SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE

COMMENTS FROM: The Institute of Clinical Research Paediatric Special Interest Group

GENERAL COMMENTS

Concern is that in the EMEA FAQ dated 12 January 07 it said that the PdCo could start with the 27 member states (MS) representatives but failed to mention the **ethical** representative which is a requirement in the regulation. It is a good document but needs to be made more user-friendly.

Some requirements are completely impossible; e.g. diagnosis and treatment of disease in each MS will vary hugely in the MS themselves. This will be a huge document and PdCo members may not have time to read it all.

Concern that PdCo should review PIPs in order of MAA deadline rather than first come first served basis or those registering in July 2008 may fail MAA.

Concern that the PdCo will be overloaded too quickly & will lack manpower to review PIPs properly.

Concerned that medicines must be named rather than numbered due to commercial confidentiality.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Introduction	Clarity on how the EMEA will stimulate academic or basic research and whether plans would be produced by this sector. These researchers will most likely be involved in generics investigations. Reference to the FP7 European based finding.	
Introduction (e)	Does this include anecdotal data or data in the public domain?	*Include reference to anecdotal data in the public domain if this is covered*
1.1	It was suggested that the term 2 to 11 years is perhaps too wide and it should perhaps be split into two groups <8 years and 8-12 years. It was	*Split age into two groups*

Date of transmission:

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	also recommended that pre-term or neonatal subjects should be differentiated. Also, a clarification of birth ages vs. gestational age would be required. Perhaps groups should be split into pubertal and pre-pubertal, and that monitoring of children going through puberty is essential possibly using the Tanner staging method. There is some ambiguity between neonatal and infant. Would you class a 24 week preterm who has reached 6 weeks of age as an "infant"? Maybe need categories of "term neonate (0-27 days)" and "pre-term baby" (birth to 27 days) or similar It was suggested we get clarification from the PdCo since some drugs may not be covered by a patent especially those fast tracked in the therapeutic areas of HIV and cancer where there is clearly an unmet medical need for children. Penalties should be in place if all relevant details relating to the medicinal product are not given Agency decisions to be made public with contact points and phone numbers. Will contact numbers be in public domain too? Is there a security risk for animal rights people?	*Clarify which indications are not covered* *Refer to any penalties that may apply if full details are not given*
1.2 A3	There was a question about whether herbal medicines are covered by this and this should be clarified.	
1.2 A6	Missing word in the last bullet point – regulatory "advice" perhaps? Clarify EAA as European Economic Area Regulatory status in every country; how much detail would be required since this could be onerous.	*Amend last bullet point to read "details of any regulatory **advice** to restrict the use of the medicinal produce in any EEA country* *Put "European Economic Area" in brackets after first reference to acronym*
1.2 A8	Does this include devices as well as medicines?	
1.2 A.9	Minor language issue	*Proposed therapeutic indication and pharmacotherapeutic group* The applicant should provide the proposed therapeutic indication which may cover the adult and/or paediatric population. Where a pharmacotherapeutic group and ATC code have been assigned, these should be included. Any other authorised medicinal products belonging to that class should be stated.

1.3 B1	There is not a lot of information there to help companies, and perhaps there should be more detail given to companies who don't know where to start. For example they refer to paediatric subsets, but it is not clear if they refer to E11. Again the paediatric age groups should be referred to. It was agreed we should add 'epidemiology' to the sentence beginning "emphasis should be….. standard textbooks" There should also be a reference to the fact that there may also different treatment for adults and children for the same indication. Does the PiP have to cover the same indication as the adult MAA or can new indications be planned?	*Reword to "Emphasis should put on the seriousness of the disease, aetiology,* ***epidemiology,*** *clinical manifestations……."*
1.3 B1 para 2	Minor language issue	Emphasis should be put on the seriousness of the disease, aetiology, clinical manifestations and prognosis, and variability in terms of genetic background, in the paediatric subsets. This maybe based on published references, or standard textbooks.
1.3 B5	There should be a mechanism whereby decisions are reviewed if new information becomes available? Disagree with para 5 page 9: implies that it is acceptable to investigate medicines early in children if there is no therapeutic alternative. It should be clear that if there is concern for safety these investigations should be deferred.	
1.4 C.2.1 para 2 and 3	Minor language issue	The safety profile of a medicinal product is usually only fully characterised after a product has been placed on the market. The justification for a waiver based on safety will therefore differ depending on the existing experience with the product. Justification may include the pharmacological properties of the product or class of product, results from non-clinical studies, clinical trials or post-marketing data. Whether a safety issue is known or suspected, it should be discussed. At an early stage of development, the absence of any available data on the safety or efficacy in the paediatric population will not be accepted as the sole justification for a waiver.
1.5 D.1.1	There was a question about whether it is the adult drug being used in the same indication in children or a whether other indications should be included.	

1.5 D.1.2	It was agreed that for various efficacy, safety, developing consent/assent, it may be best to divide the age groups up other than that presented in ICH11, e.g. preterm vs. neonatal; <8 years and 8-12 years >12 years.	*Divide the age groups up and clarify*
1.5 D.1.3	What is the requirement for pre-clinical data?	*Add sentence to clarify whether pre-clinical data is or should be included*
1.5 D.1.4	Clarification of what techniques and methodologies are acceptable for extrapolation e.g. pharmacodynamic and pharmacokinetic modelling	*Add clarification regarding extrapolation*
D.2	Consideration should be given to the ethnic and cultural differences associated with the route of administration and acceptable dosage forms. Genotyping should be mentioned here too.	*Add reference to ethnic and cultural differences being taken into account* *Add reference to genotyping*
D.3	It was agreed this section is necessarily vague. With experience of evaluating PiPs this should become more detailed and provide better guidance. Pubertal aspects, cognitive development whilst on the treatment should be included.	*Include reference to cognitive and pubertal development*
D.6 1.8	Should include definition of modification – does it cover shortfall in timings and recruitment for example?	*Include definition of modification*
D.5.4	Suggest this should also include duration of trial and anticipated acceptability of trial to children and care givers. Otherwise companies will find themselves committed to paediatric trial time lines that are impossible because the studies will not recruit. Statement here on detailed measures to reduce risk and distress.	
Section 2, para 4	If the results are generated in good faith by the company but then deemed not to be compliant with the PIP, the MAA for the NCE/new indication/new pharmaceutical form will not pass the validation phase and will not undergo assessment?	Double incentives are not permitted, therefore it seems inconsistent to allow double punishments: incentive not granted, AND the MAA in the adult population not granted.
Section 2, para 6	"If only some of the measures included in paediatric investigation plan decision have been completed the compliance statement referred to in Article 28(3) of the paediatric regulation will not be included as this requires completion of all the measures in the paediatric investigation plan." For the purpose of submissions under Article 8 of the paediatric regulation, a paediatric indication on an existing formulation may be approved prior to completion of all measures (pertaining to other planned indications and pharmaceutical forms). This will delay the placing on the market of the paediatric indication/formulation under a PUMA until completion of the remaining PIP measures, thereby delaying	"If only some of the measures included in the paediatric investigation plan decision have been completed the compliance statement referred to in Article 28(3) of the paediatric regulation will be included with the caveat that outstanding measures in the paediatric investigation plan should be completed in accordance with the previously agreed timeframe."

	access of the paediatric population to this medicine. Since, the PIP is a rolling plan, incentives should be granted in phases so that a PUMA can be used immediately for the pharmaceutical form and indication in question with subsequent updates to add indications as data become available.	
Section 2, para 11	First sentence in paragraph doesn't make sense. Is this: "the applicant's position on compliance with the key elements" supposed to mean the applicant's opinion of their own degree of compliance with the key elements?	To establish that the requirements for medicinal products that fall under the scope of Articles 7 or 8 have been met, the compliance report should indicate in the form of a table how each subset of the paediatric population and for applications falling under Article 8 of the paediatric regulation, how each of the existing and new indications, pharmaceutical forms and routes of administration have been covered by the documents referred to in Article 7(1) of the paediatric regulation. A separate table should be included covering the decision on the paediatric investigation plan, the applicant's position on compliance with the key elements, and a cross-reference for each key element of the paediatric investigation plan to the location within the submitted relevant module in the marketing authorisation application. In case of modifications to a paediatric investigation plan, the table should be based on the latest decision of the Agency.
Section 2, second last para	Minor language issue	The statement of compliance referred to in Article 28(3) of the paediatric regulation will be the following: This medicinal product has complied with all measures in the paediatric investigation plan [reference number].
Section 2, second last para	Minor language issue	Where studies fall under the provisions of Article 45(3) of the paediatric regulation the statement of compliance referred to in Article 28(3) of the paediatric regulation will be the following: This medicinal product has complied with all measures in the paediatric investigation plan [reference number] and includes significant studies.
3	Studies previously conducted would not necessarily contribute to appropriateness of PIP but could be used as supporting data. Understanding is that this is fluid and depends on quality, design and robustness of the study. It was suggested that advice/guidance should be sought in this instance by the company. It was suggested that placebo can be used for short time exposure if there is a clear exit strategy	Add sentence "placebo can be used for short term exposure if there is a clear exit strategy.

Section 3 final para	Minor language issue	In order to be considered as significant, the studies should normally cover all paediatric subsets affected by the condition where sufficient data are not available. However, exceptionally, studies conducted in a single subset of the paediatric population will be considered as significant if carried out in subset considered particularly difficult to study, for example neonates. Where sufficient data for one or more of the paediatric subsets are already available, duplication of studies should be avoided and therefore unnecessary studies will not be considered as significant.

Please feel free to add more rows if needed.