SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE

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GENERAL COMMENTS

In general BPI welcomes the draft guideline with detailed arrangements concerning the format and content of applications or modifications of paediatric investigation plans, waivers and deferrals at an early stage. Looking into the details of the draft guideline we have to state that the planned requirements are very much detailed and all in all quite high-level. Especially for small and medium sized companies developing e.g. biotech products it often will not be possible to fulfil the requirements laid down in this draft. This is especially the case when there are no experiences with pediatric development in the past. BPI urgently asks the commission not to establish too many obstacles in getting a product for paediatric use to the market. Especially in the case of the new PUMA to many obstacles will prevent medium sized companies and even bigger ones from conducting studies in children and obtaining for a PUMA. As the PUMA is not mandatory the hurdles should not be too high otherwise it will be discouraging for companies to develop medicines for children containing well-established substances and the concept of PUMA will not be successful. BPI would suggest instead of requesting too detailed data and information when applying for a marketing authorisation better to make use of the tool of risk management plans and to put the main focus on monitoring the pharmacovigilance of the approved medicinal product after its launch. This would have two main advantages: At first the development of new medicinal products would not be hampered due to inadequate requirements at the date of marketing authorisation and secondly the children in need will get the treatment as soon as possible. The safety of the medicinal product will be monitored more stringent after launch by adequate risk management. The PIP should not de too detailed because clinical trials need approvals/favourable opinions by competent authorities of the member states and the national ethics committees. There might be specific requirements in the member states that might cause too many changes of the PIP if the PIP is too detailed. If the PIP is too much detailed there might be too many changes necessary at later stage with an unnecessary heavy workload for PDCO and companies. In part D of the draft the requirements concerning quality and preclinical and clinical development are laid down too much in detail. In addition we refer to the EFPIA comments.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**

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.

Page 4, third paragraph	The addition of the word “relevant” makes it clear that not in every case all subsets have to be taken into regard.	Measures: as used in Article 15(2) of the paediatric regulation includes all studies, trials, data and pharmaceutical development necessary in a paediatric investigation plan to obtain a paediatric indication with an age appropriate formulation in all **relevant** subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan.
Page 4, last paragraph	This addition is necessary, because a new route of administration is a further possibility which is also mentioned in other chapters of this guideline.	If a paediatric investigation plan is included in the application submitted in accordance with this guideline it should focus on studies that will allow labelling the product for appropriate use in all relevant paediatric subsets, as well as the development of appropriate formulations **and/or routes of administration**, if applicable.
page 7, second paragraph	Based on experiences for example in the area of orphan drugs it is not always possible to provide all the information stated in this paragraph. Because of this it should clearly stated that applicants are asked to provide best available data but it has to taken into account that this is not always possible in any case. For example to provide details concerning the adult and pediatric population for each and any indication is not always possible neither is it possible to have all this information available for all pediatric subsets. We strongly ask to be more flexible especially in the case of a PUMA and ask to take into regard that for medicinal products with only a few patients the data sources are often limited and do not allow such in-depth analysis.	This part should **where possible** also include details on the diseases/conditions in the paediatric population including their similarity between adult and paediatric populations and within the different paediatric subsets, prevalence, incidence, diagnosis and treatment methods, and alternative treatments. This information can be provided in tabulated format for ease of reference.
page 7, B. 1, first paragraph	To provide information for each new or already authorised indication is not always possible neither is it in any case possible to have all this information available for all pediatric subsets or to name all differences or similarities between adult and pediatric populations in detail. We strongly ask to be more flexible especially in the case of a PUMA and ask to take into regard that for medicinal products with only a few patients e.g. orphan medicinal products the data sources are often limited and do not allow such in-depth analysis.	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 **where possible** state whether the paediatric population is affected. The applicant should **where possible** provide a description of the diseases or conditions, with a view to discuss any potential differences or similarities: • between the adult and the paediatric populations; • between the different paediatric subsets;

Page 7, B.2	It is not possible in any case to have all this information available for all pediatric subsets or to name all differences or similarities between adult and pediatric populations in detail. We strongly ask to be more flexible especially in the case of a PUMA and ask to take into regard that for medicinal products with only a few patients the data sources are often limited and do not allow such in-depth analysis.	The anticipated differences and similarities of the effect of the product on the diseases/conditions should **where possible** be described focussing on a comparison: • between the adult and the paediatric population; • between the different paediatric subsets.
page 7, B.3, first paragraph	To ask for incidence and prevalence will not be possible for any indication. Concerning orphan medicinal products for example the prevalence is known and has to be shown at the time of the designation. Therefore it is adequate to ask either for prevalence or for incidence. To assess the pediatric need one of these figures will be sufficient.	The applicant should provide information of the prevalence ~~and~~ **or** incidence of the diseases/conditions in the Community (and in the different Member States) if available. If possible, this could be broken down by paediatric subsets.
Page 11 ff., chapter D	In part D of the draft the requirements concerning quality and preclinical and clinical development are laid down too much in detail. Especially in a situation where the PIP application is filed in very early stages of development, what is encouraged by the regulation, all the requested information will not be available. For example the request in chapter D.5 on page 14 to provide a synopsis/outline for each planned or performed study is overshooting the mark.	
Page 11, D.1.4.	Also an extrapolation from one pediatric subset to another could be reasonable, e.g. if the metabolism of prematures or even newborns is not fully developed, but for infants the metabolism might be fully developed, an extrapolation should be possible even among different pediatric subgroups.	
Page 14, D.5.2	The referring footnote to “4” is missing.	Otherwise, if the strategy is to create a new pharmaceutical form (e.g. new dosage form, or new route of administration) then the necessary pharmaceutical development studies may need to be more extensive[4].
Page 15, 1.6 part E	Concerning the requirements for granting a deferral we think that it has to be clearly stated that studies in children are frequently only acceptable when it has been shown that the product is safe in adults. In Whereas 4 of the Pediatric Regulation it is said that aims to facilitate the development and accessibility of medicinal	

	products for use in the paediatric should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations. And in Whereas 10 of this Regulation is said that early submission of a paediatric investigation plan, combined with the submission of a deferral request will avoid delaying the authorisation for other populations. In our opinion the fact that a deferral is needed will come up quite often. Especially when we look into Article 4 (e) of the Clinical Trials Directive where it is said that clinical trials on minors are only acceptable where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods. This means that at the beginning of a clinical trial on minors it has to be shown that the results of studies in adults and even modelling or extrapolation of adult data was made and that the studies preformed on minors are needed to validate these data obtained from adults. This means that in the light of Article 4 (e) parallel clinical trials in children and adults will become difficult to conduct. Ethics committees and national competent authorities will ask for sufficient data in adults before issuing a favourable opinion/authorisation for studies on minors. Without the positive opinion/approval of ethics committees and competent authorities no clinical trial can start in the member states. Because of the situation that a positive opinion/approval is needed that should be taken into regard when defining the requirements for the PIP. The situation that a deferral will be needed because the trials in minors can only start when there is sufficient data available from trials in adults will come up quite often. This should never lead to a situation that the granting of a marketing authorisation for the adult indications would be delayed. Taking all that into account we would ask that the system of deferrals will not be regarded as some kind of exemption because it will apply quite often because in most cases clinical trials in children and adults will not be finished at the same time and the marketing authorisation application will be filed as soon as possible after finishing the adult studies. Exemption: different approach is needed for PIP and clinical trials	

	for medicinal products for children only.	
Page 16, 1.8	Concerning the modification of an agreed PIP a pragmatic approach is very much needed. It would save resources on both sides (applicant and pediatric committee) if it would be possible to modify an agreed PIP together with the requested annual report. This would avoid time consuming additional procedures. Therefore PIP should be less detailed than it is proposed in the draft.	
Page 16, section 2, fourth paragraph	The compliance check is described as a two-step process. The requirements are very much detailed. BPI would ask for a more general approach because otherwise even very small deviations of results from what was laid down in the PIP (which by the way will occur in any case) would lead to non-compliance of the results and could lead to an ineligibility for the rewards and incentives that would not be adequate. For example the different requirements of competent authorities/ethics committees in the member states for clinical trials in children may lead to different results from what was laid down previously in the PIP.	
Page 17, first paragraph	It might be that for some subsets a waiver or deferral has been granted.	for medicinal products with an agreed paediatric investigation plan, whether all of the measures in that plan (studies, trials and timelines) proposed to assess the quality, safety and efficacy of the medicinal product in all **relevant** subsets of the paediatric population concerned,
Page 17, third paragraph	This approach is very inflexible and should be reviewed. If it is not possible to adjust timeframes at later stage this situation will in a lot of cases lead to delays in obtaining the marketing authorisation for the adult indication. This cannot be in the interest of the Commission and is for sure not in the interest of patients.	At the time of the assessment of compliance, measures and timeline included in the paediatric investigation plan decision cannot be re-negotiated **except duly justified**.
Page 17, last two paragraphs of section 2		The statement of compliance referred to in Article 28(3) of the paediatric regulation will be the following: This medicinal product has complied ~~will~~ **with** all measures in the paediatric investigation plan [reference number]. 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 ~~will~~ **with** all measures in the paediatric investigation plan [reference number] and includes significant studies.
Page 18, section 3	In general the requirements to be fulfilled by a study to be regarded as “significant” should be much more flexible.	
Page 19, last paragraph	It is not possible in any case to have all this information available for all pediatric subsets. We strongly ask to be more flexible especially in the case of a PUMA and ask to take into regard that for medicinal products with only a few patients the data sources are often limitedl and do not allow such in-depth analysis.	In order to be considered as significant, the studies should ~~normally~~ **where possible** cover all paediatric subsets affected by the condition where sufficient data are not available.

Please feel free to add more rows if needed.