Amended proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL


(presented by the Commission pursuant to Article 250 (2) of the EC Treaty)
Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL


(Text with EEA relevance)

1. BACKGROUND

Adoption of the proposal- COM(2004) 599 final 29 September 2004


Opinion of the European Economic and Social Committee: 11 May 2005


2. OBJECTIVE OF THE COMMISSION PROPOSAL

The proposal aims to address the current situation in Europe whereby more than fifty percent of the medicines used to treat children 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.

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:

(1) increase the development of medicines for use in children;

(2) ensure that medicines used to treat children are subject to high quality research;

(3) ensure that medicines used to treat children are appropriately authorised for use in children;

(4) improve the information available on the use of medicines in children, and;

(5) achieve these objectives without subjecting children to unnecessary clinical trials and in full compliance with Community legislation on clinical trials (Directive 2001/20/EC).
3. OPINION OF THE COMMISSION ON THE AMENDMENTS ADOPTED BY THE PARLIAMENT

3.1. Amendments accepted by the Commission: 4, 5, 7, 10, 15 (1st part), 17, 18 (1st part), 22 (1st part), 33, 34, 35, 39, 40 (60 days, “or the request for a deferral or waiver”), 44 (1st part), 45, 46 (2nd part), 58, 62.

The Commission can accept the following amendments with the wording proposed by the European Parliament.

- Amendment 4 aimed at highlighting the objective of promoting the circulation of safe medicinal products.

- Amendment 5 aimed at highlighting that not all testing in children may be appropriate.

- Amendment 7 aimed at clarifying that the conduct of studies in children will not always be possible before granting marketing authorisations for adults and that the provisions for medicines for children should not delay marketing authorisation applications for medicines in adults.

- Amendment 10 aimed at highlighting the role of the Paediatric Committee in checking compliance with the paediatric investigation plan and in giving an opinion on the safety, quality and efficacy of a medicine in children.

- Amendment 15 (first part) aimed at highlighting the use of the data on the clinical trials database as an information source and to aid the avoidance of unnecessary studies.

“Recital 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 a European register of clinical trials of medicinal products for paediatric use comprising all ongoing, prematurely terminated, and completed paediatric studies conducted both in the Community and in third countries. […]”

- Amendment 17 aimed at stressing the importance of taking account of international data when establishing and operating a European clinical trials network.

- Amendment 18 (first part) aimed at clarifying that children should not be subjected to any unnecessary trials, be they clinical or other.

“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 or other trials and in compliance with Directive 2001/20/EC.”

- Amendment 22 (first part) aimed at clarifying that the opinion of the Paediatric Committee will be the one adopted by the majority of members and that the opinion shall mention any divergent positions.
“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 be the one adopted by the majority of members. The opinion shall mention the divergent positions, with the grounds on which they are based.”

- Amendments 33 and 39 aimed at ensuring that a rapporteur from the Paediatric Committee is appointed.

- Amendment 34 aimed at clarifying the deadline for the European Medicines Agency (hereinafter, the Agency) to inform the applicant of the Paediatric Committee’s opinion.

- Amendment 35 aimed at ensuring the list of waivers is regularly updated and is publicly accessible.

- Amendment 40 (except the last part) aimed at establishing a deadline for the Paediatric Committee to adopt an opinion and to clarify that the request and opinion may refer to a paediatric investigation plan, deferral or waiver.

“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. Within 60 days, the Paediatric Committee shall review these changes or the request for a deferral or a waiver 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.”

- Amendment 44 (first part) aimed at establishing a European logo for medicines for children.

“Article 33, first subparagraph:

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 and, below it, a European logo for any paediatric presentation.”

- Amendment 45 aimed at ensuring that existing medicines authorised for children should be labelled with the European logo.

- Amendment 46 (second part) aimed at establishing a publicly accessible register of the deadlines for placing on the market existing products newly authorised for children.

“Article 34:

Where medicinal products are authorised with 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. A publicly accessible register shall be set up by the competent authorities in order to indicate these deadlines.”

- Amendment 58 aimed at ensuring that the scope of the Commission guidance concerning the database of clinical trials includes what information should be made public and how the Agency should achieve this.

- Amendment 62 aimed at clarifying that ongoing, as well as, completed studies should be taken into consideration by the Paediatric Committee when assessing paediatric investigation plans, waivers and deferrals.

3.2. Amendments accepted in principle by the Commission: 1, 2, 6 (1st part), 6 (3rd part), 8, 9, 19 (Article 2b), 20, 21, 22 (2nd part), 26 (with 29), 27, 28, 31, 42, 43 (1st part and 2nd part), 50, 52 (re data protection), 55, 56, 57, 63, 64, 66, 67, 69

The Commission can accept in principle the following amendments:

- Amendment 1 introducing into recital 3 a specific mention of the need for suitable formulations and routes of administration for children, with a minor rewording:

“Recital 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 and suitable formulations and routes of administration, as well as the use of extemporaneous formulations to treat children which may be of poor quality.”

- Amendment 2 clarifying that the aims of the Regulation include increasing availability of medicines for children. A slight rewording is necessary; the mention of “where indicated” in the amendment is unnecessary since it is already covered by the mention of “and are appropriately authorised for use in children”:

“Recital 4:

The aim of this Regulation is to facilitate the development and accessibility 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 age populations.”

- Amendment 6 (1st and 3rd parts) concerning the independence and the requirements in terms of professional experience of the members of the Paediatric Committee, and the need to ensure that any studies in children have potential significant therapeutic benefits for them. Rewording is necessary to clarify that the members of the Committee must have experience relevant to the work of the Committee, but that this experience may have been gained other than in the pharmaceutical industry. Further rewording is necessary to clarify that, when the Paediatric Committee considers the potential significant therapeutic benefits of a medicine, these potential benefits relate to either the patients to be included in studies or the paediatric population at large.
“Recital 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. To this end the Paediatric Committee should be independent of the pharmaceutical industry. 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. 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 for the paediatric patients involved in the studies or the paediatric population at large, including the need to avoid unnecessary studies. The Paediatric Committee 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 it should avoid any delay in the authorisation of medicines for other populations as a result of the requirements for studies in children.”

Amendment 8 intended to clarify that, in some circumstances, it will not be appropriate to conduct studies in children in parallel with studies in adults. The recital should be reworded to specify the mechanisms foreseen in the Regulation (waivers and deferral) to address such a situation.

“Recital 11:

It is necessary to introduce a requirement for new medicinal products and or authorised medicinal products covered by a patent or a supplementary protection certificate to present either the results of studies in children in accordance with an agreed paediatric investigation plan, or proof of having obtained a waiver or deferral, at the time of filing 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.”

Amendments 9, 56, 63 (second part) and 64 providing for the establishment of a research programme into the paediatric use of medicinal products which are not protected by a patent or supplementary protection certificate. Rewording is required to specify that all Community funded research activities must take place within the context of the Research and Development Framework Programmes. The Commission services are currently working to include such a programme in the Specific Programme on Health of the 7th Framework Programme. Under the “health” thematic priority of its 7th Framework Programme proposal, the Commission has therefore clearly mentioned “research on child health” as one of the strategic issues which should be addressed across activities. Among the different activities where child health research could be addressed, it is in particular envisaged to put a special emphasis on the specificities of children when it comes to translating clinical outcome into clinical practice. It is also envisaged to give specific support to clinical studies which could provide evidence for the appropriate use of off-patent products currently used in the paediatric populations.
“Recital 11a:

Provision should be made for research into the paediatric use of medicinal products which are not protected by a patent or supplementary protection certificate to be financed under Community research programmes.

“Article 39a:

1. Funds for research into medicinal products for children shall be provided for in the Community budget to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate.

2. This Community funding will be delivered through the Community Framework Programmes for Research, Technological Development and Demonstration Activities or any other Community initiatives for the funding of research.”

– Amendment 19 as regards the content of the new Article 2b, concerning the inventory of therapeutic needs. The first subparagraph is accepted with the wording proposed by the European Parliament. Rewording of the second subparagraph is necessary to provide for a longer deadline for publication. The survey will take two years to complete, and the Paediatric Committee should be granted twelve months to carefully assess the data and adopt the inventory. The rewording is included in Article 42 given that the Commission does not accept amendment 19 insofar as it entails moving the survey, inventory and network (Articles 41, 42 and 43 of the Commission proposal) to a new Chapter 1a.

“Article 42:

On the basis of the information referred to in Article 41 and after consulting the Commission, the Member States and the interested parties, the Paediatric Committee shall draw up an inventory of therapeutic needs, in particular with a view to identifying research priorities.

The Agency shall make public the inventory within 3 years of the entry into force of this Regulation, and shall update it regularly.

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, and any data resulting from studies in third countries.”

– Amendment 20 requiring the Paediatric Committee to be operational within six months from the date of entry into force of the Regulation. Rewording is necessary to ensure that the dead-line can be met, considering that the appointment procedure for the members appointed by the Commission on the basis of a public call for expression of interest (referred to in Article 4(1)(c)) may take longer than six months:

“Article 3(1), first subparagraph:

Not later than 6 months after the entry into force of this Regulation, a Paediatric Committee shall be established within the European Medicines Agency set up under Regulation (EC) No 726/2004, hereinafter “the Agency”. The Paediatric Committee shall be
considered to be established once the members referred to in Article 4(1)(a) and (b) have been appointed.”

- Amendment 21 broadening the composition of the Paediatric Committee and providing for the consultation of the European Parliament before designation of the members appointed by the Commission.

The Commission accepts the part of the amendment concerning consultation of the European Parliament in the case of the members appointed by the Commission on the basis of a public call for expression of interest (referred to in Article 4(1)(c)).

Regarding the number of such members to be appointed by the Commission, it is considered that six members is sufficient to ensure that the relevant healthcare professionals and patients groups are well represented on the Paediatric Committee. Increasing the number of Commission appointees from six to ten would lead to the Committee being much larger than other committees of the Agency and could result in operational difficulties.

Regarding the range of expertise to be represented in the Committee, this amendment deals exclusively with the members appointed by the Commission. However, the composition of the Committee needs to be considered in the context of the whole of Article 4. The second subparagraph of paragraph (1) tasks the Executive Director of the Agency to ensure that the combined membership covers at least the listed areas of expertise. Of the areas of expertise that the European Parliament proposes to add, this list already includes pharmacovigilance and pharmacy; public health and general practitioners should be added to the list. The part of the amendment relating to “paediatricians and other physicians specialising in the treatment of children” is most appropriately dealt with by using the term “healthcare professionals”.

In view of the enlarged areas of expertise to be covered as a result of this amendment, it is appropriate for the Commission, appointing six members of the Committee, to cooperate closely with Member States, the European Parliament and the Agency during the appointment process.

Therefore, Article 4(1)(c) and the last subparagraph of Article 4(1) should be reworded as follows:

“(c) Six persons appointed by the Commission, on the basis of a public call for expressions of interest, and after consulting the European Parliament, in order to represent health professionals and patient associations.

For the purposes of points (a) and (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 will cover the scientific areas relevant to paediatric medicinal products, and at least including: pharmaceutical development, paediatric medicine, general practitioners, pharmacy, paediatric pharmacology, paediatric research, pharmacovigilance, ethics and public health. For the purposes of point (c), the Commission shall take into account the expertise provided by the members appointed under points (a) and (b).”

- Amendment 22 (2nd part) concerning publication of the opinions of the Paediatric Committee. This transparency measure should apply to the Agency decisions adopted after an opinion of the Paediatric Committee, which is a preparatory step for such decisions. Therefore, rather than an amendment to Article 5, a reference to publication should be
included in Article 26, which refers to the decisions of the Agency adopted on the basis of Committee’s opinion.

“Article 26(6):

Decisions of the Agency shall be made public, after deletion of any information of a commercially confidential nature.”

– Amendments 26 and 29 concerning the Paediatric Committee’s tasks as regards the inventory of therapeutic needs. The Commission accepts this amendment and the new Article 7(1)(ha). In turn, point (e) of Article 7(1) needs to be reworded to delete the reference to the inventory and avoid duplication.

“Article 7(1)(e):

to advise on the content and format of data to be collected for the survey referred to in Article 41;”

Article 7(1)(ha):

to establish a specific inventory of paediatric medicinal product needs, update it on a regular basis and make it publicly available;”

– Amendment 27 on transparency measures concerning the role of the Committee and the arrangements available for conducting pharmaceutical clinical trials. It is appropriate for the Committee to advise on communication about the conduct of clinical trials in children, but not for it to organise publicity campaigns on its own role. Rewording is therefore required:

“Article 7(1)(hb):

to advise the Agency and the Commission regarding communication on the arrangements available for conducting research into medicines for children.”

– Amendment 28 providing that the Committee takes into account the results of assessments performed in third countries. Rewording is necessary to clarify that the Committee shall consider any information available to it, including information from studies in third countries.

“Article 7(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. The Paediatric Committee shall take into account any information available to it, including any opinions, decisions or advice given by the competent authorities of third countries.”

– Amendment 31 intended to ensure that Community pharmaceutical legislation, and in particular the rules on variations to the terms of marketing authorisations, apply where relevant in the framework of this Regulation. However, the amendment is redundant. Article 28 already refers to the application of Regulation (EC) No 726/2004 and Directive 2001/83/EC, which by definition includes their implementing measures such as
Regulations (EC) No 1084/2003 and No 1085/2003, concerning variations to the terms of marketing authorisations.

- **Amendment 42** introducing a dead-line for the Agency to adopt a decision following an opinion of the Paediatric Committee and providing that such decisions will be duly motivated. Rewording is proposed to reduce the mentioned dead-line (ten days is judged sufficient for the Agency to adopt a decision) and to clarify that motivation shall be provided by annexing the Committee’s opinion.

  “Article 26(4):

  The Agency shall adopt a decision **within a period not exceeding 10 days following receipt of the Paediatric Committee’s definitive opinion.** This decision shall be communicated to the applicant in writing, and will annex the definitive opinion of the Paediatric Committee.”

- **Amendment 43 (1st and 2nd part)** clarifying that the results of all paediatric studies should be included in the summary of the product characteristics and, where the information is of use to patients, in the package leaflet, with some rewording.

  “Article 29(1), second subparagraph:

  Where authorisation is granted, the results of **all** those studies, concerning both the paediatric indications authorised and those which were not, shall be included in the summary of product characteristics and, **provided that the competent authority deems the information to be of use to patients,** in the package leaflet of the medicinal product.”

- **Amendment 50** providing that, if a company stops commercialising a product authorised for a paediatric indication when that product benefited from a reward or incentive in the Regulation, then the company will be compelled to allow another company access the marketing authorisation dossier to be able to continue marketing of the product. Rewording is necessary to clarify that the periods of protection granted by the reward or incentive should have expired for this provision to apply. It is appropriate to provide also for the possibility for marketing authorisation holders to transfer the marketing authorisation, instead of relying on Article 10c of Directive 2001/83/EC, in order to fulfil the obligations contained in this provision. It is also appropriate to add a recital to justify this new provision.

  “Recital 23a:

  It is necessary in the interest of public health to ensure the continuing availability of safe and effective medicinal products authorised for paediatric indications developed as a result of this Regulation. If a marketing authorisation holder intends to withdraw such a medicinal product from the market, then arrangements must be in place so that the paediatric population can continue to have access to it. In order to help to achieve this, the Agency must be informed in good time of any such intention and should make that intention public.

  Article 35a:

  If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from the rewards or incentives of Article 36, 37 or 38, and these periods of protection have expired, if the marketing authorisation holder
discontinues placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation or allow a third party to use the pharmaceutical, pre-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 10c of Directive 2001/83/EC.

The marketing authorisation holder shall inform the Agency of its intention to discontinue the placing on the market of the product no less than six months before the interruption in the placing on the market. The Agency shall make this fact public.”

- **Amendment 52 (2nd part)** concerning the exclusion of the extension of the supplementary protection certificate for products which have received any form of data or market exclusivity for the same paediatric use in the EU.

Data exclusivity is a form of protection which does not have to be applied for; every time a marketing authorisation for a medicinal product is granted, a period of data exclusivity starts to run pursuant to Articles 14(11) of Regulation (EC) No 726/2004 or 10 of Directive 2001/83/EC. Thus, the exclusion of an extension of the supplementary protection certificate for products which have received any form of data or market exclusivity for the same paediatric use in the EU is inappropriate, since it would mean in practice that any product with a paediatric indication already authorised would be deprived from an extension of the supplementary protection certificate, even if new research was done on the paediatric indication (e.g. to extend it to a new paediatric subpopulation or to develop a specific paediatric formulation).

However, the principle of avoiding double rewards based on the same research should apply in the following situation. The new Article 10(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, provides that the period of marketing protection shall be extended by one year if the marketing authorisation holder obtains an authorisation for a new indication which is judged to bring a significant clinical benefit in comparison with existing therapies. In the case of a new paediatric indication, this additional year of marketing exclusivity should not be granted together with the six-month extension of the supplementary protection certificate based on the same research.

To avoid these cumulative rewards, a new paragraph should be included in Article 36:

“**Article 36(5):**

In the case of an application under Article 9 which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for and obtains a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or the last subparagraph of Article 10(1) of Directive 2001/83/EC.”

- **Amendment 55** concerning public access to the inventory of incentives. Rewording is necessary to avoid inconsistency in the text of the provision which would otherwise contain references to both publication and public availability.
“Article 39(3):

Within 18 months of the entry into force of this Regulation, the Commission shall make publically available 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 and these updates shall also be made publically available.”

– Amendment 57 concerning public access to details of trials conducted in accordance with a paediatric investigation plan and included in the European database created by Directive 2001/20/EC (clinical trials directive). Since all paediatric clinical trials conducted in the Community are already covered by Directive 2001/20/EC and entered into the European database, the first paragraph of the provision needs to make it clear that the additional requirement introduced by this Regulation is to enter details of clinical trials conducted in third countries and contained in agreed paediatric investigation plan.

Rewording is also necessary in the second subparagraph of the amendment (paragraph 1a below) to clarify which clinical trials’ results should be made public, by adding a reference to trials submitted to the competent authorities on the basis of Articles 44 and 45. It is not considered appropriate for the Agency to publish conclusions on the information submitted. Rather, any conclusions reached by the competent authorities on the basis of clinical trial results should lead to updates of product information, as stated in Articles 29, 44 and 45.

In order to reflect the public availability of information concerning clinical trials in children, it is appropriate to add additional wording at the end of recital 28.

“Recital 28:

[…] Part of the information concerning paediatric clinical trials entered into the database, as well as, details of the results of all trials submitted to the competent authorities, should be made public by the Agency.”

Article 40(1) and (1a):

1. The European database created by Article 11 of Directive 2001/20/EC shall include clinical trials carried out in third countries which are contained in an agreed paediatric investigation plan, in addition to the clinical trials referred to in Articles 1 and 2 of that directive. In the case of such clinical trials carried out in third countries, the details listed in Article 11 of that directive shall be entered into the database by the addressee of the Agency’s decision on a paediatric investigation plan.

By way of derogation from that provision, the Agency shall make public part of the information on paediatric clinical trials entered in the European database.

1a. Details of the results of all the trials referred to in paragraph 1 and of any other trials submitted to competent authorities in compliance with Articles 44 and 45 shall be made public by the Agency, whether or not the trial was terminated prematurely.”

– Amendment 63 (first part) on the financing of the work of the Paediatric Committee by the Community contribution provided for in Article 67 of Regulation (EC) No 726/2004, with a minor rewording.
“Article 47:

The Community contribution provided for in Article 67 of Regulation (EC) No 726/2004 shall cover 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.”

- Amendment 66 concerning publication of the names of those infringing the regulation. Rewording is necessary to include infringement of any implementing measure adopted, and not only of implementing regulations.

“Article 48(4):

The Commission shall publish the names of anyone infringing the provisions of this Regulation or of any implementing measures adopted pursuant to it, and the amounts of and reasons for the financial penalties imposed.”

- Amendment 67 on the review of the operation of the Regulation and, in particular, of the system of rewards and incentives. Rewording is necessary to ensure that a public health assessment is conducted alongside the economic assessment, in order to be able to judge the overall benefits against costs of the Regulation, and to extend the assessment not only to the reward measures of Articles 36 and 37 but equally to the incentive measures of Article 38.

It is considered appropriate to provide for the possibility of a further report on the application of the rewards and incentives, including the public health assessment of the application of the Regulation, if insufficient data are available after six years, considering that Article 56 provides for a staggered application of the requirements of Articles 8 and 9 and the fact that the extension of the SPC or the market exclusivity for orphan medicines will occur at the end of the period of protection.

“Article 49(2):

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 a detailed inventory of all medicinal products authorised for paediatric use since its entry into force.

The report shall also contain an analysis of the application of Articles 36-38. This shall include an assessment of the economic impact of the rewards and incentives, together with an analysis of the estimated consequences for public health that have accrued as a result of the application of the Regulation, with a view to proposing any necessary amendments.

If insufficient data are available within six years of entry into force of the Regulation to analyse the application of Articles 36-38, taking into consideration particularly the number of medicinal products having obtained a reward or incentive as well as the date of expiry of such rewards or incentives, the Commission shall publish this analysis, as described in the previous subparagraph, in a further report within ten years of entry into force of the Regulation.”
– **Amendment 69** on the eligibility of paediatric studies initiated prior to entry into force to be included in a paediatric investigation plan is redundant since the Commission has accepted amendment 62 which deals with the same situation.

### 3.3. Amendments not accepted by the Commission

: 3, 6 (2nd part), 11, 12, 13, 14, 15 (2nd and 3rd part), 16, 18 (2nd part), 19 (no to moving Articles), 19 (Article 2a, Article 2c and Article 2d) 23, 24, 25, 30, 32, 36, 37, 38, 40 (last part), 41, 43 (3rd part), 44 (2nd part), 46 (1st and 3rd parts), 47, 48, 49, 51, 52 (re patents), 53, 54, 65, 68, 70, 71, 83.

– The Commission does not accept amendments 3 and 16 aimed at moving recital (29) to recital (4a), while maintaining the text of the recital unchanged. Recitals should follow the order of the Regulation and the Commission does not accept amendment 19 insofar as it entails moving the survey, inventory and network (Articles 41, 42 and 43 of the Commission proposal) to a new Chapter 1a.

– The Commission does not accept amendment 6 (second part) tasking the Paediatric Committee with the ethical assessment of paediatric investigation plans. Although ethical aspects of clinical trials in children will need to be considered by the Paediatric Committee when assessing and agreeing paediatric investigation plans, its primary responsibility will be scientific. Ethics in clinical trials are subject to the provisions of Directive 2001/20/EC, and not this Regulation, and of ethics committees, rather than the Paediatric Committee.

– The Commission does not accept amendments 11 and 46 aimed at introducing flexibility to the deadline for placing on the market existing medicinal products newly authorised for children. A provision encouraging marketing authorisation holders to place the product on the market “as much as possible” within one year does not create any legal obligation (the legal obligation is to market within two years). As regards the amendment allowing the competent authorities to grant derogations to the deadlines when they have administrative delays, Community pharmaceutical legislation contains clear deadlines for competent authorities to grant marketing authorisations for medicinal products. Community legislation also foresees deadlines for national decisions concerning the pricing and reimbursement of medicinal products.

– The Commission does not accept amendment 12 stating in a recital that a European paediatric form should be set up for the collection of data on medicinal products authorised in the Member States. There is no corresponding provision to reflect the amendment to this recital, in the Commission proposal or in the amendments proposed.

– The Commission does not accept amendment 13 providing in a recital that, where there is cause for concern and a risk management system is set after marketing authorisation, this system should operate under the responsibility of the Paediatric Committee. There is no corresponding provision in the Commission proposal or in the amendments proposed to reflect the amendment to this recital. Moreover, the marketing authorisation and the post-authorisation obligations to be fulfilled by the marketing authorisation holder are monitored by the competent authorities granting the marketing authorisation, and not by the Paediatric Committee.

– The Commission does not accept amendments 14 and 51 which aim to remove the requirement for a medicinal product to be authorised in all Member States as a prerequisite for the extension of the supplementary protection certificate. The paediatric regulation
aims to ensure that children throughout the EU are provided with safe and effective medicines, and this is achieved through the requirement that an extension of the supplementary protection certificate is available only if the product is authorised in all Member States. Experience has shown that market forces alone do not ensure the availability of medicines for children. Medicinal products are frequently not authorised in Member States where there is no patent or where the population is small.

Amendment 51 proposes that the supplementary protection certificate be granted in Member States were marketing authorisation procedures are still in progress. However, Article 36, in relation to Article 29, provides that the extension of the supplementary protection certificate is only granted if information on the paediatric studies conducted is included in the product information when an authorisation is granted. For this reason, marketing authorisation procedures should be completed for the extension of the supplementary protection certificate to be granted.

Furthermore, in the operation of the mutual recognition and decentralised procedures of Directive 2001/83/EC as amended by Directive 2004/27/EC, Member States have only 30 days from the assessment by the reference Member State to grant marketing authorisations. Differences in the operation of national competent authorities should therefore not lead to significant variation in the authorisation date in the different Member States.

– The Commission does not accept amendment 15 (second and third parts) concerning national clinical trials databases and the avoidance of the repetition of studies already performed in third countries. The need to avoid duplication of studies is adequately addressed in recital 8 of the Regulation. In addition, there is no corresponding provision to reflect the amendment to this recital, in the Commission proposal or in the amendments proposed.

– The Commission does not accept amendment 18 (second part) introducing amongst the objectives of the Regulation a specific mention of medicinal products intended for the treatment of rare congenital conditions suffered by children. The Regulation applies to all paediatric populations and to all diseases suffered by children (including rare congenital diseases) and it is not appropriate to single out in Article 1 any specific disease or condition. In any case, any specific therapeutic needs of children suffering from rare congenital conditions will be addressed through the inventory of therapeutic needs (Article 42 of the Commission proposal).

– The Commission does not accept amendment 19 insofar as it entails moving the survey, inventory and network (Articles 41, 42 and 43 of the Commission proposal) to a new Chapter 1a. The various provisions of Title VI (communication and co-ordination provisions), where the mentioned provisions are included in the Commission proposal, should be maintained to ensure the overall architecture of the Regulation.

– The Commission does not accept amendment 19 as regards the content of the new Article 2a tasking the Member States with collecting available data on existing uses of medicinal products and drawing up of an inventory of therapeutic needs within a year. The Commission proposal provides for a survey conducted by the Member States of available existing data on the use of medicines in the paediatric population (Article 41). These data are provided to the Agency and they form the basis of the European inventory of therapeutic needs of children (Article 42). It is more appropriate to have one European inventory than 25 individual Member State inventories. Besides, a one year dead-line is
impractical: the collection of such data is time consuming and, in addition, before the collection starts the Paediatric Committee is to be established (within six months of entry into force, according to amendment 20 which the Commission accepts in principle) and has to provide guidance on the form, content and format of the data to be submitted.

– The Commission does not accept amendment 19 as regards the content of the new Article 2c concerning the implementing strategy of the European network. This text on the network is the same as Article 43(3) of the Commission proposal. However, the amendment, by omitting paragraphs 1 and 2 of the same Article which provide for the creation of the network, would lead to a text which does not make sense. Therefore, Article 43 should be maintained as in the original Commission proposal.

– The Commission does not accept amendment 19 as regards the content of the new Article 2d tasking the Commission and the Member States with the establishment of a research programme into the paediatric use of medicinal products which are not protected by a patent of supplementary protection certificate. Amendments 9, 56 and 63, which the Commission accepts in principle, would lead to Community funding for off-patents medicines for children. It would not be appropriate to have a separate provision tasking the Member States with a duplicate responsibility.

– The Commission does not accept amendment 23 limiting the number of representatives of the Commission and of the Executive Director of the Agency which may attend Paediatric Committee meetings. In certain circumstances, the Commission or the Executive Director of the Agency may need to be represented by more persons, taking into consideration the items for discussion at each meeting. It should be stressed that such representatives will be observers and not members of the Committee.

– The Commission does not accept amendment 24 which provides that all direct interests of members of the Paediatric Committee relating to the pharmaceutical industry shall be entered in a publicly accessible register. The amendment is unnecessary; according to the first subparagraph of Article 6, individuals with such direct interests are excluded from serving on the Committee.

– The Commission does not accept amendment 25 aiming at specifying, in the provision listing the tasks of the Paediatric Committee, that scientific assistance will be free of charge. The free nature of scientific advice under the Regulation is already provided for in Article 27. In addition, Article 46(3) specifies that assessments by the Committee will equally be free of charge. It would be inconsistent to refer in Article 7(1) to scientific advice being free of charge and not of scientific assessments.

– The Commission does not accept amendment 30 concerning the inclusion, in the marketing authorisation application for a new product, of details of on-going paediatric studies and the time-frame for their completion, to address the situation where it will not be appropriate to conduct studies in children in parallel with studies in adults. The amendment is redundant. The possibility of a “deferral” is specifically included in the proposal to deal with this situation and is referred to explicitly in Article 8(1)(d) which deals with the marketing authorisation application requirements for new products. Thus, the marketing authorisation application must contain, alternatively, the study results (indent (a)) or the proof that the Agency has granted a deferral or a waiver (indents (b), (c) and (d)). If a deferral has been granted, the deferral decision will contain the timetable to complete studies (Article 22). Therefore, this amendment requiring a timetable for completion of
studies as well as the Agency’s decision in that regard is already contained in Article 8(1)(d).

– The Commission does not accept amendment 32 which provides that Article 9(1) of the Regulation should also apply to medicinal products falling within the scope of Article 3(2)(b) of Regulation (EC) No 726/2004 (optional scope of the centralised procedure). The amendment is unnecessary, since Article 9(1) applies to all applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration of authorised medicinal products protected by a patent or a supplementary protection certificate, regardless of the route of authorisation chosen (i.e. it also applies to products falling under the optional scope of the centralised procedure). Besides, Article 29(1) of the Commission proposal opens the centralised procedure to marketing authorisation applications which include one or more paediatric indications selected on the basis of studies conducted in compliance with an agreed paediatric investigation plan. In addition, Article 30 of the Commission proposal provides that applications referred to in Article 9 relating to products authorised through the mutual recognition procedure may obtain an opinion from the Committee on Human Medicinal Products of the Agency. This in turn will lead to a Commission Decision which will be binding on Member States.

– The Commission does not accept amendments 36, 37 and 38 providing that applications for agreement of paediatric investigation plans shall include a summary report; reducing the deadline for validation of such applications by the Agency from 30 to 10 days; and removing the deadline for industry to submit and discuss its plans for paediatric studies with the Paediatric Committee.

To have a summary report prepared by the Agency, rather than the applicant, is of significant value to the later assessment by the Paediatric Committee. This is consistent with the working of the Committee on Orphan Medicinal Products. In turn, for a summary report to be prepared by the Agency, ten days is insufficient.

As regards the deadline for submission of paediatric investigation plans, 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. It is appropriate to set a deadline for the submission of a paediatric investigation plan in order to ensure early dialogue between the sponsor and the Paediatric Committee on whether studies are required and if so, the type of studies and their timing compared to studies in adults. In fact, the deadline provided for in Article 17(1) is a deadline to submit a draft plan, and not a deadline for the initiation of studies in children. Furthermore, the plan may contain a request for a deferral of the initiation or completion of studies, and an agreed plan can be subsequently modified. The amendment, by deleting the deadline, could lead to a situation where products would almost never be investigated in children early during the product’s development and this would deny children innovation and be to the detriment of public health.

To clarify that the intention of the deadline is to allow for early dialogue, the following should be added at the end of recital 7:

“Recital 7:

[…] It is appropriate to set a deadline for the submission of a paediatric investigation plan in order to ensure early dialogue between the sponsor and the Paediatric Committee. As the
The development of medicinal products is a dynamic process dependent on the result of ongoing studies, provision should be made for modifying an agreed plan where necessary.

- The Commission does not accept amendment 40 (last part) aimed at establishing that the Paediatric Committee propose a deadline for the submission of an amended paediatric investigation plan. The provision, as contained in the Commission proposal, allows the company to request modifications to an agreed plan. This request is the modified plan, hence it is unnecessary for the opinion on the modified plan to contain a dead-line for the submission of yet another modified plan.

- The Commission does not accept amendment 41 aimed at defining the detailed rules governing the interaction between the applicant, the rapporteur and the Paediatric Committee. In keeping with the practice of other existing committees at the Agency, details on the interaction between the rapporteurs and the applicants should be detailed in the rules of procedure of the Committee, to be adopted following the procedure defined in Article 5(2).

- The Commission does not accept amendment 43 (third part) aimed at dictating that paediatric information contained in product information (the summary of product characteristics and patient information leaflet) should always clearly state the paediatric indications approved and those that are not. The way information on indications that have been approved and those that have not, as well as information on contra-indications, is presented in product information is the subject of detailed scientific guidelines at Community level. The spirit of this amendment is clearly reflected in these guidelines, which are regularly updated to reflect advances in science. It is considered that to introduce this amendment would prevent the provision of information to patients and healthcare professionals from evolving to reflect best practice.

- The Commission does not accept amendment 44 (second part) aimed at creating a European competition to design a logo to be used to label medicines for children. The choice of the logo and guidance on how it will be applied will require the expertise of specialists in paediatric medicines and the labelling of medicines. Furthermore, it is considered appropriate to have the logo chosen as soon as possible after entry into force of the regulation, and a competition to choose the logo would be likely to delay this adoption and would exclude input from relevant specialists.

It is necessary to include a new subparagraph to provide for how the logo will be selected:

"Article 33, second subparagraph:

The logo shall be selected by the Paediatric Committee within one year of entry into force of the regulation."

- The Commission does not accept amendments 47, 48, 49 and 83 which aim to duplicate or amend some of the pharmacovigilance provisions contained in the Community pharmaceutical legislation. It should be noted that the general provisions of the Community pharmaceutical legislation, which apply to all medicinal products authorised to be placed on the market of the Community, have recently been revised with the adoption of Regulation (EC) No 726/2004 and Directives 2004/27/EC and 2004/28/EC. New provisions relating to risk management systems, communication, funding of pharmacovigilance and the public accessibility of adverse reaction data are amongst the
numerous new pharmacovigilance provisions in the revised pharmaceutical legislation. To duplicate some of the measures in this Regulation and to slightly amend some of these would create legal uncertainty.

Specifically regarding amendment 47, the Commission proposal already grants the competent authority with the power, whenever it has cause for concern, to require a risk management system to be put in place. To make the requirement for a risk management system compulsory, even when there is no particular cause for concern, adds unnecessary administrative burden and will interfere with clinical care thereby acting as a barrier to access to medicines.

Specifically regarding amendment 48, the Commission agrees to the objective of the amendment. However, provisions concerning information on pharmacovigilance matters to the public already exist and apply to all medicinal products authorised in the Community (Article 24(5) of Regulation (EC) No 726/2004 and Article 104(9) of Directive 2001/83/EC). The repetition of similar provisions in this Regulation is unnecessary and could lead to difficulties of interpretation.

Specifically regarding amendment 49, the Commission agrees to the objective of the amendment. However, provisions concerning public funding of pharmacovigilance already exist and apply to all medicinal products authorised in the Community (Article 67(4) of Regulation (EC) No 726/2004 and Article 102a of Directive 2001/83/EC). The repetition of similar provisions in this Regulation is unnecessary and could lead to difficulties of interpretation.

Specifically regarding amendment 83, the Commission agrees to the objective of the amendment. However, provisions concerning the public accessibility of adverse reaction data already exist and apply to all medicinal products authorised in the Community (for example, Article 26, subparagraph 3 of Regulation (EC) No 726/2004 and Article 102, subparagraph 2 of Directive 2001/83/EC). The repetition of similar provisions in this Regulation is unnecessary and could lead to difficulties of interpretation.

– The Commission does not accept amendment 52 (first part relating to patents) which excludes an extension of the supplementary protection certificate for products whose active substance has already benefited from a patent covering the paediatric use or formulation.

This amendment would run counter to the objective, central to this Regulation, of stimulating research into medicines for children. New paediatric research into substances which may already have paediatric indications covered by a patent or supplementary protection certificate (for instance, to extend the use of the product to other paediatric subpopulations or to better adapt it to the specific needs of children) would be discouraged. Moreover, it would discourage paediatric research by third parties (different holders of patents or supplementary protection certificates). This would also be difficult to reconcile with the purpose of the regulation governing the supplementary protection certificate (Regulation (EEC) No 1768/92), which aims at giving sufficient protection to all research, including new applications of an existing product.

However, and in line with the purpose of this amendment, it is appropriate to clarify in the Regulation that the rewards associated with a completed agreed Paediatric Investigation Plan should only be triggered by research completed after entry into force of the Regulation. In this way, it will be ensured that any extension of the supplementary protection certificate or of
market exclusivity under Articles 36 and 37 of this Regulation is based on new paediatric research. Articles 29(3) and Article 44(3) should be reworded as follows:

“Article 29(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. For the purpose of the application of Article 44(3), this statement shall also indicate whether significant studies contained in the agreed Paediatric Investigation Plan have been completed after the entry into force of this regulation”

Article 44(3):

Without prejudice to the previous paragraph, the rewards of Articles 36 and 37 shall only be granted provided that significant studies contained in an agreed Paediatric Investigation Plan are completed after the entry into force of this regulation.”

- The Commission does not accept amendment 53 which aims to exclude the possibility of more than one extension of the supplementary protection certificate per medicinal product. The amendment is redundant, since the provision is already provided for in Article 52, indent (5), which amends Article 13 of Regulation (EEC) No 1768/92 (the supplementary protection certificate regulation).

- The Commission does not accept amendment 54 which aims to offer the applicant an additional possibility which would simplify the marketing authorisation procedure for orphan drugs. The procedures for authorisation of orphan medicinal products are identical to those for all other medicinal products, and they are not the subject of this Regulation. Furthermore, there are already provisions in the existing Community pharmaceutical legislation to allow, where appropriate, the early authorisation of orphan medicinal products, such as the provisions on accelerated assessment or conditional marketing authorisation of Regulation (EC) No 726/2004 (Article 14).

- The Commission does not accept amendment 65 which aims to promote the harmonisation of national measures enacting penalties, but does not provide any means to ensure such harmonisation. Harmonisation of national measures would demand the adoption of Community legislation in the field.

- The Commission does not accept amendment 68 which aims to reduce the deadline for submission of an application for an extension of the supplementary protection certificate. It takes approximately two-years to conduct the necessary studies and obtain a marketing authorisation for a generic medicinal product. If the deadline of two-years is not maintained, then there is a risk that generic manufacturers will start to invest in a new generic product and that subsequently the access to the market will be prevented by an extension of the supplementary protection certificate.

- The Commission does not accept amendment 70 which aims to introduce transitional measures relating to paediatric investigation plans. Applications submitted prior to the entry into force of the regulation cannot include findings from studies with agreed
investigation plans since there will be no legal basis in the pharmaceutical legislation or competent committee within the Agency to agree paediatric investigation plans in advance of the entry into force of the Regulation. However, this does not mean that research in advance of the entry into force is discouraged. In accordance with Article 44(2) (see amendment 62), existing and on-going studies at the time of entry into force of the regulation shall be taken into consideration by the Paediatric Committee once the regulation comes into operation.

The Commission does not accept amendment 71 which reduces the number of months from entry into force of the Regulation from which the requirements of Articles 8 and 9 shall apply. The shortened deadlines are considered unworkable. Articles 8 and 9 place requirements on applicants for marketing authorisations to present either the results of studies in children, or proof of having obtained a waiver or a deferral. After the entry into force of the regulation, the Paediatric Committee will need to be set up (within 6 months, see amendment 20). It is judged that 12 months will be required of having the Paediatric Committee operational to ensure that companies are able to agree paediatric investigation plans, deferrals or waivers, so that the requirement can function.

4. CONCLUSION

In keeping with Article 250, paragraph 2, of the EC treaty, the Commission modifies its proposal along the lines indicated above.