European Medicines Agency

London, 29 July 2008
Doc. Ref. EMEA/138931/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

PAEDIATRIC COMMITTEE (PDCO)

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

CONCEPT PAPER ON THE DEVELOPMENT OF A QUALITY GUIDELINE ON PHARMACEUTICAL DEVELOPMENT OF MEDICINES FOR PAEDIATRIC USE

AGREED BY QWP	28 February 2008
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	8 May 2008
ADOPTION BY PDCO FOR RELEASE FOR CONSULTATION	4 June 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 November 2008

Comments should be provided to qwp@emea.europa.eu

KEYWORDS	*Quality, child, paediatric*

Note:
HMPC is developing a reflection paper on the ethanol content in (traditional) herbal medicinal products used in children. The scope of the document is to reflect the need for safety limits for ethanol exposure by oral herbal medicinal products intended for the paediatric population. When available the document can be found at http://www.emea.europa.eu/htms/human/hmpc/hmpcguide.htm

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 7 418 8400 Fax (44-20) 7 418 8595
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

.

1. INTRODUCTION

Regulation (EC) No 1901/2006/EC of the European Parliament and of the Council on medicinal products for paediatric use amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 came into effect on 26 January 2007 (hereafter the Paediatric Regulation). The regulation creates a regulatory environment for the rational development and testing of age-appropriate medicinal products intended for the paediatric population. Part of this legislation (Recital 9, 10 ; Art. 15) requires that applicants for certain types of products should submit their plans for the development of such products in the form of a Paediatric Investigation Plan (PIP) for approval, or a waiver, or a deferral:

"…The paediatric investigation plan shall specify the timing and the measures proposed to assess the ***quality,*** *safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use* ***more acceptable, easier, safer or more effective*** *for different subsets of the paediatric population*[1]*…."*

2. PROBLEM STATEMENT

The current legislation foresees that before clinical studies can be performed in the paediatric population or its different subsets, pharmaceutical companies may need to develop a specific age-appropriate paediatric formulation together with an adequate packaging, user instruction and where relevant dosing device and/or medical device. All these pharmaceutical development aspects may be fundamentally different to those of the existing adult product.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

It is now well accepted that children are not simply small adults. The treatment of small children with pharmaceutical medicines poses specific problems which are not seen to the same extent in adults. For example, the lower age group subsets of the paediatric population are simply unable to swallow conventionally-sized tablets, they may be particularly sensitive to certain excipients that are otherwise acceptable in adult formulations, or there may be compliance problems since they often need to be persuaded to take their medicines, and so on. Bearing in mind these special problems, the current regulatory documents need to be augmented with guidance on the principles that should be taken into account in the development and the assessment of pharmaceutical aspects of medicinal products for paediatric use. Perhaps the most relevant current EU guidance is as follows:

1. 'Reflection paper on formulations of choice for the paediatric patient' (EMEA/CHMP/PEG/194810/2005). This paper gives a comprehensive summary of the physiological and pharmaceutical issues that could be taken into account in the development of paediatric medicines.

2. 'Guideline on excipients in the dossier for application for marketing authorization of a medicinal product' (CHMP/QWP/396951/06).
This guideline outlines the information that must be provided and emphasises the quality standards that are expected for the inactive ingredients in a formulation. It gives a specific recommendation against the use of synthetic dyes and other purely 'aesthetic' excipients in paediatric formulations, and deals with both established and novel excipients. It should be noted that this guideline is not intended to highlight safety issues concerning the use of certain specific excipients in paediatric formulations, and should not be confused with a separate European Commission guideline on safety warnings relating to specific excipients.

3. 'Guideline on excipients in the label and package leaflet of medicinal products for human use' (Eudralex 3BC7A).
This guideline defines the warning statements that must be placed in the Package Leaflet and, in some cases, the labels of medicinal products, containing certain excipients with known effects in humans.

[1] Chapter 3, Section I, Article 15.2

Obviously these warnings should also be in the SmPC. It does not generally deal with formulation development or the acceptability (or not) of excipients in the paediatric context.

Therefore, considering the limitations of each of the above documents, additional consolidated guidance would be helpful to enable proper assessment of the pharmaceutical aspects of medicinal products for paediatric use, as part of PIPs , Marketing Authorisation Applications and Variations.
Some guiding principles have already been developed, and these are presented in the Annex to this paper.

As usual, it should be kept in mind that those principles to be applied for paediatric medicines should be read in conjunction with other existing relevant guidelines.

4. RECOMMENDATION

The benefits of a medicinal product for paediatric use should outweigh the potential risks associated with its use by the different subsets of the paediatric population, namely:

- Preterm newborn infants
- Term newborn infants (0-27 days)
- Infants and toddlers (1 month to 23 months)
- Children (2 – 11 year).*
- Adolescents (12 – 16 or 18 years)

* This class may be further subdivided.

In this context, the pharmaceutical development aspects should be chosen with particular care for each subset of the paediatric population. Often, the different subsets (from pre-term newborn infants to adolescents) require different approaches. As a consequence, there might be a need to develop more than a single "formulation" which would be appropriate for all ages.

This concept paper is intended as the first step to a scientific and harmonised approach to the development of a guideline that provides adequate tools for responsible development of a medicinal product for use in these different subsets of the paediatric population. Information sharing with authorities from other regions (e.g. the FDA) would further support global development.

5. PROPOSED TIMETABLE

It is anticipated that the draft guideline for public consultation will be ready during the first half of 2009. Finalisation of this guideline is not expected before the End of 2009, since it is expected that the points of view to paediatric formulation development vary largely in Europe.

6. RESOURCE REQUIREMENTS FOR PREPARATION

This guideline will be developed by the Quality Working Party in close collaboration with the Paediatric Committee Formulation Group and the HMPC quality drafting group. The final guideline should be adopted by the Committee for Medicinal products for Human Use, the Paediatric Committee and the Committee on Herbal Medicinal Products. It is anticipated that the Safety Working Party will also be involved to provide advice on the use of certain excipients in paediatric formulations.

7. IMPACT ASSESSMENT (ANTICIPATED)

Anticipated benefits for industry and other interested parties:
Industry will benefit from clear harmonised recommendations on the aspects to be considered in the development of a specific product for use in the, or a specific subset of the, paediatric population. Clear and targeted recommendations improve adequate and timely development of industrially-manufactured and controlled medicinal products by the pharmaceutical industry. Such recommendations also reduce the risk for industry to propose a product design in the PIP, MA or Variations that is not endorsed by the Regulatory Authorities. In addition, once finalised the guideline could be used as a valuable tool of information for manufacturers that need to develop an unlicensed, extemporaneous preparation for paediatric use.

For paediatric patients and their parents, the recommendations in this guideline reduce the risk of treatment with medicinal products that are not targeted to their use and contain an avoidable risk. The recommendations are also of value in cases where the product in itself does not contain a risk to the

paediatric population, as patient compliance and patient satisfaction may be improved by products with a pharmaceutical technical design that also takes account administration problems.

As medicinal products are increasingly marketed by industry on a global scale and concepts for product development may be implemented by industry over its full portfolio, it is highly likely that the paediatric population in regions other than the EU will also benefit from this guidance.

In addition, the guideline may also be of interest to other interested parties e.g. healthcare professionals.

Anticipated benefit to the regulatory authorities:
For regulatory authorities, the proposed guideline will be conducive to a uniform approach throughout the European Community and thus will facilitate procedures for Paediatric Investigation Plans, Marketing Authorization Applications and Variations to existing Marketing Authorisations through National, Mutual Recognition, Decentralised and Centralised Procedures.

Impact for industry and other interested parties:
The proposed guideline is intended to be applied prospectively.

It is anticipated that the impact of this guideline on the pharmaceutical industry will be substantial, since the development of sound, rational formulations specifically for paediatric use could incur significant costs which may be reflected in the price of medicines. Since an overarching objective of the Paediatric Regulation is to increase the availability of paediatric medicines in the EU, any regulatory guidance should keep in mind a potential for unintended or unreasonable negative impact on this objective.

Whilst poorly-developed paediatric medicines with associated and avoidable risks will not be acceptable, it should also be mentioned that it is not the intention of regulatory authorities to always insist on a 'gold standard' product in every case. As with medicines for adults, what is important is for industry to apply objective scientific principles in pharmaceutical development to arrive at the *optimum* product and, as usual, the authorities will apply the principle of benefit/risk balance to judge the acceptability of individual cases. In this context, it has also to be acknowledged that the new Paediatric Regulation provides for considerable rewards to industry, in order to balance paediatric development costs.

As stated above, it is not the intention of the guideline to insist on the golden standard in every case, but on an optimum formulation. However, poorly developed medicines with avoidable risks will not be accepted.

Impact for assessment by regulatory authorities:
It is anticipated that the impact of this guideline on pharmaceutical assessment will be substantial, considering the fact that, until recently, assessment of products for paediatric use mainly focused on the quality of the product according to adult standards. Little attention was paid to the pharmaceutical development specific to the paediatric population.

8. INTERESTED PARTIES

Interested parties[2] and relevant external EU organizations with specific interest in this topic will be consulted during the preparation of this guideline.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. Reflection Paper: 'Formulations of choice for the Paediatric Patient'. (EMEA/CHMP/PEG/194810/2005).

[2] Pharmaceutical industry associations, health care professional groups, learned societies, consumers and patients' associations, etc.

2. ‘Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product’ (CHMP/QWP/396951/06)

3. ‘Excipients in the Label and Package leaflet of Medicinal Products for Human Use’ (Eudralex 3BC7A).

ANNEX

The following principles are to be applied in the assessment of PIP's, MA's and Scientific Advices and Variations and could also form the basis of future regulatory guidance.

- In order to protect the health of the different subsets of the paediatric population, their medicinal products should not introduce unnecessary risks for this specific and sensitive population. In this context, excipients in the formulation and the means of administering the dose should be chosen with particular care. .

- The spirit of the paediatric legislation is to encourage the development of industrially-manufactured and controlled medicines. Therefore, an extemporaneous option should not be the first option product. However, it may be acceptable in exceptional cases, if suitably justified in terms of benefit / risk balance and suitability of administration, and shown to have an acceptably low variability in the worst case.

- The first issue to be established is the 'criticality' of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window, etc.) and how the dose is to be calculated. These aspects in turn may determine the choice of pharmaceutical form, the formulation, and the dosage administration system, (e.g. fixed 'quantised' doses *vs* a continuously variable dose).

- The principle of benefit / risk balance should be applied to assess the suitability of formulations, administration devices and packaging and user instruction in paediatric medicines. For example, an excipient which raises a minor safety concern may still be allowed in exceptional cases taking into account the seriousness of the clinical indication, or the advantages offered by a particular pharmaceutical form, route of administration, or duration of treatment, etc.

- The paediatric population is composed of a number of diverse subgroups at different stages of development and a formulation which raises no concerns in children of 13 years old may not necessarily be acceptable in neonates or *vice versa*. In deciding on the acceptability of a given formulation or administration system, the focus of attention will normally be placed on:
    - the minimum age of the intended population
    - the condition to be treated
    - the maximum duration of therapy which can be foreseen
    - the availability of relevant safety data
    - the environment where the product is to be used (hospital versus community)

Therefore, on this basis, the most sensitive formulation issues could arise in the context of long term use in neonates, infants and small children, particularly when the excipients used are known to have their own undesirable properties, or when the safety data relevant to the patient population may not be as comprehensive as in adults. It is reasonable to expect that companies will develop formulations that avoid unnecessary exposure of sensitive patients in the long term.