SUBMISSION OF COMMENTS ON DRAFT COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS OR DEFERRALS AND CONCERNING THE OPERATION OF THE COMPLIANCE CHECK AND ON CRITERIA FOR ASSESSING SIGNIFICANT STUDIES

COMMENTS SUBMITTED BY PhRMA

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GENERAL COMMENTS

Regulation (EC) No 1901/2006 (the "Regulation") on medicinal products for paediatric use describes general requirements for new medicinal products or line extensions of approved medicinal products that are still protected by a supplementary protection certificate (SPC) or a patent which qualifies for the granting of an SPC to promote the development of medicinal products for children. Where applicable, the Regulation requires applicants to conduct paediatric research in relevant paediatric population subgroups in return for the grant of an extension to an intellectual property right (six month extension to an SPC, two additional years of market exclusivity, or data exclusivity on paediatric data).

This new guideline is welcomed for detailing the format and content requirements of the paediatric investigation plan (PIP), and for setting forth the underlying principles applicable for determining the paediatric data required by the EMEA. This guideline is further welcomed for clarifying the meaning of the phrase "significant studies completed before the entry into force of the Regulation", which is used to determine whether an applicant may obtain an extension to an SPC where paediatric studies may have concluded after the entry into force of the Regulation.

PhRMA and its member companies have had broad experience meeting paediatric requirements in the United States (U.S.) under the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). Significantly, this experience extends to all regions, not just to work performed in the U.S. PhRMA therefore offers the following comments with the objective of more fully harmonising global regulatory requirements.

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>

General comments:
The Paediatric Investigation Plan (PIP) described in this Guideline serves as the primary regulatory document upon which compliance with the Regulation and, in some cases, a grant of SPC extension, will be decided. This is exceedingly challenging as the PIP, at the time it is initially required, will not always contain those measures necessary to fully characterise a paediatric program. This is because much of the adult safety data will not yet have been obtained. Furthermore, it is only in Phase II that the findings of clinical pharmacology studies done in Phase I are correlated with the clinical activity of the drug, e.g. Pharmacokinetic/Pharmacodynamic correlation. In the absence of this correlation, it may be inappropriate and in some cases unethical to submit paediatric subjects to experimentation that can be accomplished in adults. One of our premises in paediatric drug development is that of Distributive Justice: Information that can be obtained in a less vulnerable population (i.e. consenting adults), should not be obtained in a more vulnerable population (i.e., non-consenting subjects – children.). This is especially important in non-therapeutic research (Phase I and II). Therefore, it is expected that numerous modifications and amendments to the PIP, as currently described, will be required. Indeed, experience with Written Requests [WRs] in the U.S. supports this conclusion as few, if any, WRs are executed without subsequent amendment. We therefore believe the guideline may not go far enough in recognising the unique challenges associated with providing information obtained extremely early in the development process (i.e., end of Phase I), and how these issues may be dealt with, especially by companies with global development programs. Thus, PhRMA believes that the success of the paediatric program will be dependent upon the ability of the EMEA to ensure a flexible, pragmatic and collaborative implementation of the new paediatric requirements. PhRMA also would encourage the EMEA to consider providing feedback on "lessons learned" at an early stage of implementation of this Guideline to better address the timing issues that companies will no doubt face in preparing their regulatory project plans.

PhRMA also urges that all reasonable efforts will be expended to develop the paediatric program with a global view towards harmonisation of regulatory requirements across all competent health authorities.

Specific comments on content of this draft guideline are noted below.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Introduction, Definitions	The definition of "Measures" should be consistent with how it is used in the Regulation.	*Amend the definition of "Measures" as follows:* (e) **Measures:** as used in Article 15(2) of the paediatric regulation includes all studies, trials, ~~data~~ and <u>other aspects of</u> pharmaceutical development necessary in a paediatric investigation plan 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, subsection 1.1, ¶ 4	Although the Paediatrics Regulation specifically states that a proposed PIP submitted in accordance with Article 7 or 8 shall cover all subsets of the paediatric population, this statement is not explicitly made within the Regulation for proposed PIPs submitted in accordance with Article 30 (PUMA)	*The obligation, subject to a waiver, to cover all subsets of the paediatric population for PUMA PIPs should be unambiguously stated in the guideline.*
Section 1, Subsection 1.1, ¶ 5	It must be clarified that, where the medicinal product is not exclusively intended for the paediatric population, the PIP covers those indications approved or for which approval is sought for the adult population.	*Amend the fifth paragraph as follows:* If a paediatric investigation plan is included in the application submitted in accordance with this guideline it should focus on studies that will allow labeling the product for appropriate use in all relevant paediatric subsets, as well as the development of appropriate formulations (~~,~~if applicable); where the medicinal product is not exclusively intended for the paediatric population or part(s) thereof, such obligation is restricted to the existing or proposed indications for adults.
Section 1, Subsection 1.1, ¶ 6	It should be made clear that summary reports and not full study reports (these should be available on request) may be provided. Moreover, applications relating to Regulation 1901/2006 should include the information that is necessary or useful for the Paediatric Committee to assess the PIP, *i.e.*, to determine whether the measures proposed by the applicant can be expected to establish significant benefit to and/or fulfil a therapeutic need of the paediatric population. It is unclear how information relating to incomplete or discontinued tests or trials on adults or indications not covered by the application could be relevant for the evaluation of the PIP.	*Amend the first sentence as follows:* All summary reports (unless full study reports are requested) and other information relevant to the evaluation of the paediatric investigation plan, as well as requests for deferrals or waivers should be included in the application whether favourable or unfavourable to the product. *Delete the second sentence of the sixth paragraph*
Section 1, subsection 1.1, ¶7	The list of therapeutic needs of the paediatric population established by the Paediatric Committee is an essential tool when assessing a	*Amend the seventh paragraph as follows:* When assessing the significant therapeutic benefit and/or the

	PIP. By way of this guideline the applicant should understand the type of information the Paediatric Committee finds relevant for the assessment of PIPs. Moreover, further clarification is requested on the therapeutic indication that will be considered by the Paediatric Committee. This paragraph could be misinterpreted as widening the scope to potential indications based on pharmacotherapeutic group, mechanism of action, or approved uses for other products of the same class, rather than the indication that is actively being pursued for adult development. Such expansion of scope would not be appropriate as the applicant will have completed its development and preclinical work only in support of its proposed indication.	fulfillment of therapeutic needs in the paediatric population, the paediatric committee may take into consideration, in addition to the proposed adult indication and the list of therapeutic needs of the paediatric population, other relevant information such as the target and mechanism of action of the medicinal product concerned without broadening the scope of the PIP beyond the existing or proposed therapeutic indications.
Section 1, Subsection 1.2, A.1, ¶ 1	Regulation 1901/2006 ties the filing of a PIP to the development of a new medicinal product or line extension of an existing medicinal product in view of its approval for marketing. An adequate link with the MA holder or expected MA applicant is required.	*Amend the first paragraph as follows:* The name and address of the applicant should be provided. The applicant may be an individual or a company. A contract research organisation may submit an application. Where the applicant is not the person or company responsible for the research and development of the medicinal product, details of the person or company responsible should be provided, including documentation demonstrating that the applicant acts in agreement with the person or company responsible for the research and development of the medicinal product.
Section 1, Subsection 1.2, A.1, ¶ 3	No information is provided regarding which elements of the Agency decisions will be made public or the timing of these publications. Publication policy will have to be addressed separately.	
Section 1, Subsection 1.2, A.1	It should be confirmed that the PIP is transferable if the product is licensed to another company.	*Add the following as the new second (2nd)paragraph:* The proposed or approved PIP may be transferred to another applicant. In such a case, the EMEA should be notified in writing of the new contact details and of any other administrative changes.
Section 1, Subsection 1.2, A.6	It should be clarified what information is required by the 5th bullet point regarding regulatory information on clinical trials within the Community. It should also be clarified that the information required by the 6th bullet point regarding scientific advice received is only for those	*Clarify the fifth bullet point* *Amend the sixth bullet point as follows:* • Details of any scientific advice from the Agency o~~f~~r any

	indications within the proposed PIP application. A word is missing from the last bullet	national competent authority <u>for those indications within the proposed PIP application</u>. *Amend the seventh bullet point as follows:* • Details of any regulatory <u>action</u> to restrict the use of the medicinal product in any EEA country.
Section 1, Subsection 1.2, A.7	While it is essential for the Paediatric Committee to know about the regulatory status of the medicinal product -- in all its indications, pharmaceutical forms, and routes of administration as well as research -- in the EU, it is unclear why the Paediatric Committee has to be informed about such status in third countries, at least with regard to adult indications, pharmaceutical forms, routes of administration, and clinical trials	*Amend the first sentence as follows*: A summary of the regulatory status and marketing history of the medicinal product outside the Community in ~~both adult and~~ paediatric populations should be provided.
Section 1, Subsection 1.2, A.9	The last sentence of this section appears to be incomplete	*Amend the last sentence as follows:* If there are authorised medicinal products belonging to that class, the~~se~~y should be stated.
Section 1, Subsection 1.3, B.1	It is unclear what is meant by "variability in terms of genetic background"	*Clarify this statement*
Section 1, Subsection 1.3, B.3, ¶ 1	Prevalence and incidence information in paediatric subpopulations are frequently not available. This is particularly the case when a condition or diagnosis is infrequent or rare in children, or when it is a growing area of awareness. For these reasons the guidance would benefit from global incidence and prevalence information	*Add the following at the end of the first paragraph:* The applicant should provide information of the prevalence and 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. <u>Where only global data is available on the prevalence and incidence of the diseases/conditions, such data should be submitted in lieu of Community (or Member State) information.</u>
Section 1, Subsection 1.3, B.4, ¶1 and new ¶6	Although unauthorised treatment methods that represent the standard of care should be noted, such use should not preclude the development of an authorized medicinal product. The text should also be made consistent with part B.5. Such information will be difficult to obtain and may be unreliable, especially where medical practice differs between Member States and for orphan drugs with limited patient numbers.	*Amend the first paragraph as follows:* […] This should include unauthorised treatment methods <u>(including the use of unauthorised medicinal products)</u> if they represent the standard of care <u>where this information is available</u>. <u>However, such unauthorised methods should not preclude the development of an authorised medicinal product</u>. If no methods exist, this should be stated.

	In anticipation of global harmonization and conduct of paediatric studies, the wording included in this guidance should be consistent with treatment guidelines of international paediatric associations, including WHO, when available (either through formal publication or website), and should reference such publications.	*Add the following as new last paragraph (¶6):* Guidelines on treatments adopted by the WHO or international paediatric associations should be referenced, when available.
Section 1, Subsection 1.3, B.5, ¶2	The guideline requires the applicant to provide a comparison of the medicinal product with the current standard of care. If a PIP is to be filed at the end of Phase I, the comparison will be on the anticipated use of the medicinal product, which has yet to be confirmed, and will be made based mostly on preclinical data at this stage. This should be acknowledged in the guideline. Moreover, as noted above, unauthorised treatment methods could prevent the conduct of studies that lead to authorized products.	*Amend the second paragraph as follows:* To enable the paediatric committee to make its assessment the applicant should provide a comparison of the medicinal product which is the subject of the application with the current standard of care ~~for the treatment, diagnosis or prevention of the diseases/conditions that are the subject of the intended indication in children~~. Where a PIP is submitted at an early stage of development (e.g., end of phase I) then the comparison should be based on the anticipated use of the medicinal product. Established treatment methods in the paediatric population (including non-pharmacological treatment methods, medical devices, prevention methods) if they exist in the EU should also be discussed. Methods of treatment, diagnosis or prevention which are not subject to marketing authorisation might be considered as standard of care if there is sufficient scientific evidence and consensus between experts in the field concerned, as to the value of such methods. However, such unauthorised methods of treatment, diagnosis or prevention shall not preclude the development of an authorised medicinal product or diagnostic.
Section 1, Subsection 1.3, B.5, ¶ 5	As indicated in the previous comment, the current standard of care can only be taken into account when authorised. The guidance should allow for quality of life improvements or compliance benefits to be included as a therapeutic benefit. Rationale: Improved compliance should translate to improved	*Amend bullet (a) as follows:* Expected improved safety and efficacy in a paediatric population compared to the current standard of care utilising authorised therapies.~~for the treatment, diagnosis or prevention of the condition concerned~~ *Add the following as last bullet points to the fifth paragraph:* (g) improved quality of life for the paediatric population. (h) improved compliance for the paediatric population.

	disease outcome. Improved quality of life will translate into improved compliance. Section B5 includes "improved dosing scheme or method of administration leading to improved safety, efficacy, or compliance."	
Section 1, Subsection 1.5, D.1.6	Subsection D.1.6 appears to be redundant as the information is provided in section 1.3 Part B.5	*Delete subsection D.1.6*
Section 1, Subsection 1.5, D.2, ¶ 2	Dosage forms are often key for the paediatric population and thus their suitability should be discussed in the PIP. However, paediatric-specific dosage forms may not be available for all molecules. It should be expressly stated that the inability to develop one or more specific paediatric dosage forms should not *per se* lead to the rejection of the PIP.	*Add the following at the end of the second paragraph:* The inability of the applicant to develop a specific paediatric dosage form is not, by itself, sufficient to reject a proposed PIP
Section 1, Subsection 1.5, D.3	Reference should be made to the Guideline on the need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications under the bullet point for Toxicology	*Add the following bullet points at the end of the bullet point Toxicology:* Reference is expressly made to the Guideline on the need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications (CHMP/SWP/169215/05).
Section 1, Subsection 1.5, D. 4, ¶ 2	The intent of this section is to describe the clinical approach for the paediatric clinical plan. Thus, this section should focus on the content of the PIP designed from the best available information.	*Amend the second and third sentences of the second paragraph as follows:* This should include critical aspects of study design and should ~~present the strengths and limitations of the proposed clinical development. It should~~ address the appropriateness of endpoints according to age (the actual design of each individual study should be described in section D5).
Section 1, Subsection 1.5, D. 4, ¶ 5	When pharmacokinetic data cannot be easily measured (e.g. inhaled dosing), clinical efficacy (e.g. reduction of seizures in epilepsy) or even side effects (e.g. cortisol suppression after ICS) can substitute	*Add the following as last bullet point under the heading "Pharmacodynamic Studies":*

	in the scaling exercise, using a population pharmacodynamics approach to make dose recommendations. Even when (sparse) pharmacokinetic data is measurable, evaluation of the 'full' pharmacodynamic response surface can enhance the paediatric treatment. Examples include: juvenile rheumatoid arthritis, epilepsy, or leukaemia, where the population modelling of the pharmacodynamic endpoints justify the recommended paediatric dosing; essentially confirming (or rejecting) pharmacological hypotheses in the most efficient way.	• Use of population pharmacodynamics, particularly when pharmacokinetics cannot easily be measured. Population pharmacodynamics or evaluation of the pharmacodynamic response surface may also be useful to refine the pediatric dose even when pharmacokinetic sampling is available.
Section 1, Subsection 1.5, D.6	Spelling/typographical errors in first sentence	*Amend the first sentence as follows:* The~~is~~ section should present the detailed timelines of the measures~~d~~ included in the paediatric investigation plan.
Section 1, Subsection 1.5, D.6	Provision of specific dates for the initiation and completion of studies in a PIP filed very early in the development of the medicinal product is not realistic and will lead to numerous procedural requests for modification.	*Amend the fourth sentence as follows:* The applicant should propose timelines for initiation and completion of each measure~~, including specific dates~~.
Section 1, Subsection 1.7	The investigator's brochure is likely to be repetitive of information requested elsewhere in the PIP request, and the review of investigator brochures is the responsibility of ethics committees and/or competent authorities prior to the conduct of the trials concerned. The inclusion of investigator brochures in the PIP request is therefore unnecessary. However, if an investigator brochure were to be needed, it could be replaced either by a draft or outline thereof where the product is not yet approved. Where the product has already been approved and is being studied in a paediatric population, then an SPC could replace the investigator brochure.	*Amend the paragraph as follows:* The annexes should include the following documents, as appropriate: • References (i.e. published literature); • Investigator brochures~~ for past or ongoing trials referred to in the application, where available~~ or draft or outline thereof or, for an approved product, the SPC; • Opinions and decisions given by Competent Authorities, including those from third countries; • Scientific advice given by Competent Authorities, including those from third countries; • Latest approved product information (SPC, PL, Labeling) for a product already authorised;
Section 2, ¶ 2	As with other applications, minor deficiencies should not automatically lead to invalidation of the application and the applicant should be given the opportunity to rectify the deficiencies (see, for instance, Nta, Vol.2A, Chapter 2, Section 3.3.2).	*Amend the second paragraph as follows:* Substantial n~~N~~on-compliance with the requirements of Articles 7 and 8 of the paediatric regulation may result~~s~~ in applications falling within the scope of those Articles being invalid. For minor deficiencies, the applicant will be given the opportunity to rectify the application within a specific, reasonable deadline after he has been

		notified of the problems.
Section 2, ¶ 5	The difference between the validity of the application for marketing authorisation or line extension and compliance with the PIP should be distinguished more clearly, and it should be clarified that the first step (validation of the application) has to be done in accordance with the Notice to Applicants (Chapters 2, 4, and 7).	*Amend the fifth paragraph as follows:* The determination of compliance in view of validation will therefore include: • whether or not the documents submitted pursuant to Article 7(1) of the paediatric regulation cover all relevant subsets of the paediatric population, • for applications falling within the scope of Article 8 of the paediatric regulation, whether the documents submitted pursuant to Article 7(1) cover the existing and the new indications, pharmaceutical forms and routes of administration. Validation of the application should be made in accordance with the standard validation procedure specified in the Notice to Applicant. The determination of compliance in view of inclusion of the compliance statement in the marketing authorisation will include: • 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 subsets of the paediatric population concerned, including any measure to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population have been carried out in accordance with the paediatric investigation plan decision.
Section 2, ¶8	The requirement for full study reports to perform the compliance checks is likely to lead to a delay in the MAA submission since these reports are usually on the critical path to submission. It is proposed that submission of the completed ICH format study synopses should be sufficient for the compliance check.	*Amend the eight paragraph as follows:* Compliance may be judged ~~only if full study reports are provided~~ on the basis of submission of ICH format study synopses.
Section 2, last paragraph	Grammatical error (the word, “will” was used where “with” was meant)	*Amend the last paragraph as follows:* 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 wi~~ll~~th all measures in the paediatric investigation plan [reference number] and includes significant studies.
Section 3, Subsection 3.1	In general, it should be clarified that: - the assessment of significance is limited to studies started before and completed after the entry into force of Regulation 1901/2006; - the purpose of the statement of compliance is to enable the marketing authorisation holder or applicant to claim the benefit of the reward; - significance of studies is to be assessed in view of all the studies to be conducted under a specific PIP.	*Add the following at the end of the second paragraph:* The statement of compliance enables the applicant to claim the rewards set in the paediatric regulation. *Add the following as last paragraph:* Assessment of significance is limited to studies started before and completed after the entry into force of the paediatric regulation and thus is a transitional measure. The significance of a study is determined in view of all the studies to be conducted under the PIP concerned.
Section 3, Subsection 3.2, ¶ 2	The moment at which a study is considered as completed must be consistent with the Community rules on clinical trials. Article 10 (c) of the Clinical Trials Directive requires the sponsor to notify the competent regulatory authorities and ethics committees of the end of the trial. Volume 10 of the Notice to Applicant refers to the date of the last visit of the last patient undergoing the trial but specified that this applies in most cases and that exceptions are possible if justified (see Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration to the end of the trial, October 2005, p.20).	*Add a new sentence and amend the second sentence of the second paragraph as follows:* Studies that have been or are being conducted in the EU or EEA, either partially or entirely for the purpose of supporting marketing authorisation, will be considered as completed as of the date mentioned in the end of trial notification required by Article 10 (c) of Directive 2001/20/EC. Studies that have been conducted in third countries ~~A study~~ will be considered as completed when the last visit of the last patient has occurred, as foreseen in the latest version of the protocol (as submitted to competent authorities) unless another date is provided for in the latest version of the protocol (as submitted to competent authorities) ~~and falls after the date of entry into force of the paediatric regulation~~.
Section 3, Subsection 3.2, ¶ 3	Article 45.4 of Regulation 1901/2006 states that the Commission, in consultation with the Agency, should draft guidelines to establish criteria for assessing whether a studiy shall be deemed significant. The guideline does not contain such criteria. It calls for a case-by-case analysis and gives mere examples of significant studies. More general criteria should be set on which the pharmaceutical industry can rely, as required by Regulation 1901/2006.	*Amend the third paragraph as follows:* The Agency or competent authorities will assess the significance of each study proposed in a paediatric investigation plan on a case-by-case basis. In general, a study will be considered significant if it is necessary to evaluate an authorisation for use in all or part of the paediatric population. ~~However,~~ The examples below are provided as a guide to the assessment of the significance of studies.

Section 3, Subsection 3.2, ¶ 4	Pharmacokinetic studies should be added to the list of examples of significant studies.	*Amend the fourth paragraph as follows:* Either of ~~T~~the following study types will normally be considered as significant: […] 5. Pharmacokinetic studies.
Section 3, Subsection 3.2, ¶ 6	Generally tying the concept of "significance" to the conduct of a study in all the subsets of the paediatric population is too restrictive, as most of the studies are conducted on a specific subset of the paediatric population. It is not in line with Regulation 1901/2006. Moreover, significance should only be tied to existing data where such data are available to the applicant. A company must not be deprived from the benefit of the reward simply because it started an authorized study without knowing that another company had already conducted a same or similar study. In other words, a company should not be penalised by the lack of publicity given to paediatric studies by other companies before the adoption of Regulation 1901/2006	*Amend the sixth paragraph as follows:* 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 also be considered as significant if carried out in a subset considered particularly difficult to study, for example neonates, or in a subset of clear medical relevance. Where sufficient data for one or more of the paediatric subsets are already available (*i.e.*, obtained by the applicant or published by third parties at the time the applicant initiated the studies), duplication of studies should be avoided and therefore unnecessary studies will not be considered as significant.