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Medicines for children: time for Europe to act

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The use of unlicensed and off-label medicines in children has increasingly been the subject of controversy over the years. The future European paediatric Regulation aims to change the situation in Europe with respect to the availability of medicines suitably adopted for use in children. The proposed legislative measures are based on a combination of reward/incentives and requirements for both products with ongoing patent protection and those off-patent. After extensive consultation, the first draft has recently been published. Following the experience gathered in the United States, and the recent European experience with Orphan drugs, it is expected that more clinical trials will be performed in children in the near future, and that more medicines with proper information and suitable formulation will become available for use in children.

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Introduction

More than 20 years after the initial attempts to provide more prescribing information for medicines used in children, the situation in Europe is still far from satisfactory. It is well known that medicines, including many that are widely used in children, have rarely been tested for use in children. Unlicensed and off-label use remains the main basis for prescription of medicines to children, who are denied access to well-studied and assessed treatments and diagnoses. The literature repeatedly shows that off-label use of medicines is associated with an increased risk of both adverse drug reactions and medication errors[1,2].

The primary aim of the European pharmaceuticals law is to safeguard public health while encouraging the development of the pharmaceutical industry and the creation of a single market for pharmaceuticals in the European Union (EU). At the same time, the highest standards need to be maintained to ensure the quality, safety and efficacy of medicines authorised in the Community. Over the past 40 years, the Community legislative framework has established and harmonised many aspects of regulating the production, distribution and use of medicines in the EU. A major step was taken in 1995 with the creation of the European Medicines Agency (EMEA) and the establishment of the centralised procedure, leading to the single EU-wide evaluation and community

approval of new medicines[3]. The framework is consistently evolving and developing to resolve emerging problems and to meet new challenges and advances.

The European pharmaceutical legislation has recently been reviewed[4]. However, the current legislative framework remains inadequate in relation to the development of medicines for the paediatric population. In the past few years, the need to establish proper requirements for the study of medicines in children has nonetheless been recognised, as the voluntary system for submission of the data by companies has not proved to be effective. This has been supported by the experience from the USA where the measures introduced have stimulated the research and increased the number of products labelled for children, but have brought little benefit to the children of Europe[5].

Consequently, after a long phase of consultation, the European Commission released, on 29 September 2004, a proposal for a Regulation of the Council and European Parliament on medicinal products for paediatric use[6]. This article gives a brief summary of the main steps leading to the development of the legislative proposal, and provides an overview of the key measures proposed in the draft Regulation.

Background

Over the years, several EU Member States have attempted to introduce measures to increase the availability of authorised medicines that are specifically adapted for use in children but, in practice, these have largely failed to translate into real changes. The only major development in the 1990s in Europe was the release of the note for guidance on the clinical investigation of medicinal products in children by the scientific committee of the EMEA[7]. This guidance addressed two major points: firstly, the classification of children into different age groups, i.e. neonates (two groups – preterm and term), infants and toddlers (1–23 months), children and adolescents and secondly, the timing of clinical trials in relation to the type of medicines.

The European Commission then took the initiative and brought this topic to an international level. In the context of the International Conference on Harmonisation (ICH), an organisation working for the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and US, the "Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population" (E11) was agreed (http://www.ich.org). This guidance, which superseded the previous European guideline, has been in force since July 2002 (http://www.emea.eu.int/pdfs/human/ich/2711/99/EN.pdf). Despite this document, which is not legally binding, the situation in terms of availability of information on medicines for use in children did not significantly improve[8].

The need to take concerted action at the European level led the EMEA, in collaboration with the European Commission, to convene in December 1997, a round table discussion with clinical pharmacologists and paediatricians from throughout the EU together with representatives from European Parliament, learned societies and industry. One of the conclusions of the meeting was that there was a need to strengthen the legislation, in particular by introducing a system of incentives[9].

The next notable step came three years later, when the European Council of Ministers, under the French presidency, adopted a Resolution in December 2000. This Resolution asked the European 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 medicines for children and medicines already on the market are fully adapted to the specific needs of children. The response to this Council Resolution came in September 2004, with the release by the European Commission of the draft legislative proposal for a Regulation on medicinal products for paediatric use[10].

During the preparatory phase, the European Commission extensively consulted interested parties (Table 1). In November 2001, the European Commission organised a brainstorming meeting with representatives of EU Member States and the research-based industry. This was followed by the release of a public consultation paper in February 2002. Because of the complexity of healthcare delivery and the pharmaceutical sector, an environmental risk assessment was conducted to

Table 1 Chronology of events

December 2000	Council Resolution
January – June 2001	Informal discussion with industry, attendance at workshops, conferences
7 November 2001	Meeting with industry/paediatricians (IFIP, Paris)
15 November 2001	Brainstorming meeting with Member States
2 December 2001	Discussion with European Group of Paediatricians (CESP)
5 April 2002	Workshop in France with all interested parties
November 2002	Circulation of reflection paper to Member States
15 May 2003	Discussion with Member States in the Pharmaceutical Committee
22 July 2003	First meeting of ad-hoc group of the Pharmaceutical Committee on paediatric medicines
29 September 2004	Release of the Proposal for a Regulation on Medicinal Products for Paediatric Use.

look at the potential social, economic and environmental consequences of a Regulation on the different stakeholders involved[11]. The proposed Regulation 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[12] and on the 2000 Community legislation on Orphan medicinal products[13].

In parallel to the legislative development, in 2001 the scientific committee of the EMEA, the Committee for Medicinal Products for Human Use (CHMP) decided to set up a paediatric expert group (PEG) with the following objectives:

- obtain information on medicinal products currently used in children and agree where there are medical needs for the paediatric population
- contribute to guidelines relating to the development of medicinal products for paediatric use
- define the means and ways to make the information on paediatric medicinal products available to health care professionals and the general public
- advise the European Commission on matters relating to paediatric medicines

Proposal for a Regulation of the Council and of the Parliament on Medicinal Products for Paediatric Use

The draft proposal aims to improve the health of the children of Europe by stimulating the research, development and authorisation of medicines to treat children without subjecting children to unnecessary clinical trials and without delaying the authorisation of medicinal products for other populations. It directly interfaces with the existing Community framework for the regulation of medicines, including the protection of clinical trials subjects and databases[14], orphan drug designation, marketing authorisation procedures and the community structures.

Marketing authorisation requirements

The proposal holds that for new medicines and those still patent protected, companies will be required to present the results of studies performed in children at the time of the marketing authorisation application or application for a new indication, new dosage form or new route of administration. The studies would have to be conducted according to an agreed paediatric investigation plan. The basic concept is that development of medicines for children should be an integral part of the development of medicines, integrated in the development programme for adults. This paediatric investigation plan will have to be agreed by a Paediatric Committee, to be set up. When assessing such plans, the Committee will have to take into consideration two essential principles: that the studies should only be performed if there is a potential therapeutic benefit to children, with the aim to avoid unnecessary studies, and that the requirements for studies in children should not delay the authorisation of medicines for other populations (e.g. adults). The proposal aims to ensure that medicines are tested in children only when it is safe to do so. A system of waivers from the requirement is also proposed to deal with the cases of medicines unlikely to benefit children (i.e. diseases specific to adults).

There would be a mixed reward and incentive for compliance with the requirement in the form of 6 months extension of the supplementary patent protection (SPC), in effect a patent extension of the active moiety – or if the product is an orphan medicinal product, two additional years of the market exclusivity added to the existing ten years awarded under the EU orphan regulation.

Paediatric use marketing authorisation

For older products, already on the market but no longer patent protected, a new type of authorisation is proposed (paediatric use marketing authorisation or PUMA). It would be specifically for off-patent products developed exclusively for use in children. It would cover the paediatric indication and its formulation. As for new medicines, the development would have to be performed in accordance with a paediatric investigation plan. If obtained, the PUMA would allow 10 years of data protection for innovation (new studies).

Paediatric Committee

At the centre of the proposal is the setting up of a new scientific committee, the Paediatric Committee, with expertise in all aspects of the research, development, authorisation and use of medicines for children. It will be mainly responsible for the assessment of and agreement on companies' paediatric investigation plans as well as waivers and deferrals. This Committee will be within the EMEA, allowing coordination with other EU scientific committees already operating.

Other measures

The draft Regulation includes other provisions:

- measures to increase the robustness of pharmacovigilance and risk management (safety monitoring) for medicines marketed for children

- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines
- an EU network of investigators and clinical trial centres to conduct research and development on medicines for children
- a system of free scientific advice for the industry, provided by the EMEA
- a database of paediatric studies.

There is also a requirement for industry to submit to the authorities study reports they already hold on the use of their medicines in children, to maximise the utility of existing data and knowledge. These studies will not be eligible for the proposed rewards and incentives. Finally, there is a reference to the creation of a paediatric study programme: Medicines Investigation for the Children of Europe (MICE) aiming to stimulate research and development of off-patent medicines in Europe.

Discussion

The Commission's proposal for a Regulation on Medicinal Products for Paediatric Use is more than welcomed and it is a critical step toward the long deferred goal of having adequate information on medicines for children. The health of the child is central to the proposal and the overall objectives are strongly supported. The whole problem is complex but it has to be recognised that the proposal encompasses all situations. Indeed measures are proposed to address both medicines still under patent protection and those without protection, and consist of a mixed system of requirements and reward/incentives. The requirement, as it is suggested, should ensure that medicines are developed for children based on their therapeutic needs. Because the reward is for conducting the studies in children and not for demonstrating that a medicine is safe and effective in children, the reward will be granted even when the indication in children is not granted. Relevant information on use in children will have to be included in authorised product information. The need to have an authorisation in all Member States in order to get the reward will ensure community wide benefits to child health.

The proposal, as it stands, presents some uncertainties. For instance, whereas earlier discussion papers made provisions for transparency and wide communication of clinical trials conducted in children according to a paediatric investigation plan, such measures are no longer included in the present proposal. This is probably to comply with the requirements for confidentiality laid down in the Clinical Trials Directive. Early access to information on ongoing clinical studies performed in paediatric patients, including the results, is essential to protect children from unnecessary clinical studies. This is of particular importance for the clinical trials which do not lead to a marketing authorisation application due to negative results, as the information is generally not published.

It is also unclear whether the measures proposed for older products would be sufficient to encourage industry to undertake the necessary studies in view of the market size. Such paediatric research would most likely be conducted in academic settings, which would need European public funds. The setting up of the proposed MICE, its funding and its operation, needs to be defined in another proposal.

Finally, one of the most challenging and existing measures in the draft proposal, will be for the EMEA, together with the Paediatric Committee, to establish a European network of existing national and European networks of investigators and centres. As this is a new experience for any regulatory authority, consultation with the different partners and stakeholders, particularly the existing academic research networks will be essential to find the best way to put in place such network to support paediatric research in Europe.

Conclusion

The long awaited forthcoming European Regulation on Medicinal Products for Paediatric Use addresses the unmet medical needs of children by encouraging research and development of medicines for use in the paediatric population. Although some questions remain open, the proposal aims to improve the health of children in Europe by increasing the research, development and authorisation of medicines for use in children. The public debate is now launched as the draft is under discussion at the Council and EU Parliament. Based on the success of the US paediatric initiatives and of the European Orphan Drug legislation, the success of the measures laid down by the Regulation is anticipated.

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