SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE

COMMENTS FROM
Astellas Pharma Europe BV,
Elisabethhof 19,
2353EW Leiderdorp,
The Netherlands

GENERAL COMMENTS

A guiding document on the interpretation of the Paediatric Regulation is certainly a welcome initiative, as it can help providing clarity on the requirements for the contents of a PIP.
However, in several instances the guideline requests very detailed levels of information, and it may not be possible to either generate or collect the requested information. The proposed level of detail will often inflict a heavy burden on the applicant and as the relevance of the requested information for assessing a PIP is often not clear this is highly undesirable. The interpretation of the Paediatric Regulation in the guideline tends to go beyond what is requested in the basic document, i.e. the Regulation *per se*.

For the purpose of easy of review the comments have been divided into minor and major type.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
P. 1 Title page	Comment (minor) A reference to Regulation EC/1901/2006 is absent.	To include a reference to Regulation EC/1901/2006.
P. 2 Table of contents	Comment (minor) Page numbers are missing.	To include page numbers.

Date of transmission:

Submit all comments to: by email to peter.arlett@ec.europa.eu in word format please.
Deadline for comments: <30 March 2007>
These comments and the identity of the sender may be published on the European Commission website unless a specific justified objection is received by the European Commission.

P. 3 Introduction Para 1 and onwards	Comment (major) The usefulness of this document would greatly increase with the inclusion of a flow chart, including timelines, describing the activities and events in the case of submission of a PIP, up to the submission of an MA that includes a PIP.	To include a flow-chart, with all durations of activities and clock-stops.
P. 3 Introduction Para 5	Comment (major) Condition: A definition of the word 'condition' is provided here. However, and strikingly, 200/83/EC in article 1, only uses the terminology 'disease' in relationship with 'medicinal product'. The term 'condition' is used in 2001/83/EC to indicate a prerequisite or stipulation. It is even used in the context of ‘conditional approval’ in other European legislation. Regulation EC/1901/2006 uses both 'disease' and 'condition' to indicate a 'medical condition'. This is likely to cause confusion.	To include an unambiguous definition of disease / condition.
P. 3 Introduction Para 6	Comment (major) Paediatric investigation plan indication: The definition of 'paediatric investigation plan indication' and the definition of 'proposed therapeutic indication' on page 4 partly overlap. This is likely to cause misunderstanding.	To provide clear and unambiguous definitions.
P. 3 Introduction Para 6	Comment (major) Paediatric investigation plan indication: The specification of ‘diagnosis, prevention, or treatment of condition’ does not match the definition of a medicinal product as laid down in 2001/83/EC, article 1.	To bring text in agreement with 2001/83/EC. .
P. 4 Introduction Para 1	Comment (major) Proposed therapeutic indication: See comment made on the definition of 'paediatric investigation plan indication' and the definition of 'proposed therapeutic indication' as they appear to partly overlap. This is likely to cause misunderstanding.	To provide clear and unambiguous definitions.

P. 4 Introduction Para 2	Comment (minor) Granted therapeutic indication: 2001/83/EC mentions 'authorised indications'.	To adapt the text in line with 2001/83/EC, article 5, in order to provide an unambiguous definition.
P. 4 Introduction Para 2	Comment (minor) Granted therapeutic indication: The words 'This will be the result ....assessment ... submitted ... authorisation application' are superfluous, as already covered in 2001/83/EC..	To delete the words 'This will … authorisation application'.
P. 4 Introduction Para 3	Comment (major) Measures: The definition of 'measures' as applied here, goes beyond what is implied in article 15(2) of the regulation. In particular, the Regulation talks about _assessing_ quality, safety, efficacy, whereas the definition here mentions _obtaining_ a paediatric indication. Secondly, the use of the word 'all'in 'all studies …' and in 'all subsets' does not find a basis in the Regulation.	To bring the text into line with the Regulation, as the spirit of the Regulation is to reward properly performed scientific work, even when it does not lead to a viable paediatric indication. To remove the word 'all'.
P. 4 1.1 General principles and format Para 8	Comment (minor) Labelling: According to 2001/83/EC 'Labelling' is information on the immediate or outer packaging. Thus this terminology must no be used here.	To use 'Summary of Product Characteristics'.
P. 5 1.1 General principles and format Para 2	Comment (major) Target: It is not clear what is meant with 'target'; it could be the target medical condition, target organ. Clarification is needed.	To provide clarity on 'target' or to reword the paragraph.
P. 5 2.A.1 Name of (...) Para 5	Comment (minor) Individual or a company: Applications can be submitted by natural persons, or legal entities, and the latter ones do not necessarily have to be a company.	To reword the text and the title in a legally correct way.

P. 5 2.A.1 Name of (...) Para 7	Comment (minor) Make public with the decisions: We propose that it should be left to the decision of the applicant to provide a _general_ contact point, rather that the name of a specific person, for reasons of privacy of personnel.	To allow the applicant to decide on the nature of a general contact point, without disclosing details of personnel.
P. 5 1.2.A.2 Name of (...) Para 8	Comment (major) Name and address of the manufacturer of the active substance (…): This is irrelevant for an early stage of development, and is likely to alter as development continues. In addition, the Regulation does not appear to require the submission of such data.	To delete paragraph A2.
P. 5 1.2.A.3 Name of (...) Para 9	Comment (major) Name of active substance: In an early stage of development the medicinal product (and the active substance) may only be known by their lab-code. An INN may not be available. It is therefore reasonable to permit the use of such lab-codes. In addition, the text appears to be conflicting with the last paragraph of A3, on page 6.	To allow the use of company and lab codes at all stages of development.
P. 6 1.2.A.4 Type of (...) Para 3	Comment (minor) Target: It is not clear what is meant with 'target': for example: target organ, target disease, target population? The text also seems to duplicate to duplicate what is said on page 5 regarding ‘target’.	To provide clarity on 'target' and to avoid duplications. As a suggestion: to use the terminology ‘pharmacological target’.
P. 6 1.2.A.6 Regulatory (...)	Comment (major) Clinical trials: For authorised compounds this information is an integral part of the dossier. Ongoing studies are available on the EudraCT database (and usually summarized in an Investigators Brochure). ‘Hence it is unclear what is required in addition.	To provide only high level information on ongoing clinical trials.

P. 6 1.2.A.7 Regulatory (...) Para 6	Comment (major) The medicinal product: It is not clear how 'the medicinal product' is to be understood here. Is it a product with exactly the same qualitative and quantitative composition in terms of the active ingredient, or is it defined by and at the level of substance?	To provide clarity on 'the medicinal product'.
P. 6 1.2.A.8 Conditions Para 1	Comment (minor) Conditions: We refer to earlier comments made on the use of the terminology 'condition(s)'.	To use harmonised terminology for 'condition(s)'.
P. 7 1.2.A.9 Proposed (...) Para 1	Comment (minor) Proposed therapeutic indication We make reference to an earlier comment on the definition of 'paediatric investigation plan indication' and 'proposed therapeutic indication'.	To revise the text in line with any revised definition(s).
P. 7 1.3 Part B Overall (…) Para 1	Comment (minor) target diseases / conditions (in title) We recommend avoiding the use of the words disease and condition.	To replace 'target diseases / conditions' with 'proposed paediatric indication'.

P. 7 1.3 Part B Overall (…) Para 1	Comment (major) This paragraph asks for very detailed information, e.g. similarity of between adult and paediatric populations, (…) subsets, prevalence, incidence, diagnosis, treatment methods, alternative treatment. It appears that such request is outside the scope of the Regulation, is difficult to compile, collect. Moreover, diagnostic and treatment methods may differ from country to country, and are best left at the decision of the competent clinician. Some of the items are discussed in more detail below. Diagnosis: Information on diagnosis could only be relevant if the medicinal product is relevant for making a clinical diagnosis, all in agreement with 2001/83/EC, article 1, definitions. Otherwise, 'diagnosis can be deleted. Alternative treatments: It is not clear what is meant with these 'alternative methods'. Are these for example methods of which the balance therapeutic efficacy / safety (therapeutic value) has not been demonstrated, e.g. homoeopathic products? We therefore propose to delete 'alternative methods'.	To leave out the request for such detailed non-pharmaceutical information, and to replace it with only high level information on the medical condition.
P. 7 1.3 B 1. Discussion (...) similarities Para 3	Comment (minor) Disease or condition already authorised: Diseases or conditions cannot be authorised, whereas medicinal products can.	Text to be amended in line with 2001/83/EC.

P. 7 1.3 B 1. Discussion (...) similarities Para 3	Comment (major) Emphasis: Emphasis (…) seriousness of the disease, aetiology, clinical manifestations and prognosis, and variability in terms of genetic background, in the paediatric subsets. (…) standard textbooks. Here a lot of detail is requested, which apparently goes beyond what is required by the Regulation. Many of the different topics mentioned here may not even be known. It is for example difficult to see what the relevance of different genetic backgrounds could be for a development programme.	The information to be provided should be limited to a high level description of the medical condition as it is present in the paediatric population.
P. 7 1.3 B 2. Discussion anticipated (…) Para 4	Comment (minor) Effect: Is this therapeutic effect only, or does it also include undesirable effects?	To amend the text. It should be borne in mind that the applicant of a PIP will only be able to give limited information (if any at all) and that much will be based on assumptions, as the clinical development programme for the new medicinal product is likely to be at an early stage, leaving many uncertainties.
P 7 1.3 B.3. Prevalence (...) Para 5	Comment (minor) Prevalence / incidence (…) in the different member states: The regulation should not impede the free movement of goods. In order to avoid situations in which discussion on national prevalences could take a prominent role, the words "(and in the different Member States)" must be deleted. This request goes outside the scope of the Regulation. See preambule 5 of the Regulation.	To delete text "(and in the different Member States)".
P. 8 1.3 B.4 Current (...) Para 1	Comment (minor) Diseases or conditions authorised: These cannot be authorised; medicinal products can.	To reword text.

P. 8 1.3 B.4 Current (...) Para 1 (and onwards)	Comment (major) The level of detail requested in this section B4 is far too much, while taking into account diverging clinical practices of paediatricians. Moreover, no registry of such practices is available. Consequently, this is best left to the 'clinical field'. Some of the items are discussed in more detail below (para 1 / 3 / 4).	This chapter should be considerably reduced with regard to the level of detail that it requests.
(Para 1)	(Para 1) Unauthorised treatment methods: It is not clear whether 'methods' is here to be read as medicinal products, i.e. in the sense of off-label use. Making comparisons with treatments other than medicinal products, is not in the spirit of the Regulation, and consequently, the text should be modified / deleted.	See also general comment given on P. 8, 1.3 B.4 Current (...), Para 1 (and onwards).
(Para 3)	(Para 3) The applicant (...) in the Community. The Regulation does not request a comparison with other forms of therapies to be performed. Paediatric medicines, like medicines for adult patients, need to comply with standards of quality, efficacy, and safety, as laid down in 2001/83/EC as amended. There are no additional requirements regarding these standards for paediatric use products. In this respect it should be borne in mind that the Regulation is mainly aimed at setting standards for the proper conduct of a clinical development programme for paediatric patients. See for example preambule 4. Moreover, any comparison with existing therapies (of any sort) is only required in the case that an applicant wants to apply for a product specific or a class waiver, see article 11(1)C.	See also general comment given on P. 8, 1.3 B.4 Current (...), Para 1 (and onwards).

(Para 4)	(Para 4) For medical devices (...) this Directive. The Regulation does not request a comparison with a medical device to be made, and in view of the totally different characteristics of medicinal products vs medical devices, such a comparison is likely to become unbalanced or impossible. Moreover, there is no community register that can provide the information on 'all devices placed on the market', and this leads to unbalanced burden for the future paediatric applicant.	See also general comment given on P. 8, 1.3 B.4 Current (...), Para 1 (and onwards).
P. 8 1.3 B.5 Significant (...) Para 5	Comment (minor) Children: It is not appropriate to use the word 'children' here, as that word relates to a specific population.	To use 'paediatric population' or equivalent terminology.
P. 8 1.3 B.5 Significant (...) Para 6	Comment (major) Comparison of the medicinal product (…): The reviewer wishes to make reference to earlier comments. In general, at an early stage of development data is lacking both for adults and most likely also for the paediatric population. This makes any comparison difficult, or perhaps even impossible to perform. The consequence is limited validity and value for making an assessment. Thus it would be more appropriate for an applicant of a PIP to provide only high level information. In this respect we would like to remark that the Regulation does not stipulate making comparisons, and neither does 2001/83/EC as amended.	The applicant should be allowed to provide only high level information.
P. 9 1.3 B.5 Significant (...) Para 1	Comment (minor) b) (...) Substantial improvement. As substantial is subject to many interpretations, it should be deleted.	To delete: substantial.
P. 10 1.4 C.2.1 Grounds (…) efficacy Para 4	Comment (major) All available data (…) support lack of efficacy (…): The reviewer proposes rewording of the text: 'Data should be submitted – if available – describing the lack of efficacy'. The revised text does justice to expected paucity of data.	To reword the text: 'Data should be submitted – if available – describing the lack of efficacy'.

P. 10 1.4 C.2.3 Grounds (...) lack (…) benefit Para 8	Comment (major) (…) based on a lack of significant therapeutic benefit: Article 11, paragraph 1 mentions the word 'evidence' in this respect.	To amend the text (...) 'evidence of a lack of significant' (…). The title should be amended accordingly.
P. 11 1.5 D.1 Overall (...) Para 1	Comment (major) Overall strategy: The reviewer wishes to note that at an early stage of development the data package is likely to be small and that consequently there may be little information to be submitted, or to base an opinion on. The guidance document should reflect this.	To add an introductory text: 'At an early stage of development the data package is likely to be small and that consequently there may be little information to be submitted, or to base an opinion on'.
P. 11 1.5 D.1.6 Significant (...) Para 6	Comment (minor) Information and ... Part B5: Since this information is largely covered in B5 it could be deleted here. Alternatively, as summary of B5 could be given.	To either - delete D.1.6 or - summarise B5.
P. 12 1.5 D.2 Strategy (...) quality Para 1	Comment (major) Bullet point 4: Food cultures: This section goes beyond what is required in accordance with 2001/83/EC and should therefore be amended. Moreover, it is not feasible to do such studies, bearing in mind the likelihood of already small numbers of patients available for studies.	To delete the section on food cultures.
P. 12 1.5 D.3 Strategy (...) non-clinical Para 1	Comment (major) Bullet point 1 / 2 / 3: Pharmacology / pharmacokinetics / Toxicology (juvenile animals) The use of juvenile animal models is currently under debate, and therefore these bullet points should be removed entirely. Moreover, the discussion on juvenile animal models is beyond the scope of this guideline. ICH is a more suitable forum.	To delete the reference to juvenile models. Alternatively, the applicant may wish, be should not be obliged, to discuss the use of juvenile models.

P. 12 1.5 D.4 Strategy (...) clinical Para 6 (and on page 13)	Comment (major) (…) Discuss (…) justify strategy strategy for the clinical paediatric development, in relation to the standard development (including that in adults and in relation to existing data (…) overall clinical approach: It is difficult to see how the overall clinical approach (i.e. including adults) should be part of the PIP, as the PIP has to be agreed with the competent authority. Failure to do the PIP as agreed will lead to an official failure to comply. However, it is not in agreement with the Regulation that a PIP can fail to comply on the basis of an 'adult component' in the PIP, which by definition does not belong in a PIP.	The references to the adult (overall) development plan must be deleted, as being outside the scope of the Regulation. Moreover, at an early stage of development, the amount of information on which a development programme can be based is generally very limited. The adult clinical approach must be seen as not being part of the PIP, only as supportive information, that does not affect the PIP. Here the applicant should have the freedom decide his development programme, and to submit (or not) as he pleases.
P. 13 1.5 D.4 Strategy (...) clinical Para 3	Comment (minor) The applicant (…) inclusion (…) representative (…) used: This text is so obvious that it should be deleted.	To delete para 2: “The applicant (…) inclusion (…) representative (…) used’.
P. 13 1.5 D.4 Strategy (...) clinical Para 5 (3 bullet points	Comment (major) Bullet points: pharmacodynamic studies / pharmacokinetic studies / efficacy and safety studies: In view of the reviewer there is far too much detail and overlap with ‘Part B’. Consequently, a reduction of text is recommended.	To refer to only ‘high level’ information.
P. 14 D.5 Planned measures for the paediatric development	Comment (major) Planned measures for the paediatric development: This chapter would benefit from a statement that only measures that are specific for paediatric development need to be addressed, and not for other developmental purposes. Alternatively, the title could be adapted accordingly.	To state that only measures that are specific to paediatric development need to be addressed.
P 14 1.5 D.5.2 Outline (...) pharmaceutical (…) Para 4 onwards	Comment (major) Pharmaceutical development: While the topics mentioned here are relevant, they are only remotely related to the ethical conduct of clinical studies in the paediatric population in particular(see preambule 4).	In view of the general character of the text, to shorten or delete the text.

P. 14 D.5.3 Synopsis (…) non-clinical studies	Comment (major) Synopsis / outline of protocol of each of the planned or performed non-clinical studies: The requested information can be provided in the form of an investigator brochure or IMPD. Such approach reduces the need fir duplication of texts. This should be added to the guiding document.	To add: The requested information can be provided in the form of an investigator brochure or IMPD.
P. 14 D.5.4 Synopsis (…) clinical studies (…)	Comment (major) D.5.4 Synopsis / outline of protocol of each of the planned or performed clinical studies or trials: The requested information can be provided in the form of an investigator brochure or IMPD. Such approach reduces the need fir duplication of texts. This should be added to the guiding document.	To add: The requested information can be provided in the form of an investigator brochure or IMPD.
P 15 D.5.4 Synopsis Para 1	Comment (major) Location (Regions): This level of detail regarding clinical study logistics should not be included into a PIP. It is not meaningful for the clinical assessment of the development, and at an early stage of development it will not be possible to decide on the location of studies.	To delete Locations / Regions.
P. 15 D.5.4 Synopsis Para 1	Comment (major) Study design: Only information that is particularly relevant for paediatric studies should be provided, not on others.	To add a statement that only information on paediatric studies should be provided, not on others.
P. 14 / 15 D. General comment / D.5.5	Comment (major) D. General comment on Part D (PIP): Currently there is no specific chapter where the applicant can provide a justification in regard to the significance of studies. A clear statement of the applicant which studies are considered to be significant and an agreement with the paediatric committee on the proposed studies may improve the chances for a later incentive (patent prolongation). Further this may clarify the situation for the authority and the applicant. Therefore it would be useful to place a proposal in the PIP to simplify the assessment for authorities later on.	To add: Additional header Section D 5: D5.5 Proposed significant studies

P. 15 1.5 D.6 Timeline (...) Para 2	Comment (minor) Measured: Typo: to read measures.	Correct typo.
P. 15 D 6 Timeline (...) Para 2	Comment (major) Detailed timelines: There is no basis in the Regulation for a request for _detailed_ timelines. Article 15(2) merely states: the PIP shall specify the timing and the measures proposed (...). In addition, at early stages of development predicting timelines is not possible, in particular not because of foreseeable difficulties in recruiting paediatric patients for clinical studies.	To delete: detailed (also in other parts of this draft guideline).
P. 15 1.5 D.6 Timeline (...) Para 2	Comment`(major) Predicted timing of application: This requirement goes beyond the scope of the Regulation. Moreover, at the early stages of development a prediction of the timing of the application is not possible because of the potential occurrence of problems (chem.-pharm, preclinical and clinical) during development.	To delete of the text regarding the predicted timing of the application.
P. 16 1.7 F Annexes (...) Para 1	Comment (minor) (…) documents, as appropriate: Since not all documents might be available, it is better to state 'if available',	To change 'as appropriate' into 'if available'.
P. 16 1.7 F Annexes (...) Para 1	Comment (minor) should include: to read may include. The reason is that not all documents might be available.	To replace 'should include' with 'may include'.
P. 16 1.7 F Annexes (...) Para 1	Comment (minor) Investigator brochure: this can be supplemented with IMPD (simplified, if applicable).	To add: IMPD (simplified, if applicable).

P. 16 1.7 F Annexes (...) Para 1	Comment (minor) Latest approved SmPC, PIL, labelling: It should be sufficient to provide the SmPC, not the PIL and the labelling. The SmPC provides the scientific information, and in fact the other textual components will have been derived from this document.	To delete: PIL, labelling.
P. 16 1.7 F Annexes (...) Para 1	Comment (minor) There should be the option for the applicant to include statements issued by experts in the relevant (paediatric) discipline.	To add: To allow for expert statements to be included.
P. 17 Section 2 (...) Para 1	Comment (minor) The 1st bullet point on page 17: This should stay as closely as possible to text of article 15(2) of the Regulation.	To amend the text in accordance with the regulation. .
P. 18 Section 3.1 Background (...) Para 6	Comment (minor) Statement of compliance: There is no basis in article 45 of the Regulation to specifically indicate in the statement of compliance whether the studies in the paediatric investigation plane were initiated before prior to entry into force of the aforesaid regulation.	To delete the paragraph entirely (The statement … paediatric regulation).

P. 18 Section 3.2 Assessment criteria Para 3	Comment (major) Study types ... considered as significant: The types of studies listed here are certainly significant. However, the list should be supplemented with studies in which pharmacokinetics are studied, in view of the relevance of the data for dose finding and dose selection, and because of the difficulties in obtaining pharmacokinetic data in the paediatric population. We refer to EMEA/CHMP/EWP/147013/2004. Comment on Section 3: Listed significance criteria, p 19 One goal of the paediatric regulation is to reduce or eliminate any negative impact of medicinal products on growth and development of children. Studies aiming at reducing such negative effects on children by applying new formulations, dosing regimens or co-medications are currently not listed in Section 3. But these studies can definitely contribute to making the use of a medicinal product more acceptable, easier, safer or more effective according to Article 15(2) of Regulation 1901/2006. Efficacy or safety studies as currently listed in Section 3 of the guideline are not consequentially studies investigating improvements of growth and development of children receiving a medicinal product.	Please add to the list additional bullets: - paediatric studies involving the collection of pharmacokinetic data. - studies assessing the effect of the medicinal product on growth or development in the paediatric population.
P. 18 Section 3.2 Assessment criteria Para 4	Comment (minor) Typo: ... if carried out _in_ a subset considered	Please amend: (…) carried out in a subset (…)
P. 19 Electronic submissions (not included in the guideline)	Comment (major) In these ages and times of eCTDs it should be explicitly allowed for the applicant to submit the documentation in an electronic format, e.g. pdf.	Proposal: An application can be submitted in electronic format. With only the cover letter being required as paper copy, because of the need for a signature.

Please feel free to add more rows if needed.