EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
**Pharmaceuticals**

Brussels, 24 November 2008
DG ENTR/F/2 PRA/sdh/D/27286

# Overview of comments on the public consultation on the Commission Guideline on the format and content of applications for agreement or modification of paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on the criteria for assessing significant studies

The European Commission conducted a public consultation on its "Commission Guideline on the format and content of applications for agreement or modification of paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on the criteria for assessing significant studies". Interested parties were invited to submit their comments between 31 January 2007 and 30 March 2007. The feedback received from this consultation was used to finalise the Guideline.

## Contributors

By the deadline, the Commission received **17 contributions**.

In summary, the respondents can be subdivided into three groups:

- Industry (individuals, companies or associations) – 9 responses
- Regulators (individuals or agencies / authorities) – 3 responses
- Other, including clinical research groups, a good clinical practice group, research networks, European patient associations and a European healthcare professionals association – 5 responses (including one joint response covering six organisations)

A complete list of these responders is annexed at the end of this document and individual responses will be made available at:
http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/index.htm.

## Summary of contributions

*Overall comments*

In terms of overall comments, numerous comments were received, however, the following are highlighted:

Commission européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299 11 11.
Office: BREY 10/118. Telephone: direct line (32-2) 2961268. Fax: (32-2) 2998046.
E-mail: peter.arlett@ec.europa.eu

- The majority of responses who made introductory remarks welcomed the draft guideline and the initiative of the paediatric regulation.
- Many of the responses and most notably those from industry suggested that the level of detail of information requested in the draft guideline was too high overall. Of these responses many pointed out that for medicinal products in early clinical development much of the information requested will not be available at the time the application is made.
- The workload required to maintain paediatric investigation plans is highlighted particularly if detailed information is included in the paediatric investigation plan decisions.
- A number of responder suggested that the structure of the guideline was complex and furthermore that there may be duplication between different subsections.
- One European industry association requested that studies in children of radiopharmaceuticals not be required (this exclusion is not provided for in the paediatric regulation).

*Comments on the introduction*

Apart from numerous comments on points of detail, the following points are highlighted:

- Several responders questioned the value of the definitions.
- Despite the explicit scope of the guideline provided for in legislation some responders ask for additional definitions to facilitate implementation of the paediatric regulation such as for new indication, new pharmaceutical form and new route of administration to be included.

*Comments on Section 1*

Apart from numerous comments on points of detail, the following points are highlighted:

- There were suggestions to reorganize Part A "Administrative and Product Information" to simplify it and link it more closely to whether the application relates to: 1. a medicinal product not yet on the market which will subsequently be caught by the requirements of Article 7 of the paediatric regulation, 2. a medicinal product on the market and covered by a supplementary protection certificate or a patent which qualifies for the grating of the supplementary protection certificate, which will subsequently be caught by Article 8 of the paediatric regulation, or 3. is a product being developed for a paediatric use marketing authorisation
- Several responders question the meaning and implications of the paragraph linking significant therapeutic benefit and/or the fulfillment of therapeutic needs to target / mechanism of action. This is considered by some to suggest that the paediatric committee may extend the indications of the product beyond the disease / condition being developed for adults. It is suggested that there is no legal basis for this extrapolation.
- Despite the wording of the relevant provisions of the paediatric regulation and the link between completing all measures in an agreed paediatric investigation plan to important rewards and incentives in Articles 36, 37 and 38 of the paediatric regulations, several responders request that industry be allowed to submit separate paediatric investigation plans for different indications (rather than one per product as is intended by the paediatric regulation). These responders do not highlight that this would reduce the amount of research and development required to access the rewards.
- Several responders question the value of including information on manufacturer of the active substance.
- Responders request that when providing information on existing clinical trials whether they are conducted inside or outside the EEA this should include a statement on

whether each clinical trial was conducted according to Good Clinical Practice (GCP). Including information on ethical aspects is also suggested.

- The need for comprehensive information on clinical trials is raised by some responders.
- The need is questioned for the level of detail requested on prevalence and incidence of the conditions / diseases in different countries as well as the diagnosis, prevention and treatment of conditions / diseases.
- Reference to unauthorized treatments is questioned. The concept of 'standard of care' is questioned, particularly given the different medical cultures in different Member States.
- Despite the explicit need to assess significant therapeutic benefit / fulfillment of therapeutic need in the paediatric regulation, some responders question the basis for requesting information on comparative / existing treatment methods. Numerous specific comments are made on the assessment of these criteria.
- In section 1.4 Part C, Applications for Product Specific Waivers, there is a request to utilize the exact wording in Article 11 of the paediatric regulation.
- Despite the paediatric regulation not differentiating between vaccines and other medicinal products, some responders suggest that such a distinction be included in the guideline. Specific reference is made to the existing scientific guideline CHMP/VWP/164653/2005.
- In section 1.5 D.3 non-clinical strategy, despite the stem of this section stating "discuss the strategy for the non-clinical development, which is needed in addition to standard non clinical development or to already existing data" some responders question the reference to juvenile animal studies (implying that the guideline introduces requirements for such studies which it does not).
- In section 1.5 D.4 clinical strategy, some responders question whether information on development of the medicinal product in adults should be included in the application. It appears that the guideline needs to make it clearer that the contents of sections D5 ("Planned measures for the paediatric development") and D6 "Timeline of measures in the paediatric investigation plan" would form the basis for the EMEA Decision on the Paediatric Investigation Plan.
- Section 1.5 D.5 "Planned measures for the paediatric development", despite the fact that this section is critical for the formulation of the EMEA Decision on the Paediatric Investigation Plan some responders question the amount of detail included.
- Section D, despite the fact the requirement for 'significant studies' in order to access the rewards of the paediatric regulation (Article 45(3) of the paediatric regulation) are dealt with in section 3 of the guideline and this requirement only applies to studies started before the entry into force of the paediatric regulation, some responders request a specific subsection in 1.D for applicants to justify significance.
- Section 1.5 D.6 "Timeline of measures in the paediatric investigation plan", some responders question the need for detailed timing and particularly the feasibility of giving detailed timings when applications are made early in product development.

*Comments on Section 2 operation of the compliance check*

Apart from numerous comments on points of detail, the following points are highlighted:

- Greater clarity on the compliance check is requested by some responders including timing and re-examination.
- Despite the explicit provisions of Articles 23 and 24 of the paediatric regulation some responders question the fact that one compliance standard is checked by the competent authorities in a two step process.

*Comments on Section 3 assessment criteria for the significance of studies*
Apart from numerous comments on points of detail, the following points are highlighted:

- Some responders suggest that various additional study types should be included in the list of study types that will generally be considered as significant.

**Pharmaceuticals Unit,**
**DG Enterprise and Industry,**
**European Commission**

## Annex: List of respondents

Clicking on the specific consultation line will lead you directly to the original contribution.

**Industry**

1. EFPIA (The European Federation of Pharmaceutical Industries and Associations)
2. IFPMA (The International Plasma Fractionation Association)
3. AIPES (Association of Imaging Producers and Equipment Suppliers (Nuclear medicine and Molecular healthcare)
4. BIA (BioIndustry Association)
5. BPI (German Pharmaceutical Industry Association)
6. Astellas Pharma Europe BV
7. Pierre Fabre Medicament
8. Voisin Consulting
9. PhRMA (Pharmaceutical Research and Manufacturers of America)

**Regulators**

10. EMEA (European Medicines Agency)
11. BfArM (German competent authority)
12. Medical Products Agency, Sweden (MPA)

**Other**

13. Francis Crawley on behalf of:

- Good Clinical Practice Alliance
- Ethics Working Group, Confederation of European Specialists in Paediatrics (CESP)
- Working Group on Paediatrics, Institute of Clinical Research (ICR)
- European Network of Alternating Hemiplegia in Childhood (ENRAH)
- European Federation of Allergy and Airways Diseases Patients' Organisation (EFA)
- Reasearch Committee, International Primary Care Respiratory Group (IPCRG)

14. The Institute of Clinical Research Paediatric Special Interest Group
15. Paediatric Research Consultancy (Jane Lamprill)
16. TEDDY (Task-force in Europe for Drug Development for the Young)
17. UK Medicines for Children Research Network