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Single market : management & legislation for consumer goods  
Pharmaceuticals : regulatory framework and market authorisations

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## **Better Medicines for Children**

### **Proposed regulatory actions on Paediatric medicinal products**

#### **Consultation document**

#### **SUMMARY**

Before any adult is treated with a medicine, he or she can be sure that it has been extensively tested to assure that it is safe, effective and of high quality for use in adults. The same may not be true for medicines used in children. It is estimated that over 50% of those used, particularly in specialised medicine, have never actually been studied for use in children. The absence of suitable authorised medicinal products to treat diseases in children which have been both tested and assessed is an issue that has been of concern for some time. As a result existing EU medicines frequently do not include information on safe and effective use in paediatric populations. This in turn leads to the use of unauthorised medicinal products and /or medicines used outside their approved terms "off-label" and may result in significant risks, including lack of efficacy and /or unexpected adverse effects, even death. The issue has been raised by regulators, individual Member States, Members of the European Parliament, by paediatricians, and parents. In December 2000, the European Health Council asked the Commission to take specific action to remedy the problem.

This document outlines some suggested approaches which could be taken to address the lack of suitably adapted medicinal products. It examines a number of possibilities for incentives in the form of intellectual property protection and proposes the creation of a dedicated European expert group as well as a European network of paediatricians with specific competence in the oversight of appropriate trials in children.

Issues of information and transparency are discussed as well as the need to ensure the highest ethical standards as laid down in the EU directive on Good Clinical Practices when performing all trials on children.

The need for sources of funding for children oriented research into medicinal products which are no longer associated with any intellectual property protection is also outlined and some options are explored.

This paper represents one of the first steps in the fulfilment of the Commission's commitment to address this problem and follows a Brainstorming Meeting with Member States organised in the framework of the Commission's Pharmaceutical Committee in November 2001.

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## **I. INTRODUCTION**

Before any adult is treated with a medicine, the product 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 adult population. The same may not be true for medicines used to treat children. 50% or more of medicines used have never actually been studied in children. Children represent a vulnerable population with developmental, physiological and psychological differences from adults. These differences make age and development related research particularly important.

The absence of suitable authorised medicinal products to treat diseases in children is an issue that has been of concern for some time. This is a result of the failure of pharmaceutical companies to perform the necessary tests and trials to adapt medicinal products to the needs of children. It leads to the use of “off-label” and unauthorised products and to risks of inefficacy and/or adverse effects and thus a public health concern. The issue has been raised by regulators, individual Member States, Members of the European Parliament and by paediatricians. These concerns have also been expressed through the adoption, on 14<sup>th</sup> December 2000, of a Health Council Resolution on paediatric medicinal products. This resolution 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.

## **II. BACKGROUND**

### *Current situation*

In the European Union, children, the 0-16 years old population, represent about 75 million people, i.e., 20%, a fifth of the total population. Although this population may appear relatively large, the majority of medicines are still only developed and assessed for use in adult populations. This is further compounded by the fact that this 0-16 years group may be further divided into specific sub-populations ranging from neonates to teenagers, with different developmental and behavioural characteristics which need to be addressed.

It is estimated that somewhere between 50 and 90% of medicinal products depending on therapeutic areas, used in children have never been specifically evaluated for use in children. The range reflected by these figures represents the difference between the figures in non- specialist and specialist situations respectively and may also reflect differences between approaches taken in different Member States.

### *Reluctance of industry and resulting problems for children*

Pharmaceutical companies have traditionally been reluctant to invest in developing specific treatments or adapting existing medicines to meet the needs of the paediatric population, mainly because the market is small and therefore of lower priority to them and the risks associated with paediatric treatments are generally higher, (e.g. need for long term follow-up of adverse effects). Specific clinical studies may be difficult to design and as a result may be costly, and the revenue from the paediatric development of the products is not perceived as justifying the cost of the clinical trials. However, due to age-related differences in the drug handling or drug effects which may lead to different

dose requirements to achieve efficacy or to avoid adverse effects, specific clinical trials in paediatric populations are normally required. In addition, the pharmaceutical industry tends not to develop specific paediatric formulations. This may cause problems especially for younger patients, e.g. difficulties with swallowing tablets as compared with liquid preparations, risks of fatal inhalation. More significantly it may lead to serious calculation errors in adjusting adult formulations to paediatric dosage forms. Other problems resulting from the absence of suitably adapted medicines include the following:

- Inadequate dosing information leading to increased risks of adverse reactions including death;
- Ineffective treatment through underdosing;
- Non-availability to children of therapeutic advances;
- Extemporaneous formulations for children which may be poorly or inconsistently bioavailable.

#### Previous EU Regulatory activities and international examples

In 1997 a round table was organised by the Commission in the premises of the EMEA (European Agency for the Evaluation of Medicinal Products) to discuss this issue. One of the conclusions at that time was that there was a need to strengthen the legislation, in particular by introducing a system of incentives. In 1998, the Commission supported the need for international discussion on the performance of clinical trials in children and an ICH (International Conference on Harmonisation - discussions on harmonisation of pharmaceutical regulatory requirements between the EU, Japan and US) guideline was agreed and subsequently adopted as a European guideline in July of 2000. Directive 2001/20/EC on Good Clinical Practice which was adopted in April 2001 also takes into account some specific concerns of performing clinical trials in children, and in particular lays down criteria for their protection in clinical trials. However, even if there is a clear therapeutic need for the product, there is currently no legal provision for obliging these studies to be performed if the company does not present the product for use in the paediatric population.

#### **Example of Regulation on Orphan medicinal products**

There are many similarities between the absence of research into medicinal products for children and the absence of research into treatments for rare diseases which led the Commission to propose the Regulation on Orphan medicinal products, subsequently adopted in December 1999. Therefore there are elements of this existing regulation which could be taken as a model for future activities.

#### **International examples**

In the US, specific rules to encourage the performance of clinical trials in children were introduced by the so-called “paediatric rule” and “paediatric exclusivity” adopted in 1998 and 1997 respectively. These pieces of legislation are complementary.

The “paediatric rule” allows the US Food and Drug Administration (FDA) to require companies to perform such studies and/or to develop paediatric formulations for certain new and already marketed medicinal products if the product is likely to be used in a

substantial number of paediatric patients or if it would provide a meaningful therapeutic benefit to paediatric patients over existing treatments.

The “paediatric exclusivity” provision provides an incentive (6 months additional exclusivity or patent protection on the active moiety) for companies who perform clinical studies in paediatric populations irrespective of the results of these studies but on the condition that studies comply with criteria set by the FDA on the basis of public health needs. In addition it required the FDA to draw up guidelines and a “paediatric list”, i.e. a list of drugs for which additional paediatric information was expected to be beneficial.

After three years of operation, the paediatric exclusivity provision has just been reviewed by the US Congress. Due to its perceived success in stimulating new studies on medicinal products to treat children of different age groups (21 labelling changes and more than 400 studies started in 3 years), it has been extended in a slightly modified manner. The paediatric list was found not to be successful and has not been retained. In particular, a fund dedicated to the study of off-patent medicinal products for use in children has been created to the tune of \$200 million annually

### **III. PROPOSED OBJECTIVES OF NEW EU REGULATORY INITIATIVES ON PAEDIATRIC MEDICINAL PRODUCTS**

Prerequisites for any European regulatory action to solve the problems identified include the need to ensure that the measures taken would benefit European children throughout the Community, thus emphasising the importance of a truly European approach and the need to ensure that any studies performed in children fully comply with the highest ethical principles as laid down in the recently adopted Directive 2001/20/EC on Good Clinical Practice, (GCP). Additional and specific provisions to protect children in this directive include the need to ensure that appropriate informed consent procedures are developed and used, the wishes of the child are respected, measures to minimise pain and distress are taken and that the responsible ethics committee has involved specific expertise in the field of paediatrics.

Six sets of objectives can be described:

**1. Increasing the availability** of authorised medicinal products which are suitably adapted to the needs of children of different age groups by:

- Encouraging the performance of appropriate paediatric studies to ensure that new medicinal products may be safely and effectively used in children of different age groups
- Encouraging the development of appropriate paediatric studies on existing authorised medicinal products, in cases where a perceived therapeutic need in paediatric populations exists, in order to ensure that they are suitably adapted to the needs of children of these different age groups.
- Encouraging the development of suitably adapted formulations.
- Facilitating the performance of appropriate paediatric studies through the provision of scientific advice on how studies should be performed and/on alternative ways of presenting the product e.g. a new formulation.

- Encouraging transparency of information on products and treatments currently used in children through the establishment of a database, and including also information where studies have resulted in contraindications or other restrictions to use in children.
- Facilitating international collaboration and exchange of regulatory information.

**2. Ensuring that pharmacovigilance mechanisms are adapted** to meet the challenges of possible long-term effects in specific cases

Consideration of whether there is a need to develop specific post-authorisation obligations for specific medicinal products to be used in children.

**3. Facilitating the avoidance of unnecessary studies** through the publication of details of clinical trials already initiated and better exchange of information.

**4. Establishment of a list of priorities for research** on existing authorised medicinal products in accordance with public health needs and which may include priorities in **different therapeutic classes**.

**5. Developing European excellence in the field of research, development and assessment of clinical trials** for paediatric medicinal products, through the creation of a specific and dedicated committee or expert group within the European Medicines Evaluation Agency (EMA) and through promoting the creation of a European paediatric network for performing paediatric studies.

6. Ensuring that the **highest ethical criteria** are met, as laid down in the specific provisions for the protection of children in the recently adopted **Directive 2001/20/EC on Good Clinical Practice** and as described above.

#### **IV. AVENUES TO EXPLORE OR PROPOSED MEANS OF ACHIEVING THESE OBJECTIVES**

It is suggested that a new set of legislative provisions may be necessary to achieve the objectives outlined. At the November 2001 Brainstorming meeting of Member States, held within the framework of the Commission's Pharmaceutical Committee, the importance of taking a European wide approach was stressed, taken into account single market considerations and development efficiencies.

##### **1. Incentives for research**

In the EU, as in the US, it is clear that market forces are inadequate to stimulate the necessary studies in children. A system of Community incentives is necessary both to encourage appropriate studies on products already on the market and to ensure that new applications for marketing authorisations will include the necessary studies to ensure they are adapted to the needs of children of different age groups.

A number of possible incentive mechanisms could be considered. These are not mutually exclusive:

*Encouraging the performance of appropriate studies for medicinal products for which protection of intellectual property exists*

It is proposed to introduce an additional period of market exclusivity as a reward for submitting one or more validated clinical studies on children of one or more age groups.

This period of market exclusivity would apply at the end of the existing period of patent or Supplementary Protection Certificate (SPC) protection. Regulatory authorities would be required not to accept applications for generic marketing authorisations until this additional period had elapsed. A mechanism similar to the “written request” system in the US could be developed in order to ensure that the studies performed were both useful and appropriate. One possibility would be to ask companies to submit a development plan, which would be assessed by an EU expert group before agreeing eligibility for the clinical studies to be considered within the new legal provisions. A mechanism to pre-define criteria in order to avoid unnecessary studies could also be put in place.

*Encouraging the performance of appropriate studies for already marketed medicinal products for which no intellectual property exists*

a) Introduction of a period of data protection for a marketing authorisation with a paediatric indication (in a similar way to the exclusivity provided to the orphan indication in the EU regulation for orphan medicinal products) through the creation of a new type of “kid” marketing authorisation.

The protection would be valid for the active substance/indication combination. In order to help this to work in practice, it would be possible to create a new kind of marketing authorisation, possibly with a specific prefix or suffix, e.g. “Kid – XYZ (drug)” or “Paed-drug”. This would facilitate the distinction with an existing marketing authorisation and would help to ensure that the new paediatric data was protected and thus a valuable commodity. It would be applicable for medicinal products where no intellectual property right existed. In addition it would allow companies who were not the originator to exploit known medicinal products and develop specific formulations supported by specific studies.

Only the paediatric indication would benefit from the data protection provisions.

b) Creation of a fund which could be used to fund clinical or non-clinical paediatric research. Current estimates from the US National Institute of Health indicate that a safety and efficacy study may cost between \$1 and \$7.5 million, depending on the number of children participating and the type of medicinal product being studied. Industry sources quote higher estimates from \$5 to \$35 million. For the 400 studies started in the US between 1997 and 2001, this represents an annual budgetary requirement of approximately \$670 million. The new recently adopted US act allocates \$200 million annually. In Europe, based on an average estimate of €5 million per trial, 20 studies could be performed annually at a cost of about €100 million.

Despite the variance in these estimates, it is clear that a significant source of income is required in an area where there is little other incentive to do this work and that a source of income to finance these studies must be found. One possibility would be to use some of the proceeds from the additional profits made by the extension of the intellectual property or market exclusivity provisions to create a fund, which could then be used for further studies on already marketed products. In principle, this fund could then be used to contract out certain research projects.

c) Investigation of existing national and community sources of research funding.

In the provisions of the chapter on *Strengthening the Foundations of the European Research Area*, in the text of the sixth framework programme, specific mention of efforts

to co-ordinate research activities in the area of health, including health issues in children is made. Additionally there may be a possibility to support clinical trials in children in the area of cancer research or in other areas such as diabetes, and rare diseases provided that the trials incorporate some aspects of “genomic” research in one way or another.

Investigation of research funding at national level - certain limited funding has already been sought at national level for similar initiatives in some Member States, notably UK and Germany. For example, in Germany there is a possibility of funding from the Federal Ministry of Education and Research (BMBF) sufficient to cover one or two studies annually.

## **2. New applications for marketing authorisations – legal requirement for clinical trials in children**

It is suggested that an approach similar to that adopted in the context of the US paediatric rule be taken, that is to routinely require studies in paediatric populations as part of the marketing authorisation application requirements. Applicants would be required to submit the results of studies performed as a requirement for validation. Paediatric applications would be screened by a European expert group, which would determine whether or not the studies were acceptable in principle (e.g. corresponding to pre-defined criteria) The assessment of the studies would then form part of the normal assessment of the marketing authorisation. The possibility of a waiver would be necessary in certain justified cases where there is no therapeutic need in paediatric populations (e.g. Alzheimer’s disease, certain heart conditions). It would be the responsibility of the applicant to justify the need for a waiver. In certain cases it may be possible to defer the completion of the studies until after the application for the adult population had been submitted, on the basis of a development plan and justification provided by the applicant.

In any event, compliance with Directive 2001/20/EC on clinical trials and with ethical principles will be assured.

## **3. Transparency- creation of a central database**

### *a) Existing data on medicinal products (including off-label use in children)*

Although published data indicates that most of medicinal products used to treat paediatric populations have never been studied in the target population, in fact there is a certain amount of published (often poorly documented) experience with the use of certain medicinal products in children, particularly in the area of intensive care and specialist treatments. An attempt to collect this information would be useful in order to determine priorities for future work and/or to ensure that the same information and treatment possibilities were available throughout the EU.

It should be noted that, although they may not have official endorsement, “paediatric formularies” have already been put together in several countries such as the British Formulary on Medicines for Children in the UK and the “Vidal pédiatrique” in France.

It is suggested that a central database to ensure that this information is collected and made available should be set up.

Information on all new approved indications and on the outcomes of negative trials should also be collected and made publicly available.

*b) Use of the database foreseen by Directive 2001/20/EC for information on clinical trials*

In order to avoid the possible repetition of studies in children which do not add to the collective knowledge, the scope and application of the European database foreseen in Article 11 of Directive 2001/20 should be examined in the specific context of clinical trials in children. A method to avoid this type of repetition, prior to their commencement, should be developed.

**4. Developing European excellence –establishment of an EU scientific expert group**

One of the advantages that the US has over the EU in the area of clinical trial development is the fact that there is regulatory oversight through the “IND” Investigational New Drug application from an early stage of product development. This contributes also to the development and maintenance of specific regulatory expertise. Although the traditional EU approach has been less interventional when it comes to the design of clinical trials, the growth of the “scientific advice” facility in the EU marketing authorisation application process and the requests for protocol assistance in the context of the development of orphan medicinal products shows clearly that there is growing support for EU regulatory intervention at an early stage of the product development.

It is proposed to create an EU expert group or working party within the European Medicines Evaluation Agency (EMA) with specific responsibility for all aspects relating to the development, availability and follow up of paediatric medicines.

**5. Encouraging submission of trials in Europe that have been accepted internationally**

The US paediatric exclusivity provision has to-date (January 2002) encouraged over 400 specific studies to be performed, resulting in a large amount of information on paediatric use and 21 labelling changes. So far there is little evidence that these studies have been submitted for regulatory approval in the EU and/or to support labelling changes in medicinal products that have been authorised in the EU.

If a clinical study has been performed according to internationally accepted GCP standards and in accordance with the internationally accepted guidelines on medicinal products in children (ICH E11) then it would be expected that this clinical study would be accepted with minimal additional requests for information. If acceptable and robust studies have been performed, then it cannot be ethically justified either to repeat these studies or to require significant additional data.

Ideally any studies that have already been performed outside of the EU should be used to introduce useful information, in particular to support or to contraindicate paediatric indications in medicinal products that are on the EU market. This depends on the studies being submitted as part of a marketing authorisation, variation, or extension application to an EU regulatory authority. It is therefore important to have a mechanism to ensure that these studies will actually be submitted as part of an application for authorisation in the EU and assessed in a harmonised manner.

**6. Post-authorisation issues – possible need for long term follow-up**

Although the requirement to report adverse reactions on medicinal products used in treatments applies in the same way as for adult medicines, the fact that there is such a large percentage of unauthorised or “off-label” use implies that the extent of adverse reactions actually reported may be significantly less than those encountered in medical practice. This, combined with the small size of many treated paediatric populations raises the question as to whether a system of spontaneous adverse reaction reporting is the only appropriate mechanism to properly manage the risk of medicinal products used in children. The possibility of requiring more dedicated follow-up pharmacovigilance studies for certain high-risk products could be considered. Cases where a specific adverse reaction is anticipated, specific studies to monitor these reactions could be requested.

An additional concern with respect to the effect of medicinal products used in young children on their future development and maturity exists. As with all medicines there is a careful balance between benefits and risks to be achieved. However in order for this to be properly assessed in the case of medicines to treat children, there may be a need, in specific cases to include a provision to monitor treated children for a longer term and in some cases throughout their entire lives. This type of exercise would inevitably be both difficult and costly for companies to perform.

## **7. Creation of a Pan-European network of clinical excellence for performance of paediatric studies**

Clinical trials in children may require specific expertise, specific methodology and in some cases, specific facilities. One of the challenges of creating a system which will effectively increase the number of clinical trials performed to develop or adapt medicines for use in children is the need to ensure that these studies are carried out in suitably adapted facilities by appropriately trained investigators and paediatricians. A number of initiatives to create networks of paediatricians have been taken at national level in Europe, for example initiatives in France, Germany and United Kingdom, but there has been little attempt at cross border collaboration. Consideration should be given to the creation of a Pan-European network which would link together existing national initiatives in order to build up the necessary competences at a European level and to facilitate co-operation and avoid duplication.

## **V. CONCLUSION**

Similar measures to those already taken in the US are urgently needed for European children. These must take account of the specificities and structure of the Community market and pharmaceutical regulatory system. Achieving the right combination of incentives and regulatory obligations which will ensure that both existing and new medicinal products are suitably adapted for the needs of paediatric populations in the Community in a resource efficient manner is a challenge that must be met in order to ensure the best and safest treatments for our children. The aim of this paper is to outline potential options of addressing this challenge by new pharmaceutical legislation.

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Feedback and comments from all interested parties are invited before the **30<sup>th</sup> April 2002** at the following address:

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