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### ICH Topic E11 ; Clinical investigation of medicinal products in the paediatric population.

CESP welcomes the opportunity to comment on the ICH document, CESP discussed this at its general assembly and distributed the document to national delegates for comment. The general tenor of the responses has been very favourable and supportive. CESP would like to see more pharmacokinetic and pharmaceutical studies being performed in children. CESP also recognises that practising hospital and community paediatricians need to be more greatly involved in the conduct of such trials.

I am appending some comments on the document using the same paragraph numbering system as in the ICH document.

- 1.3 It was noted that the sentence "ethics of paediatric clinical investigation" might better read "ethics involved in all steps of paediatric clinical investigation". The consensus from paediatricians was that it could be more clearly stated that the obligation to protect children from the risks of drugs trials has to be balanced against the obligation to protect children from the risks of clinical management that it not fully supported by hard data from properly conducted trials. It was also felt that drugs, which were indicated only for a small group of patients, need also to be investigated.
- 1.4 General Principles. It should be stated that children should not be used for the purpose of research related to adults. Neither should children be involved in research under conditions where the primary motivation is to advance the interest of science and where there is no prospect of related benefits to the paediatric population.
- 2.1 Issues when initiating paediatric medicinal product programmes. Some paediatricians felt that the statement "Paediatric studies should not delay the completion of adult studies" might give the impression that adults are more important than children are. It was also noted that the document does not clarify the respective roles of the pharmaceutical industry, the licensing authorities and child health practitioners in defining whether a product should be used in the paediatric population or in the assessment of which products are considered inappropriate.
- 2.2 Paediatric formulations. The document should state that the development of specific paediatric formulations is important; at the moment such formulations and dose schedules are often lacking.
- 2.3 Timing of studies. Adequate evaluation of medicinal products for use in children cannot always be achieved in adult studies because of physiological differences between children and adults, because children suffer from different diseases from adults and have differing

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pharmokinetic mechanisms. For this reason clinical studies are imperative at different ages and stages of physiological maturation.

2.4 Types of Studies. It was noted that pharmacokinetic studies are particularly required in new-born babies and infants under one year. Dosage cannot be safely drawn from adult studies.

2.4 Age classification of paediatric patients. The RCPCH in London suggested that the ICH document would benefit from a more explicit harmonisation with the age arrangements recommended in 1996 reports as follows:

Birth to one month (subsection infants under 37 week's gestation). Further separation of infants under 37 weeks may be required for certain medications.

One month to twenty three months.

Two to eleven years (subsection: under 6 years old need appropriate formation)

Twelve to eighteen years. (children aged 12 to 18 have mature metabolic processes similar to adults. Drugs specifically required for adolescents should be tested in adolescents. ICH should seek international agreement on paediatric age bands for pharmaceutical studies.

It was noted that aerosol and nebulized bronchodilator antibiotic and other forms of inhaled therapy are widely used in paediatrics with little or no information regarding deposition in the lung or systemic absorption. It was suggested that this needs to be considered.

2.5 Ethical issues in paediatric studies. The following points were noted,

- because children are more vulnerable, special measures should be taken to protect them.
- The protection of the integrity of the child must be respected in all periods of life including handicapped children and those unable to participate in the informed consent or assent process.
- Research on children should focus on the knowledge, cure, relief or amelioration of diseases and conditions affecting children.
- Easily understandable and child appropriate written information sheet should be prepared. Children of an intellectual age of 9 years and up might be considered appropriate to be included in the assent process.
- Refusal to be involved in clinical trials should not imply any reduction in the level of care offered to that child.
- Monetary reward should not be given to parents to induce involvement of their children in pharmacokinetic or pharmaceutical research projects.

2.6. Minimising risk. In attempting to minimise risk to children in pharmacological research, the following general principles should pertain.

- safety data from adult studies should be available before paediatric clinical trials are started except in circumstances where no treatment exists in unique paediatric disease disorders
- appropriate toxicity studies reproductive toxicity studies and genotoxicity should be completed prior to the initiation of trials in children.
- The number of children required to provide statistical conclusions should be minimised consistent with good study design.

- Children should not be exposed knowingly to doses of medicinal products they do not need.
- The minimum number of examinations and invasive procedures that are essential should be performed.
- The development of appropriate micro-methods using small volumes of blood for laboratory measurement is important.
- Protocols and investigations should be adapted for children by researchers experienced in paediatrics. Protocols should be approved by responsible IRB's/IEC's, with experts experienced in working with children.

These comments are made in a constructive sense. Paediatricians feel strongly that the current climate whereby children are exposed to drugs with inadequate safety, efficacy and pharmacokinetic data must not be allowed to persist. Greater onus needs to be placed on paediatricians to ensure that appropriate pharmacological research is conducted and that appropriate pharmaceutical agents and dosing schedules for children be available. CESP would be willing to encourage European paediatricians to take on this role.

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