2011	2012 and subs. Years	Total
1) Technical and administrative assistance	N.A.						
a) Technical assistance offices							
b) Other technical and administrative assistance: - intra muros: - extra muros: *of which for construction and maintenance of computerised management systems*							
Subtotal 1							
2) Support expenditure							
a) Studies							
b) Meetings of experts							
c) Information and publications							
Subtotal 2							
TOTAL							

6.2. Calculation of costs by measure envisaged in Part B (over the entire programming period)[3]

(Where there is more than one action, give sufficient detail of the specific measures to be taken for each one to allow the volume and costs of the outputs to be estimated.)

Commitments (in EUR million to three decimal places)

Breakdown	Type of outputs (projects, files)	Number of outputs (total for years 2007-2012)	Average unit cost	Total cost (total for years 2007-2012)
	1	2	3	4=(2X3)
Paediatric medicines management - *Measure 1*	Paediatric activities costs for the EMEA general subsidy Staff Expenditure other.			*17,455* *3,827*
TOTAL COST				21,282

These costs are mainly due to: 1. the supplementary staff needed to perform the tasks induced by the new regulation on medicinal products for paediatric use, 2. scientific advice being given without a fee, and, 3. fee reductions for marketing authorisation applications.

Staff will be required to: provide the secretariat of the new expert committee the Paediatric Committee, administer requests for opinions from the Paediatric Committee, create and maintain an inventory of the therapeutic needs of the children of Europe, create and maintain an EU network of clinical trial centres to conduct tests of medicines for children, and, collation and publication of information about medicines for children. Projections for 2011 foresee that 24 people (14,5 A and 9,5 C) will be necessary to support the EMEA work related to the paediatric regulation. Support staff will bring the overall figure to 26.

Regarding scientific advice, currently, requests for such advice command a fee from the EMEA. This fee is used mainly to pay experts from the National agencies who conduct the scientific evaluation of the requests (with their accompanying dossiers). The draft paediatric regulation will lead to such scientific advice being given without the payment of fees. Therefore the EMEA will have to pay money to the National agencies and this will have to be

[3] For further information, see separate explanatory note.

covered. Furthermore, the total number of requests for scientific advice is predicted to increase dramatically as a result of the paediatric regulation. The current average fee for scientific advice is about 40 000 € and it is predicted that, For the period of six years starting in 2007, about 330 free pieces of scientific advice will be given.

Regarding fee reductions for marketing authorisation applications, the current fee is approximately 200 000 €. This pays mainly for the scientific evaluation conducted by experts from the National agencies. The fee reduction foreseen in the paediatric regulation is 50% and this will apply to a small proportion of all paediatric marketing authorisations (the so called Paediatric Use Marketing Authorisations – PUMAs). For the period of six-years starting in 2007 it is estimated that about 30 paediatric use marketing authorisation applications will be made that will attract the 50% fee reduction. Hence the EMEA will have to pay the National agencies but this will not be covered by adequate fees.

Staff requirement	2007	2008	2009	2010	2011	2012 and subs. Years
Secretariat Paediatric Committee Paediatric	1	3	3	3	3	3
Investigation Plan applications	1	10	10	10	14	14
Paediatric Research Network		1	1	1	3	3
			1	2	2	2
Funding of studies	1	2	2	2	4	4
Support staff						
TOTAL	**3**	**16**	**17**	**18**	**26**	**26**

Expenditure costs will mostly cover the reimbursement of the experts in relation with the new committee 'Paediatric Committee', as well as other missions and trainings. Some IT developments will also be necessary in order to include this new category of medicinal products in the several existing databases.

Expenditure Other	2007	2008	2009	2010	2011	2012 and subs. Years
Meetings Paediatric Committee						
31 members and 5 experts 11 x 2-day meetings	0,050	0,413	0,452	0,474	0,498	0,523
Workshops, trainings and missions	0,100	0,119	0,127	0,133	0,165	0,173
IT development and web publication	0,050	0,110	0,110	0,110	0,110	0,110
TOTAL	**0,200**	**0,642**	**0,689**	**0,717**	**0,773**	**0,806**

7 IMPACT ON STAFF AND ADMINISTRATIVE EXPENDITURE

7.1. Impact on human resources

Types of post		Staff to be assigned to management of the action using existing resources		Total	Description of tasks deriving from the action
		Number of permanent posts	Number of temporary posts		
Officials or temporary staff	A B C	N.A.			*If necessary, a fuller description of the tasks may be annexed.*
Other human resources					
Total					

7.2. Overall financial impact of human resources

Type of human resources	Amount (€)	Method of calculation *
Officials Temporary staff	N.A.	
Other human resources (specify budget line)		
Total		

The amounts are total expenditure for twelve months.

7.3. Other administrative expenditure deriving from the action

Budget line (number and heading)	Amount €	Method of calculation
Overall allocation (Title A7) ex A0701 – Missions ex A07030 – Meetings ex A07031 – Compulsory committees [1] Paediatric Committee A07032 – Non-compulsory committees [1] A07040 – Conferences ex A0705 – Studies and consultations Other expenditure (specify) Training	N.A.	
Information systems (A-5001/A-4300)		
Other expenditure - Part A (specify) IT developments		
Total		

The amounts are total expenditure for twelve months.

[1] Specify the type of committee and the group to which it belongs.

I.	Annual total (7.2 + 7.3) in 2011
II.	Duration of action
III.	Total cost of action (2007 to 2012)

The needs for human and administrative resources shall be covered within the allocation granted to the managing DG in the framework of the annual allocation procedure

8. FOLLOW-UP AND EVALUATION

8.1. Follow-up arrangements

Many of the effects of the draft paediatric legislation lend themselves to measurement. Others, including the overall objective of improved child health will be more difficult to measure due to a lack of robust EU-wide data. Collection of the following data is possible.

- The dates on which the Paediatric Committee and EU network of clinical trialists are established and guidelines and first inventory of therapeutic needs are adopted.
- The date on which the database of paediatric studies becomes operational.
- The number of clinical trials in children initiated and completed (broken down by country and type of trial).
- The number of children enrolled into clinical trials.
- The number of draft paediatric investigation plans submitted for assessment and the number of paediatric investigation plans agreed by the Paediatric Committee.
- The number of requests for waivers and the number of waivers granted by the Paediatric Committee.
- The number of requests for deferrals and the number of deferrals granted by the Paediatric Committee.
- The number of requests for scientific advice.
- The numbers of marketing authorisation applications made and granted for adults and children.
- The number of PUMA applications made and PUMAs (with their associated data protection) granted.
- The number of requests for post-marketing studies, pharmacovigilance plans and risk management systems and the delivery against those plans.
- The number of existing studies in children submitted and the number of marketing authorisations updated as a result.

- The number of times marketing authorisations record that a paediatric investigation plan has been complied with. This provides a measure of the number of supplementary protection certificates that can be extended.

- Impact on the budget of the EMEA.

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

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

Section 4 of the extended impact assessment points out that the impact, both financial and social, of improved health of the children of Europe is very difficult to measure. Unless there is major investment in the central collection of indices of EU child health, this difficulty will remain when attempting to measure, in the future, the impact of the draft paediatric Regulation.

8.2. Arrangements and schedule for the planned evaluation

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

Through these measures, specifically proposed in the draft paediatric Regulation, *ex post* evaluation is already planned. The general report will likely be based on the indices listed in section 8.1. Furthermore, the need for a designated independent study to support the general report should be considered. Such an independent study could include within its scope the financial and social impacts for which prospective data collection is problematic.

9. ANTI-FRAUD MEASURES

The European Medicines Agency has specific budgetary control mechanisms and procedures. The Management Board, which comprises representatives of the Member States, the Commission and the European Parliament, adopts the draft budget (Article 57.5) as well as the final budget (Article 57.6). The European Court of Auditors examines the execution of the budget each year (Article 57.9) and the Management Board gives a discharge to the Director regarding the budget (Article 57.10). In addition the Agency adopted on 1 June 1999 a decision concerning co-operation with the European Anti-Fraud Office (EMEA/D/15007/99).

The Quality Management System applied by the Agency supports a continuous review with the intention of ensuring that the correct procedures are followed and that these procedures and policies are pertinent and efficient. Several internal audits are undertaken each year as part of this process.