COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS OR DEFERRALS AND CONCERNING THE OPERATION OF THE COMPLIANCE CHECK AND ON CRITERIA FOR ASSESSING SIGNIFICANT STUDIES

http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/draft_guideline_pip_2007-02.pdf

Comments on section 1.2 PART A

A.4 Type of product

The applicant should specify what type of product the application is for (e.g. a new chemical entity, a new biological product, a vaccine, a gene therapy product, somatic cell therapy medicinal product etc). In addition, the applicant should specify the target and mechanism of action.

The term “product” should be replaced by “active substance/compound” for the classification. A drop-down menu would be helpful for the classification.

A.5 Details of the medicinal product

If available, the proposed invented name, strength, pharmaceutical form and route of administration should be provided.

The wording should be clarified: the pharmaceutical form and method of application should always be given, as this information is necessary to evaluate its use in the specific paediatric population.

A.7 Regulatory status of the product outside the Community

A summary of the worldwide regulatory status and marketing history of the medicinal product in both adult and paediatric populations should be provided. This includes marketing authorisation application status (including refused applications), details of the indications for which the medicinal product is approved in third countries, and regulatory information on clinical trials and any actions taken against the medicinal product in any country. The applicant should provide the paediatric committee with any decisions, opinions or advice (including scientific advice) given by competent authorities of third countries on the paediatric development of the medicinal product. A copy of any relevant documents should be included in Part F.

A statement should be added whether the clinical trials in third countries were performed according to GCP.

Comments on section 1.5 PART D

D.1.3 Outline of the quality, non-clinical and clinical data.

The applicant should outline the development of the medicinal product which is relevant for paediatric development and its results when available. An outline of the planned studies in adults should also be provided. This could take the form of an "investigator brochure" style summary. The full study reports of non-clinical and clinical studies undertaken need not be provided but should be made available upon request.

Although the heading lists quality, non-clinical and clinical data, no details on quality aspects are provided in this section.

D.5.4. Synopsis /outline of protocol(s) of each of the planned or performed clinical studies or trials

The following should be detailed as relevant according to the study:

- **Type of study**
- **Study design**
- **Type of control (placebo or active control with dose to be used)**
- **Location (regions)**
- **Test(s) products; Dosage regimen; Route of administration**
- **Objective(s) of the study**
- **Number of subjects (M/F), ages, number per ICH age groups or other relevant age group**
- **Duration of treatment**
- **Main inclusion/ exclusion criteria**
- **Parameters or endpoints (primary, secondary)**
- **Sample size (more or less detailed as appropriate)**
- **Power calculation: describe effect size expected**
- **Options in case of recruitment issues, interim analyses and stopping rules**
- **Statistical methods (Statistical methods used to compare groups for primary outcome, and for additional analyses if relevant)**

In addition to the duration of treatment, information on the duration of the post-treatment observation phase should be required.
According to article 16 of regulation (EC) 1901/2006 the paediatric investigation plan (PIP) should be submitted "not later than upon completion of the human pharmaco-kinetic studies in adults …" This is usually at the end of phase I when only limited data on therapeutic effects even in adults are available. We therefore believe that a sponsor is not able to provide reasonable estimates for power calculation or sample size. Also, the "inclusion and exclusion criteria" and "duration of treatment" can only be provided to a limited degree as results from phase II studies might be required to plan the trial population and treatment strategy for paediatric trials. We would like to suggest that the level of detail should be reduced to a more suitable and appropriate level.

Section 2: Operation of the Compliance Check

It is outlined in the guideline that checking of compliance by the competent authorities can be seen as a two step process with non-compliance leading to non-validation of applications falling under Articles 7 and 8 of the paediatric regulation, and for validated applications, non-inclusion in the marketing authorisation of the compliance statement referred to in Article 28 (3) leading to ineligibility for the rewards and incentives. Furthermore, it is stated that the

confirmation of compliance is not linked to the assessment of the data, i.e. compliance is not lined to the scientific judgement on the quality, safety and efficacy of the medicinal product based on data generated as a result of the agreed paediatric investigation plan.

The section lacks clarity on what really is the basis for the compliance check requested during validation compared to the scientific judgement to be made during the evaluation phase. Clarification should be provided. In addition, validation of applications up to now only comprises checking whether certain documents and declarations are contained in the application file, the content of these documents is not evaluated. The newly introduced requirements pose a challenge to competent authorities given the tight timeframe of 10 days for validation as it can not be outruled that assessors need to be involved in the compliance check as presently described. It would be helpful if the guideline would first of all give more information on the actual scope/content of the compliance check. In addition, it should be checked whether there is any possibility to make the compliance report to be submitted by the applicant a mandatory requirement. In any case, the structure of such a report should be outlined in the guideline.

General issues:
The PIP procedure also raises questions about the interdependence of an approved PIP and the clinical trials application procedure. Does and agreed PIP preclude the competent authority from raising objections against a clinical trial application? Shall the competent authorities check the compliance with the PIP during a clinical trial application? If so, what are the consequences if a trial protocol is not compliant with the trial outline laid down in the PIP? Currently the non-compliance would not be a reason for non-acceptance of a clinical trial application (at least in Germany). And what happens if a sponsor claims that a given trial is not intended for regulatory purposes within the EU but for the USA or Japan and therefore is not willing to stick to the trial outline given in the PIP?