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SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE

COMMENTS FROM EMEA

GENERAL COMMENTS

- The EMEA congratulates the European Commission on the guidance, which is generally clear and comprehensive. The EMEA notes that some technical and administrative aspects have been excluded from the scope of the document, and will therefore be addressed in EMEA recommendations (e.g. number of copies, IT format of submission)
- **Our major comment** on the draft guideline relates to the proposed principle of having one PIP application covering several indications developed simultaneously. After further consideration, the EMEA came to the conclusion that a request for PIP or waiver should only cover one indication for applications in the context of Article 7 of Regulation (EC) No 1901/2006 as well as Article 8. This would avoid the potentially complex management of opinions and decisions, the difficulty of compliance checks on PIPs covering more than one indication and potential difficulties for applicants to complete all measures included in such PIPs.

- We also believe that a paragraph should be added in relation to the timing of submissions of application for PIP or waiver as it is an important requirement from the legislation. This paragraph should clarify what is meant by "not later than upon completion of adult pharmacokinetic studies' and addresses the specific case of medicinal products for which there are usually no adult pharmacokinetic studies.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
	The title of the Commission Guideline is descriptive but very long. A shorter title would be welcome (in addition to its official title) as it will facilitate reference to this guideline in future documents	Suggested 'running title': Commission guideline on procedures and applications relating to paediatric development

Date of transmission:

Submit all comments to: by email to peter.arlett@ec.europa.eu in word forma 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.

Introduction 2nd paragraph	In the 3rd sentence "support measures" should be replaced by "a framework"	The paediatric regulation also creates a framework to manage the operation of the paediatric regulation including the paediatric committee within the European Medicines Agency (hereinafter "the Agency").
Introduction Definitions	The definition of a PIP should be added	
Item (e) definition of "measures"	We suggest to replace "necessary in a paediatric investigation plan" by "proposed" to be more in line with the Regulation.	(e) as used in Article 15(2) of the paediatric regulation, all studies, trials, data and pharmaceutical development proposed to obtain a paediatric indication with an age appropriate formulation in all subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan.
Section 1.1	A sentence should be added to indicate that this guideline should be read in conjunction with all the relevant scientific guidelines	
2nd paragraph	To improve the readability of the section, it could be wise to briefly describe the legal references of Art 7 and 8.	
6th paragraph	2nd line to be more accurate "in particular all relevant details should be given" should be replaced by "This includes details"	"All information relevant to the evaluation of the paediatric investigation plan, requests for deferrals or waivers should be included in the application whether favourable or unfavourable to the product. **This includes** details of any incomplete or discontinued pharmaco-toxicological test or clinical study or trial relating to the medicinal product, and/or completed trials concerning indications not covered by the application."
Last paragraph	We suggest to re-arrange the order and reword it to improve the readability.	"The holder shall provide to the Agency, without delay, any new information which might entail the Opinion of the Committee and/or Decision of Agency together with a proposal for modification of the paediatric investigation plan and/or a request for waiver or deferral as appropriate."
1.2 Part A	To improve the readability of the first paragraph we suggest to re-arrange the order and reword it.	"Applicants should always complete all sections of Part A using the forms annexed to this Guideline and where information is not available this should be stated. It is acknowledged that at an early stage. It may not be possible to complete in full all sections of the application".

	We suggest to re-order the indents as follows:	Proposed new order A.1 Name or corporate name and address of the applicant and contact person A.2 Name of the active substance A.3 Type of product A.4 Details of the medicinal product A.5 Conditions to be treated, diagnosed or prevented A.6 Proposed therapeutic indication and pharmacotherapeutic group A.7 Name of the manufacturer of the active substance and medicinal product A.8 Regulatory status of the product inside the Community A.9 Regulatory status of the product outside the Community
A.4	Delete "new" to cover the cases of submission of PIP for authorised products. We suggest to delete the last sentence as this does not really refer to the type of product and is addressed in other sections	"The applicant should specify what type of product the application is for (e.g a chemical entity, a biological product, a vaccine, a gene therapy product, a somatic cell therapy medicinal product etc..)"
A.6 *5th bullet point*	This deserves to be more specific with respect to the type of information on clinical trials to be given in this section, such as listing with reference to Eudract number	
A.6 *6 th bullet point*	The word "details" could be misleading and therefore we propose rewording	**"List** of any scientific advice from the agency of any national competent authority **(with cross-reference to Part F Annexes)"**
A.6 *2nd sentence*	Add "**as appropriate"**	"This should include **as appropriate**:"
A.6 *7th bullet point*	A word is missing	"details of any regulatory **action taken** to …"
A.7	Same comments as above; the information in this section should be brief therefore the word "details" may be misleading	A summary of 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), **list** of the indications for which the medicinal product is approved outside the Community, regulatory

		information on clinical trials and any regulatory actions taken to restrict the use of the medicinal product in any non-EU country(ies).
A.8	The first sentence is incomplete to cover all the situations under article 8. A rewording is proposed.	For products not yet authorised in the Community or, for authorised products where a new indication, **new pharmaceutical form or new route of administration** is proposed for development, the condition(s), whether in adults or children, that the medicinal product is intended to diagnose, prevent or treat, as envisaged at the time of submission, should be stated, following an agreed classification system, such as the World Health Organisation International Classification of Diseases (ICD-10).
A.9	The last sentence should be deleted. The information is partly covered in other sections.	
1.3 Part B	The last sentence should be moved to section B.4 as it referred to the way of presenting the information on the diagnosis, treatment methods and alternative.	
B.1	The word pathophysiology should be added	"Emphasis should put on the seriousness of the disease, aetiology, clinical manifestations, prognosis, **pathophysiology** and variability in terms of genetic background, in the paediatric subsets
B1	Last sentence we propose to delete the word "standard"	"This may be based on published references, or textbooks."
B	We suggest to reorder and merge certain paragraphs as follows B.1 Discussion on similarities and differences of the disease/condition between populations (including B1 and 3) B.2 Current methods of diagnosis, prevention or treatment in paediatric populations (current B4) B.3 Significant therapeutic benefit and/or fulfilment of therapeutic needs (including B2 and B5; see below for proposed wording)	
B.2		New paragraph in previous B.5 should start with:

		"Whether the use of the medicinal product either through use as an authorised product or through the conduct of clinical trials in children is expected to be of significant therapeutic benefit **and/or** fulfil a therapeutic need in children will be ….granted" "Significant therapeutic benefit and/or fulfilment of unmet need might also be recognised on the basis that existing treatments are not satisfactory and alternative methods with an improved expected benefit risk balance are needed." To enable the paediatric committee to make its assessment the applicant should: - Discuss the anticipated differences and similarities of the effect of the product on the diseases /conditions on a comparison: • between the adult and the paediatric population; • between the different paediatric subsets. And/or - Provide a comparison of the medicinal product which is the subject of the application with the current methods of diagnosis, prevention or treatment as listed in section B.4 of the diseases/conditions that are the subject of the intended indication in children….as to the value of such method…."
B.3	We suggest to move the content of current B.3 at the end B.1 as it gives broad information on the diseases/conditions before addressing the more specific aspects, and to reword it as follows.	"Information on the age of onset of the diseases/conditions or the age range concerned should be provided, as well as incidence and/or prevalence in the Community if available, especially if the applicant intends to apply for a product specific waiver."
B.4	As mentioned above (1.3 Part B) to avoid that applicants provide extensive information on the current methods, this information should be provided in a synthetic manner in a tabular format. 1st paragraph, 2nd sentence "standard of care" should be defined. Therefore a wording is proposed.	"For each disease or condition already authorised, as well as for each disease or condition which is the subject of new development (i.e. for new medicinal products or new indications for authorised medicinal products) the applicant should identify the diagnosis, prevention and treatment methods available in the Community, making reference to scientific and medical literature or other relevant information. This should include unauthorised treatment methods if they represent the standard of care, **for example, if they are mentioned in treatment guidelines internationally recognised such as GINA. This should**

		be presented in tabulated format for ease of reference.
B.5	The title should be modified to be in line with legislation (art 6(2))	**“Significant therapeutic benefit and/or fulfilment of therapeutic need”**
B.5 *1st paragraph*	1st sentence the word “and” should be added	“Whether the use of the medicinal product either through use as an authorised product or through the conduct of clinical trials in children is expected to be of significant therapeutic benefit **and/or** fulfil a therapeutic need in children will be ….granted”
B.5 *2nd paragraph*	2nd part is a repetition of B4 therefore we suggest to delete and include a cross-reference to the section.	“To enable the paediatric committee to make its assessment the applicant should provide in section B.4 a comparison of the medicinal product which is the subject of the application with the current methods of diagnosis, prevention or treatment of the diseases/conditions that are the subject of the intended indication in children (see section B.4)
B.5 *3rd paragraph*	It should be moved to become 2nd paragraph of B.5 and should be rephrased	**“Significant therapeutic benefit and/or fulfilment of unmet need might also be expected on the basis that existing treatments are not satisfactory and alternative methods with an improved expected benefit risk balance are needed.”**
B.5 *5th paragraph,*	b) for accuracy replace “events” by “reactions” - rewording proposed. We suggest also to move the current point f) after point b)	b) expected substantial improvement in safety in relation to either adverse **~~events~~ reactions** or potential medication errors **in a paediatric population compared to the current standard of care for the treatment, diagnostic or prevention of the condition concerned**
B.5 *7th paragraph*	The word “fully” should be deleted	If significant therapeutic benefit cannot be justified at that early stage of the development of a medicinal product, the paediatric committee may consider a waiver or deferral, as appropriate
B.5 *8th paragraph*	As it refers to request to waiver therefore we suggest to move it under section C 2.3	
C.1 *3 rd paragraph*	1st line delete “class” and replace by “all” in line with Paediatric Regulation	“It should be noted that the Agency will make public **all** waivers …regulation”.
C.2	It should be mentioned that for this section there is no need to repeat information from previous section(s) but insert cross-reference where appropriate	

D 1.3	2nd line add only the main results should be provided therefore this should be specified. (further rewording proposed under D.1.5 below)	
D. 1-4	Cross-reference to B.1 and B.2 should be made wherever appropriate.	
D.1.5	This section could be deleted and information could be included under D.1.3	New paragraph for D1.3 "The applicant should outline the development of the medicinal product **in adult population** which is relevant for paediatric development and its **main** 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. In addition the applicant should include a review of any information on the product in the paediatric population, making reference to scientific and medical literature or other relevant information, such as reports from off label or unlicensed use, or accidental exposures, as well as known class effects."
D.1.6	To be deleted as already addressed in comments on B5	
D.2	The importance of having an acceptable formulation needs to be emphasised. In addition, as mentioned in the SPC guideline in the exceptional case where no formulation would be possible, the applicant would have to ensure information for extemporaneous formulation.	New bullet point to add • The acceptability of the formulation (including palatability) – i.e. its 'fitness for purpose', justified from a physico-chemical, biological and physiological point of view. Alternatively, in case it is not possible to develop a formulation which is relevant and acceptable for paediatric use on an industrial scale, the applicant should state how it intends to facilitate the extemporaneous magistral preparation of an individual ready-for-use paediatric formulation. This information would ultimately be included in the Summary of Product Characteristics. "
D.2	Last paragraph concerns not only the existing pharmaceutical form which may be unsuitable but also the strength so rewording is proposed to reflect this aspect	The addition of a paediatric indication may result in the need for a new pharmaceutical form **or new strength** for example a liquid rather than a tablet or a tablet of a new strength, because the existing pharmaceutical form **or strength** may be unsuitable for use in all or part of the paediatric population. This means that the suitability of existing pharmaceutical forms**/strengths** should always be discussed in the paediatric investigation plan."

D.3	The introductory statement could be expanded to capture that the need for any specific studies should be carefully analysed.	• "This section should discuss the strategy for the non-clinical development, which is needed in addition to **classical** non-clinical development or to already existing data. **The need for non-clinical studies (species; age; duration) should be scientifically justified taking into consideration the conditions for paediatric use (target organs of concern, age range, indication, duration..)"**
D.4 *4th paragraph*	We suggest to add an ethical reminder to justify the studied populations or subset, and to go into the least vulnerable subset it might be appropriate to add a sentence such as "	"These studies should be performed in the least vulnerable groups whenever possible (i.e in adults rather than in children, in older children rather than younger ones). If results cannot be extrapolated to younger groups, this should be justified".
D.4 *Pharmacokinetic studies*	In the context changing the wording "adults and older age groups" to "adults and older paediatric age groups" would improve readability. And further down "expected high kinetic variability" should be changed to "expected high pharmacokinetic variability"	
D.4 *Efficacy and safety studies*	*2nd bullet point* Delete "the" in "issues of **the** relevance The choice of the comparator (placebo or active) is an important point to be addressed there we suggest to add it. *3rd bullet point* There is a need to distinguish between products with an existing risk management plan and products without. A rewording of this bullet is therefore suggested	"Discussion of issues of relevance across the proposed studies, such as **use of placebo or active control**, age appropriateness of endpoints, use of surrogate markers, use of alternative study design and analysis, potential need for short term and long term safety and potential risks by age group. • **If there is an approved EU-RMP for a product which is already authorised for use in the adult population, any risk minimisation activities appropriate for the paediatric population should be taken into account in developing the PIP. If there are pharmacovigilance studies in the EU-RMP which involve a paediatric population, they should also be cross-referred to in the PIP** **The need for long-term safety studies in the paediatric population should always be discussed in the PIP. If such studies are considered necessary, the details should be provided in the RMP,**

		or its update, submitted at the time of the application for marketing authorisation, but in principle would not form part of the agreed PIP.
D.5	To avoid any confusion we suggest to amend the title	"**Measures for the development in paediatric population"**
D.5.1	This section concerns only the planned and ongoing measures and not the performed ones therefore a rewording is suggested We suggest including the text of D6 regarding timelines. A reference to applications that fall under article 30 is missing. This should be added.	"A table should be included providing an overview of all measures planned **and/or ongoing** by the applicant **in the paediatric population**. This table should include the detailed timelines of the measured included in the paediatric investigation plan. Particular emphasis should be placed on the timing of the measures in the paediatric investigation plan compared to the development for adults, as expressed for example in ICH E 11. The predicted timing of applications which fall under Articles 7, 8 and *and* **30** of the paediatric regulation should be provided and the timing of the measures in the paediatric investigation plan should refer to these applications. The applicant should propose timelines for initiation and completion of each measure, including specific dates. The applicant should include in its proposal a reasonable amount of time for unforeseen circumstances to complete, analyse and report the studies of the application."
D.5.2	For the same reasons as mentioned in 5.1, title to be amended	"Outline of each of the planned **and/or ongoing** studies and steps in the pharmaceutical development"
	Under the 1st bullet point there is a footnote (4) without content.	A footnote is proposed **"**In any case, the full range of pharmaceutical development studies to confirm process and product uniformity and stability would be required at the stage of application for Marketing Authorisation. Existing Agency guidelines in this area should be consulted to decide which studies could be relevant within the strategy proposed in Section D.2**"**
D.6	As mentioned above we suggest to delete this section and move the information under D.1	
1.6 Part E	The deferral may be in relation to the development in adult population. Therefore a new sentence is proposed	"The paediatric regulation allows for deferral of the initiation or completion of the measures included in a paediatric investigation plan. **Timelines may be expressed in relation to the development in adults**. Any request for deferrals of the start or the completion of measures should be justified by indication, route of administration and

		pharmaceutical form."
1.7 Part F	The annexes should also contain the existing EU risk-management plans for authorised medicinal products therefore this should be added as the last bullet point	**"Latest approved EU-RMP for a product already authorised"**
Section 2	As a general comment, a reference to article 30 should also be added.	
	This whole section would benefit from clarifications, as the legal references are not self explanatory. It is suggested to add an introductory statement to briefly explain the purpose/principle of compliance and the timing (prior, or during validation of an application and later on). Under paragraph 4, to ease the reading the 2-step process should be clearly defined. Under paragraph 5 for accuracy we suggest to refer simply to article 7 Under paragraph 11 the 1st sentence may be difficult to understand. Under 1st bullet point, a rewording is suggested. The proposed statement on compliance should be reworded since it is not the medicinal product which complies with the PIP. The second proposed statement should clarified with respect to the legal reference	"The relevant Competent Authority or **the Agency** will perform a detailed check of each binding element **of the EMEA decision on paediatric investigation plan** against what has actually been submitted." "**The development of this product in the paediatric population has complied with all the measures in the agreed paediatric investigation plan"** **"When studies completed after the entry into force of the Regulation have been included.."**
Section 3 *Proposed statements on compliance*	In the two statements to add "agreed" PIP In the second statement to include studies "started after the entry into force of the Paediatric Regulation"	"This medicinal product has complied with all measures in the **agreed** paediatric…" "This medicinal product has complied with all measures in the **agreed** paediatric…and includes significant studies **completed after the entry into force of the Paediatric Regulation**"

Section 3.1	1st sentence add the actual date of the entry into force of the Regulation to ease the reading.	
Section 3.2	It is suggested to reword the 1st sentence to improve readability	**In general, the significance of studies is determined by the clinical relevance of data generated for the paediatric indication rather than by the number of the studies.**
	Last paragraph line 4 should be reworded	• " if carried out **in** a subset considered"….