



## **REPORT ON THE EXPERTS ROUND TABLE ON THE DIFFICULTIES RELATED TO THE USE OF NEW MEDICINAL PRODUCTS IN CHILDREN HELD ON 18 DECEMBER 1997**

### **BACKGROUND**

Following discussions at the September 1997 Management Board meeting, the European Commission highlighted the necessity to initiate a debate to determine whether there was any need to reinforce the EU current regulatory framework and issued a Concept Paper on Clinical Trials in Children (Annex 1). The paper outlined the problems that competent authorities face in providing information on the use of new medicinal products in children when data on the use in this population are not included in applications for marketing authorisations.

In order to discuss the current situation at a European level, the EMEA in collaboration with the European Commission, on 18 December 1997, convened a round table of experts in the field of paediatrics. Clinical pharmacologists and paediatricians from throughout the EU were invited to participate together with representatives from European Parliament and representatives of European Associations with experts in this area. This group, under the chairmanship of Prof. J-M Alexandre, considered a number of specific issues related to the use of new medicines in children, with the view to making specific recommendations to the Commission.

This note summarises the main points of the discussion.

The Food and Drug Administration recently addressed the problem in the US by proposing a new paediatric rule in August 1997, that would require manufacturers to supply data on the effects of new drugs and biologics in children if the product is expected to be frequently used in this population, or offers a "meaningful benefit" over existing therapies for children, unless a waiver is granted on the initiative of the FDA or at the request of the applicant.

In the EU at present there is no mandatory requirement for pharmaceutical companies to investigate new medicinal products in children. The current updated CPMP Note for Guidance on the Clinical Investigation of Medicinal Products in children (CPMP/EWP/462/95) came into operation in September 1997. The updated guideline, like the previous 1988 version, encourages the pharmaceutical industry to investigate the safety and efficacy of a product in children, if it is likely to be of therapeutic benefit in this age-group, and to develop suitable formulations, even if the usage is likely to be small.

### **CURRENT SITUATION**

The round table of experts agreed that there is a general lack of information and appropriate pharmaceutical formulations to support the administration of many medicinal products to children. Practical examples were provided by several experts highlighting the lack of well-designed clinical studies in this population and the insufficient availability of suitable pharmaceutical formulations, which leads to a lack of appropriate dosage recommendations for children. This results in frequent off-label use of licensed medicines in children (with regard to indication, age-group or dose) and the use of unlicensed medicines in this population.

### **OBSTACLES TO THE USE OF NEW MEDICINES IN CHILDREN**

*Ethical Concerns:* No major ethical obstacles to the use of new medicines in children were raised by the group. It was agreed that it was important to take ethical considerations into account in the design and conduct of clinical trials. In this respect, informed consent was highlighted as an issue which

sometimes may pose practical difficulties. Overall, the ethical problems which arise when prescribing off-label medicinal products in children clearly outweigh the ethical considerations which are linked to the conduct of controlled paediatric clinical trials.

*Technical and methodological concerns:* The group did not consider there to be major technical or methodological obstacles for the conduct clinical trials in children. It was recognised that the CPMP guideline offers the appropriate methodological framework for the design of such trials.

*Practical considerations:* From a practical viewpoint, the number of investigators available does not appear to be a crucial issue at present, but there are insufficient sponsors. Pharmaceutical companies are often reluctant to provide technical and financial assistance to conduct such studies. A further major practical obstacle which was highlighted is the lack of public funding to support clinical research in this field.

## **RECOMMENDATIONS**

The group agreed that, in light of the difficulties which exist in using both old and new medicinal products in children, there is a need to improve the current situation, taking into account ethical, technical and legal difficulties. The group proposed the following recommendations to the European Commission in order to overcome current barriers that prevent the use of new medicinal products in children.

### **Review of old drugs**

A review should be carried out on old products to ascertain the availability of clinical data on the use of these products in children and in order to complete labelling for different categories of age. A list of medicinal products for which information is necessary has been drawn up by the American Association of Paediatrics. Priorities need to be established and links made with the FDA and other international regulatory authorities in order to avoid duplication of the work.

### **Clinical Trials and Pharmaceutical Formulations**

*Requirements:* A strengthening of EU legislation should be considered by the European Commission in order to impose requirements on pharmaceutical companies to conduct paediatric studies for medicinal products that are widely used in paediatric patients or that are indicated for a very significant or life-threatening illness.

The possibility of including specific waivers to these requirements and exclusivity clauses in some cases should be considered, together with the timing for initiation and submission of such studies.

#### *Incentives:*

- Regulatory advice and technical assistance should be made available to the industry when planning paediatric development programmes.
- A period of exclusivity could be considered for orphan indications, to stimulate development of medicinal products in these areas, in line with the current draft Regulation on orphan drugs.
- Support the establishment of an EU paediatric clinical research network, involving clinical pharmacologists specialised in this field and clinical paediatricians, to increase and expedite recruitment of patients and speed up clinical development through international multicentre clinical trials.
- An allocation of public funding from the European Commission is needed to overcome financial constraints limiting the conduct of clinical trials in children.

## **FOLLOW-UP OF THE MEETING**

In order to substantiate the current situation with regard to the general lack of information, the experts agreed to submit examples to the EMEA, together with publications and overviews on the current situation.

## ANNEX 1

### CONCEPT PAPER ON CLINICAL TRIALS IN CHILDREN

#### Background

In developing a new medicinal product, demonstration of safety and efficacy is through clinical trials conducted in accordance with GCP (Good Clinical Practice). Normally clinical trials will be conducted initially on an adult population. However, clinical data on specific population groups such as geriatrics, pregnant women, children is also necessary in order that correct information on the safe use of the product can be provided.

Guidelines on the conduct of paediatric clinical trials have recently been prepared by the EMEA/CPMP (CPMP/EWP/462/95) and published by the Commission in the *Rules governing medicinal products in the European Union*.

#### Problem Statement

Applications for new innovative medicines do often not contain sufficient data on the correct use of the medicinal products in children. Regulators are therefore faced with the dilemma of either contra-indicating the use of the product in this sub-population (thereby denying children access to potentially life-saving medicines) or including general information for which the scientific basis has not been demonstrated. Neither of these situations are acceptable.

This problem is not unique to the European Union, as evidenced by the recent FDA Proposed Rule which would require paediatric studies for certain new medicinal products and also for a limited class of marketed products.

Unless the use of a medicinal product is clearly inappropriate, competent authorities will expect the presentation of clinical trials in children.

A number of specific issues can be considered:

- legal and technical requirements to conduct studies in children,
- ethical implications of the conduct of clinical trials in children,
- practical possibilities for the conduct of clinical trials.

#### Proposed action

As a first step, a Round Table of experts could be convened to elaborate the above issues, within the European context, and to draft proposals for solutions. Following this, a structured programme for action could be developed for :

- the establishment of a network for clinical trials sites for the co-ordinated conduct of clinical trials in children,
- the review of selected marketed products for the availability of clinical data on the safe use in children,
- the systematic requirement for clinical data on pediatric use in all new marketing authorisations applications (this requirement could be introduced through an amendment to the recent Proposal for a Parliament and Council Directive on clinical trials, or through a Commission Directive amending Directive 75/318/EEC).

In order to draw on a wide range of expertise, the following groups could be invited to contribute:

- EMEA/CPMP
- European Federation of Paediatric Physicians,
- Committee of European Doctors,
- European Patient Organisations,
- European Federation of Pharmaceutical Industries Associations.

In the Commission, DGs III, V and XII could collaborate and bring together their respective contributions.

Further action would be concerted within the ICH process.