SUBMISSION OF COMMENTS ON COMMISSION's Paediatrics 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

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GENERAL COMMENTS
A major issue for EFPIA is the requirement that one single comprehensive PIP should be submitted in cases where more than one indication/development is being pursued simultaneously. It is felt that such a general overriding requirement is not applicable to all situations, and is not foreseen in the original Regulation 1901/2006. Therefore, the guideline should clarify that applicants are allowed to submit single individual PIPs for each separate indication/development. This can lead to a variety of practical advantages for both the applicants and the PDCO, particularly in cases where a variety of disparate indications are being pursued. In case an applicant is able or willing to submit a single comprehensive PIP (eg in cases where the nature of the pursued indications are tightly linked and interrelated), it should be clarified within the guidance that there will be one finally agreed-upon reference PIP which provides the plan commitment upon which the six-month SPC extension incentive will be granted. Further modifications or additional indications from that point should not affect the incentive. Otherwise, if compliance with all subsequent modifications or indications is required this may risk delaying the SPC extension application beyond the SPC extension deadline, and therefore make the intended SPC incentive rewards impossible.
The level of detail and information required generally appears to be excessive (e.g. World-wide regulatory and marketing status of approved products in the field, including indications). In this regard, it seems logical that neither the Paediatric Committee nor applicants should be burdened with resubmission and re-review of material that has already been submitted and adequately reviewed by a regulatory authority in the frame of a clinical trial application, for instance. This does not seem in accordance with current initiatives of the Commission to promote better regulation by simplification, and will impact adversely on the workload of the Paediatric Committee.
It is not clear exactly what level of information will be required for a PIP update. Many relatively minor details of a paediatric clinical trial/programme frequently change either prior to or during the conduct of studies and the need to update the PIP with all these changes could prove very burdensome both for industry and the regulatory agencies. The guidance should clarify that PIP updates should concentrate on the key information required for a high quality paediatric clinical programme. Multiple modifications submissions should be avoided to save resource both at the PDCO and in companies. Companies should be encouraged to minimise the number of stages at which the PIP is updated and re-reviewed.
Additional guidance is required for applications for already authorised products. There is lack of clarity in the guidance on how the application should be completed when there is an already authorised product, which may have multiple pharmaceutical forms and an ongoing programme of expansion of indications. Furthermore, more information should be provided on the structure and content of PIPs for non-patented products (i.e. PUMAs), which could be different in content (more simplified) from a PIP for a new molecule.
Despite a general acknowledgment, the guidance should stress more clearly that any early initial PIP will be a top-level overview document and should provide better guidance on expectations of the paediatric committee at various developmental stages (e.g. phase I, phase II, phase III etc), particularly early stages. For instance, many early PIPs will not be able to cover more than a descriptive review of the indication (some of part B), with possibly a discussion of the likelihood of

deferral, or an application for a waiver. Parts D1 to 4 will not be able to be provided until possibly late in phase II, or later and the detailed descriptions of studies that are requested in D5 (especially in relation to clinical data, e.g. appropriateness of end-points) will not be available until phase III. The PIP content described in the guideline assumes availability of the majority of 'non-clinical' data at a relatively late stage in the overall development plan. If PIPs are submitted at an early stage the majority of these data will not be available to allow for a detailed proposal of the non-clinical support of the paediatric plan.

It is noticed that various elements such as existing therapies, significant benefit, fulfilment of therapeutic needs, prevalence are similar to those in the orphan regulations. However, it would be recommendable to add some guidance on how to deal with Orphan designated products in this Guideline. This is especially important in light of the small heterogeneous patient populations available (and thus even smaller if the subpopulation of paediatrics need to subdivided in up to 5 subsets) and in light of discussion on fulfilment of therapeutic needs. It is recommended to include guidance dealing with these issues.

It would be useful to have guidance on length i.e. guidance is given on the length of Clinical Overview (approx 30 pages). Expected size of the submissions and range of pages should be given for the chapters. Overall it would be useful to have a summary to guide the applicant on the relevant sections to be completed per application type i.e.

Application type	**A**	**B**	**C**	**D**	**E**	**F**
PIP	✓	✓		✓		✓
Waiver	✓	✓	✓			✓
Deferral	✓	✓			✓	✓
Combination	✓	✓	✓	✓	✓	✓

The operation of the compliance check is confusing and requires further clarification. It appears that paediatric study results will be checked twice for compliance with the PIP: once to ensure validation and again to evaluate eligibility for rewards and incentives. Such repetition is unnecessary, and could lead to a delay or even refusal of validation, and a consequential delay in assessment and approval of a product for other populations, which is against the principles of the Regulation. The check performed at validation of an application under Art.7 or 8 of the paediatric regulation should be a simple verification that the dossier includes the documents described in Art.7, or that the applicant has already obtained confirmation of compliance under Art.23(2)(a). Further information on expected procedures for the PIP Compliance check should be provided. Compliance review timelines (including clock-stops), procedure for compliance check during MAA validation etc., would ensure that compliance checks run smoothly and can be planned for during the pre-submission phase. 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 the completed ICH format study synopses are provided for the compliance check, as this should be acceptable for completion of the check.

Further clarification is requested on the therapeutic indications that will be considered by the Paediatric Committee. Some sections of the guidance (e.g. page 5 second paragraph) appear to allow the Paediatric Committee to widen the scope to potentially include additional paediatric indications based on pharmacotherapeutic group, mechanism of action or approved uses for other products of the same class, outside the scope of the indication being actively pursued for adult development. This potential for a far-reaching expansion of the scope of the indications could have significant consequences for innovative companies and is not understood to be the intent or spirit of the Regulation.

In several places “standard of care” is mentioned. The guidance however does not address how to define standard of care for the PIP nor does it explain how to handle if standard of care differs per country. This may be very likely in light of the large off label use of medicines in paediatric populations.
With regard to vaccines, the guidance is not always fully applicable. It needs to be acknowledged that a very large proportion of vaccines are specifically and solely developed for use in children. Since the approach to clinical and preclinical evaluation for vaccines differs fundamentally from what is normally applied to pharmaceuticals, it seems reasonable to expect that this differentiation should also apply to the manner in which the paediatric regulation is applied to vaccines, and hence to the manner the Commission guideline is applied to vaccines. For instance, the clinical evaluation of vaccines is conducted in accordance with the specific EMEA Guideline (CHMP/VWP/164653/2005), which requires already that the clinical development of a vaccine is designed towards the target population for which a vaccine will be indicated (i.e. paediatric, adult, elderly,…); the guideline says that the planning of studies needs to take into consideration the nature of the target population (e.g. infants…), and if the vaccine is intended for use in patients with impaired immune function (e.g. premature infants), the guideline recommends to explore schedules specific to such groups. In addition, the approach to clinical development of a vaccine differs fundamentally from what is normally done for pharmaceuticals. For example, pharmacokinetic studies are usually not required for vaccines.

SPECIFIC COMMENTS ON TEXT		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
INTRODUCTION		
Paragraph 5 p. 3/19	The provided definition should also cover medicinal product intended to modify physiological function. As teenagers may be prescribed contraceptive pills, contraceptive indications should also be addressed.	
Paragraphs 6 and 7 p. 3-4/19	Clarification is sought on the difference between term (b)="Paediatric investigation plan indication" and term (c)="Proposed Therapeutic Indication"	
Last paragraph p. 3-4/19	"…to obtain a paediatric indication…" According to the Commission's summary of the Paediatric Regulation, its objectives include: - Increasing the development of medicines for use in children, - Improving the information available on the use of medicines in children. EFPIA strongly believes that the requirement for a PIP to only include measures (ie research activities) with the sole aim to obtain a paediatric indication is clearly limiting the intention of the Regulation related to improving the information available on the use of medicines in children. This stringent requirement excludes specific research activities which are aimed at developing a new dosage form or obtaining important safety information in children which are not available. Article 15(2) provides that the PIP should contain "measures to assess quality, safety and efficacy of a medicinal product in all subsets of the paediatric population….it shall describe any measures to adapt the formulation of the medicinal product as to make its use more acceptable, easier, safer or more effective…..". Clearly, this	Please change definition to read: '**Measures:** as used in article 15(2) of the paediatric regulation includes all research activities related to studies, data and pharmaceutical development necessary in a paediatric investigational plan to generate new scientific information ~~to obtain a paediatric indication~~, which is not yet available, where relevant and possible with an age appropriate formulation, in all subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan.'

	does not limit the scope of a PIP to research activities related to "obtaining an indication." We acknowledge that the scope of a PIP for a PUMA may be limited to obtaining a paediatric indication, however, we do not agree with a general limitation.	
Additional paragraph p. 4/19	Definitions of "new indication", "new pharmaceutical form" and "new route of administration" must be included in the guideline, or appropriate references provided to other guidance, so that it is clear to applicants which applications fall under the scope of Article 8 of the regulation.	Add definitions or appropriate references to definitions for: "New indication" "New pharmaceutical form" "New route of administration"
SECTION 1.1 GENERAL PRINCIPLES AND FORMAT		
General	This section provides information applicable to marketing authorisation applications requiring submission of a PIP in accordance with article 7 (new MAA), 8 (line extension) or 30 (PUMA) of the Paediatrics Regulation, and also information specific to the different articles. However, the section is not subdivided and so is confusing to read and ambiguous with regard to which requirements apply in which circumstances.	Subdivide section 1.1 into the following subsections: • General provisions applicable to all PIPs submitted. • Provisions specific to PIPs submitted in accordance with Article 7. • Provisions specific to PIPs submitted in accordance with Article 8. • Provisions specific to PIPs submitted in accordance with Article 30.
General p. 4-5/19	Throughout this section, the term 'application' is used to refer to both submission of a proposed PIP for review by the PDCO and submission of the Marketing Authorisation Application (MAA); this is confusing and ambiguous with regard to which procedure is being referred to.	Amend this section to remove the general use of the term 'application' and specifically refer to submission of proposed PIP or submission of the Marketing Authorisation Application as appropriate.
General p. 4-5/19	The regulation requires that PIP or waiver requests should be submitted not later than upon completion of adult pharmacokinetic studies. The EMEA's frequently asked questions (EMEA/520085/2006) includes some advice on the timing of these requests, and we also understand that there is no specific requirement for the timing of PIP/waiver requests relating to applications under Article 8 of the regulation. It would be helpful to provide this information on timing of requests in this guideline.	Add a paragraph concerning timing of requests: 'Requests for PIPs, deferrals or waivers should, in the case of new medicinal products, be submitted not later than upon completion of adult pharmacokinetic studies, although a later submission date may be justified. If a product is already developed beyond such studies, this legal deadline for the submission of those requests is not applicable. In relation to this deadline it is up to applicants to determine for themselves when would be the best time for them to submit a request for a paediatric investigation plan, or for a waiver, for their medicinal product.'
Paragraph 2	With specific regard to PUMAs, although the Paediatrics Regulation	The need (or not) to cover all subsets of the paediatric population for

& 4 p. 4/19	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 made within the Regulation for proposed PIPs submitted in accordance with article 30 (PUMA). This ambiguity is reflected in the draft guidance, where on page 4 it states that the applicant 'should' cover all subsets of the paediatric population (referencing article 7) whereas the applicant is 'encouraged to consider' all subsets (referring to PUMAs).	PUMA PIPs should be unambiguously stated in the guideline.
Paragraph 2 p. 4/19	Reference is made to "all subsets" of the paediatric population. We suggest that reference be made to ICH E11 in order to introduce the next paragraph with ICH definitions.	Applications should cover all subsets of the paediatric population as defined in ICH E11 and as required by Article 7(2) of the paediatric Regulation.
Paragraph 2 p. 4/19	The phrase "In the latter case or…" in the second sentence remains unclear. Does the paragraph intend to say that all information related to planned paediatric development and existing data of one chemical/biological entity should be included in one comprehensive application including all indications, pharmaceutical forms and routes of administrations? Or are there circumstances where separate applications are to be prepared? It may also be of help to provide a recommendation how to organize the information on different subsets, indications, forms, etc. under the proposed headers of the application or whether sections of the applications should be repeated.	
Paragraph 2 p. 4/19	The second paragraph starts as "Applications should cover all subsets of the paediatric population as required by Article 7(2) of the paediatric regulation....".	It would be appreciated to insert a cross-reference to "1.4 Part C: Applications for product specific waivers" as the guideline allows to ask for waivers for one or more specified subsets of the paediatric population. This would help to exclude any misunderstanding or contradiction.
Paragraph 2, p. 4/19	EFPIA is mainly concerned that the draft guideline requires only one single comprehensive PIP being submitted in case more than one indication/development is being pursued simultaneously. It is felt that such a general overriding requirement is not applicable to all situations, and is not foreseen in the original Regulation 1901/2006. Therefore, the guideline should clarify that applicants are allowed to submit single individual PIPs for each separate indication/development. This can lead to a variety of practical advantages for both the applicants and the PDCO, particularly in case	In the latter case or when an applicant intends to develop several indications simultaneously, the applicant will have the option to appropriately divide the paediatric investigation plan, i.e. one paediatric investigation plan per indication/formulation and it should be possible to cross refer to relevant sections of a previously or parallel submitted paediatric investigation plan. When a first paediatric investigation plan is completed and if all the requirements for obtaining the SPC-extension reward are fulfilled, then completion of this first plan will be the basis for granting the reward. Applicants, should also be allowed, where appropriate, to submit only one

	a variety of disparate indications are being pursued in case an applicant is able or willing to submit a single comprehensive PIP (eg in case the nature of the pursued indications are tightly linked and interrelated) It should be clarified within the guidance that there will be one finally agreed-upon reference PIP which provides the plan commitment upon which the six-month SPC extension incentive will be granted. (see 'General Comments'). Further modifications or additional indications from that point should not affect the incentive. If there are multiple indications there should be one lead indication/formulation/MAA within a comprehensive PIP, compliance with which will determine the receipt of SPC-extension rewards. In other words, if the PIP is subsequently modified with additional indications, or if subsequent PIPs are generated, the compliance and subsequent modifications/new PIPs should not determine the granting of the SPC-extension reward, which should remain contingent upon compliance with the originally agreed upon PIP and/or lead indication/formulation/MAA. Otherwise, if compliance with all subsequent modifications or indications is required this may risk delaying the SPC extension application beyond the SPC extension deadline, and therefore make the intended SPC incentive rewards impossible.	comprehensive paediatric investigation plan in the application. <u>However, in such cases there will be a single identified lead indication or development, fulfilment of which will determine the granting of the six-month SPC extension.</u>
Paragraph 3 Page 5/19,	"*Following an Agency …for a waiver or deferral as appropriate*" When an indication proposed for approval in adults does not exist in children the company might decide to ask first for a waiver but at a later stage, when new scientific knowledge becomes available, the waiver might be reversed. This paragraph should include more clearly this possibility to revoke a previously granted waiver if new information becomes available suggesting a potential indication in children.	
Paragraph 5 p. 4/19	Article 15 of Regulation 1901/2006 sets out the content of a PIP. It results from Article 15 that a PIP describes the studies that will allow the appropriate use of the product in all relevant paediatric subsets and the development of appropriate formulations. A PIP should not contain anything else than those studies. The term "focus" is confusing as it implies that a PIP could contain something else than	*Amend the fifth paragraph as follows:* If a paediatric investigation plan is included in the application submitted in accordance with this guideline it <u>should</u> <u>detail proposed</u> ~~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, if applicable.

	those studies.	
Paragraph 5 p. 4/19	This paragraph is unclear and does not seem to add useful information to the guideline.	Delete paragraph 5 of section 1.1
Paragraph 6 p. 5/19	Applications relating to Regulation 1901/2006 should include any 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 be of significant benefit to and/or fulfil a therapeutic need of the paediatric population. It is unclear how information relating to indications not covered by the application could be relevant for the evaluation of the PIP.	*Amend the second sentence of the sixth paragraph as follows:* In particular, ~~all~~ relevant details should be given of any incomplete or discontinued paediatric pharmaco-toxicological test or clinical study or trial relating to the medicinal product, and/or completed paediatric trials concerning indications ~~not~~ covered by the application. It is the responsibility of the applicant to ensure that additional data relevant to the evaluation of the PIP is included in the document. Applicants will need to consider the relevance of data from existing, completed or discontinued studies
Paragraph 7 p. 5/19	It is stated that the PDCO may take into consideration other information such as the target and mechanism of action. This implies that the committee may widen the scope of the indications to be investigated. This is not considered appropriate, as the applicant will have completed its development and preclinical work only in support of its proposed indication. In addition, provision of such information is likely to be speculative and, especially at an early development stage, difficult to assess. Firmer evidence will be forthcoming in the indications proposed by the company for study, and in the interests of avoiding unnecessary studies in children any PIP should concentrate on those indications if relevant to paediatric use (i.e. if not waived).	Delete paragraph.
Last paragraph p. 5/19	EFPIA believes that it is the responsibility of the applicant to ensure that an approved PIP is available for the compliance check. Hence, the decision on the timing of requesting modification to an agreed plan should be left to the applicant. There may be the need to combine several modifications into one modification request to conserve resources for the Agency, PDCO and Industry. According to Article 10b of the Clinical Trials Directive, the sponsor shall forthwith inform the competent authorities of any events during a clinical trial, which is likely to affect the safety of the subjects. As a consequence, any "new" information related to safety of the children in ongoing trials is notified to authorities immediately.	Please rephrase to read:" Following an Agency decision on a request for a waiver or paediatric investigation plan or a deferral, if important new information becomes available which has an impact on the decision of the Agency, this should be submitted to the Agency ~~without delay~~ with a proposal to modify the paediatric investigation plan together with a request for a waiver or deferral as appropriate."

	Hence, there is no need to include such a stringent modification requirement into the guideline.	
SECTION 1.2 PART A: ADMINISTRATIVE AND PRODUCT INFORMATION		
Introduction p. 5/19	It is stated that 'applicants should always complete all sections of Part A', however it is unlikely that all of this information will be available at the end of Phase I when proposed PIPs are required to be submitted.	Revise to 'applicants should ~~always~~ complete all sections of Part A or provide justification where data are not available'
Section A.1 General p. 5/19	It should be confirmed in this section that the PIP is transferable if the product is licensed to another company	Add The proposed or approved PIP may be transferred to another applicant. If this occurs, the EMEA should be notified in writing of the new contact details and of any other administrative changes.
Section A.1 General p. 5/19	There are significant objections to publish the names and contact of individuals on an external web site for privacy reasons. A general contact number for the company may be provided. In addition, the publication of PIPs may occur at a point in time where the attrition rates for projects in early development mean the success of a project is not entirely sure and this may create false expectations for the public. Hence, we believe it is premature to provide specific individual contact details for the public for enquiries at that stage. Physicians who are interested to enroll children in ongoing trials can contact the company through the information provided in the appropriate Clinical trial registries.	Delete paragraph 3 and the last paragraph of A.1
Section A2 p. 5/19	The names of manufacturer of the active substance and medicinal product are not relevant to the application and may change during product development. Furthermore these are assessed in the Clinical Trial applications and marketing authorization applications.	Delete section A.2.
Section A3 General p. 5/19	The company code is in fact the best designation to use for the product, it may be the only available identifier at early stages, and is maintained throughout development. Recording all successive name changes is an unnecessary burden. Company codes are established as acceptable designations for Clinical Trial Applications and Investigators' Brochures	Remove the sentence "A company or laboratory code should not be used"

Section A3 Paragraph 2 p. 6/19	Reference is made to Herbal Medicinal products while these are exempted from the requirements of the regulation (Article 9).	Delete reference to Herbal Medicinal Products or clarify in which context a PIP applies to them.
Section A4 p. 6/19	The Mode of action may not be known at the time of submission of the PIP although would be known by the time the MAA is submitted.	Change the sentence to: 'In addition, and where possible, the applicant should specify the target and mechanism of action, when understood'.
Section A6 General p. 6/19	This is not mentioned in the regulation. 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 be of significant benefit to and/or fulfil a therapeutic need of the paediatric population. According to Article 41 of the Paediatric Regulation, paragraph 1: *"The European database created by Article 11 of Directive 2001/20/EC shall include clinical trials carried out in third countries which are contained in an agreed paediatric investigation plan, in addition to the clinical trials referred to in Articles 1 and 2 of that Directive. In the case of such clinical trials carried out in third countries, the details listed in Article 11 of that Directive shall be entered into the database by the addressee of the Agency's decision on a paediatric investigation plan."* If the medicinal product is authorised in the Community, it should be sufficient to reference the relevant SPC(s) included in Part F Annexes. All the regulatory information on clinical trials within the Community will be available in EUDRACT and it would be an unnecessary duplication of information/work. The terms "Community" and "EEA" are used in the guideline. For the sake of consistency, it would be better to keep all along the guideline a same and clear definition, i.e. "EEA" countries. Otherwise, it should be stated clearly that "Community" stands for "EEA" countries.	Amend the section A.6 as follows: • marketing authorisation status (including refused applications) in individual EU Member States, or through the centralised procedure • EUDRACT numbers for ongoing clinical trials within the Community, • ~~details of the authorised indications~~ • ~~details of the authorised routes of administration~~ • ~~details of the authorised dosage forms~~ • ~~regulatory information on clinical trials within the community~~ • details of any paediatric scientific advice from the Agency of any national competent authority. Outcomes of other scientific advice may be added at the discretion of the applicant • details of any regulatory action to restrict the use of the medicinal product in the paediatric population in any EEA country.

Section A7 General p. 6/19	As part of the regulatory status of the product, it is requested that regulatory information on clinical trials and any actions taken against the medicinal product in any country is provided. Given the broad potential scope of this information, clarification is needed of what type of information is expected.	
Section A9 p. 7/19	*"If there are authorised medicinal products belonging to that class should be stated."* This information can be obtained from EudraPharm.	The sentence should be deleted.
SECTION 1.3 PART B: OVERALL DEVELOPMENT OF THE MEDICINAL PRODUCT INCLUDING INFORMATION ON THE TARGET DISEASES/CONDITIONS		
Introduction p. 7-9/19	It should be useful to clarify that it may not be possible to provide (full) answers to all subsections like for instance in the event of a waiver application.	*Specific guidance should be added.* In B3 similarly as for orphan products reference should be made to using publicly available databases.
Introduction p. 7-9/19	It is not considered realistic that the applicant be expected to know all "treatment methods" and all "alternative treatments". The former differs from country to country as determined by the standard of care in that market. The latter is not clear since paediatric medicines do not currently exist for the most part.	Change the sentence to: 'prevalence, incidence, authorised diagnosis and treatment methods, and authorised alternative treatments'.
Section B1/B2 General p. 7/19	The elements of these sections that refer to similarities/differences between adults and paediatrics are only relevant where extrapolation of data is being considered. This is covered under section D4. B2 seems to duplicate B1, and is a good example of information that will only be known at the end of the development, and possibly not until the clinical research in children and the PIP is completed.	Delete B1/B2 and: • address relationships between populations as part of any justification for extrapolation under D4. Combine B.1 and B.2 and include "if any" with respect to discussing anticipated similarities and differences in effect. • cover occurrence of disease in children under A9 and/or B5
Although we recommend to merge information from sections B1 and B2 and address it in another section of the document, the following comments are provided for consideration on the current wording:		
Section B1 Paragraph 1 p. 7/19	"For each disease or condition already *authorised*…" The meaning of this phrase is unclear.	Please clarify that this is only applicable for products which are already authorised for adults with a given indication.
Section B1	This section states "…the applicant should state whether the	' .... the applicant should state whether ~~the paediatric population is affected~~

Paragraph 1 p. 7/19	paediatric population is affected." How is "affected" defined?	the disease or condition is prevalent in the paediatric population and to what extent.'
Section B1 Last paragraph p. 7/19	It is unclear what is meant by "variability in terms of genetic background".	Clarify this statement.
Section B3 General p. 7/19	It is unclear how prevalence/incidence should be calculated. We recommend that this can be provided by reference to a publication and that this should not become an onerous task to review many sources of literature/databases. Where provision of the information is appropriate and relevant treatment guidelines exist, cross-reference to these guidelines should be an acceptable approach to provision of the information.	It should be clear that provision of this information is optional. Delete B3 and cover under B5 (identifying a therapeutic need) and C2 grounds for waiver. It should be clarified that prevalence/incidence can be referenced by publication.
Although we recommend to delete section B3 and include the requested data in section B5, if relevant, we would like to propose some comments on the current wording:		
Section B3 Paragraph 1 p. 7/19	We suggest that the prevalence and incidence of the disease/condition should be researched by using databases which are not restricted to the Community population. The requirement to only use community figures may not be representative to allow the proper prevalence and incidence estimates for a disease.	Please change first sentence to read: 'The applicant should provide information of the prevalence and incidence of the disease/conditions.'
Section B3 Paragraph 1 p. 7/19	If the prevalence or incidence is very low, the impact on the feasibility of clinical trials should be discussed and may serve as a reason for not conducting clinical trials in specific paediatric subsets.	Please include: 'If the prevalence or incidence is very low, the impact on the feasibility of clinical trials should be discussed and may serve as a reason for not conducting clinical trials in specific paediatric subsets'.
Section B4 p. 8/19	This section is unnecessary. Reference to current treatments should be limited to what is required to outline a significant therapeutic benefit as per concept outlined in second paragraph of B5 (i.e. likely to be most widely used current treatment(s) and/or other compounds in the same therapeutic class/closely related therapeutic classes).	Delete section B4
Although we recommend to delete section B4 and include the requested data in section B5, if relevant, we would like to propose some comments on the current wording:		

Section B4 Paragraph 1 p. 8/19	Unauthorised treatment methods might represent the standard of care but are often not based on scientific grounds and only reported anecdotally. Although the Paediatric Committee may need to know about the unauthorised treatment methods that represent the standard of care, it should not take such methods into account when assessing a PIP. Otherwise, unauthorised treatment methods could prevent the conduct of studies that lead to authorised products. Medical approaches can differ substantially in different Member States, depending on diverse medical culture and perception of standard of care. The assessment of unauthorized treatments with respect to their evaluation in terms of standard of care should be strictly limited to a level of pan –European relevance.	Please refer to proposed revised wording below.
Section B4 Paragraph 1 and 3 p. 8/19	The need for a company to provide the registration status of a medicinal product not owned by them is unrealistic. The information on other treatments should be limited to drug substance. The expectations should be clarified – perhaps to current standard textbook knowledge. It should be recognised that for some conditions in adults that are already authorised, the disease does not exist in children. There may however be a condition, specific to children, where the concerned medicinal product is expected to have a positive benefit/risk ratio It is not clear whether unauthorised medicinal products are included in the term 'unauthorised treatment methods' and if they should be considered if regarded as a standard of care. Although information on the use of unauthorised medicinal products may be useful when evaluating current treatment options, such use should not preclude the development of an authorised medicinal product. The text should also be made consistent with section 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.	Para 1: 'For each disease or condition already authorised <u>in adults</u>, 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) <u>affecting the paediatric population</u> the applicant should identify the diagnosis, prevention and treatment methods available <u>in the pediatric population</u> in the Community, making reference to scientific and medical literature or other relevant information. This ~~should~~ <u>may</u> include unauthorised treatment methods <u>(including the use of unauthorised medicinal products)</u> if they represent the standard of care <u>across the Community</u> <u>where this information is available. However, such unauthorised methods may not be taken into account for the assessment of a PIP, and should not preclude the development of an authorised medicinal product</u>. If no methods exist, this should be stated.' Para 3: 'The applicant should indicate, as far as possible, other methods of diagnosis, prevention or treatment for the disease or condition in question, such as surgical interventions, radiological techniques, diet and physical means used in the Community <u>(as published in current standard textbooks or other relevant literature)</u>.'
Section B4 Paragraph 2	The information requested should be kept at level of details of immediate relevance for the medicinal product under discussion. The information included in a PIP should be limited to authorized	<u>Proposed re-wording</u>: "… in case of authorized medicinal products, the list should include those authorised ~~nationally in at least one Member State and by the Community~~ nationally in more than one member state. ~~This can be~~

p. 8/19	medicinal products approved in the Community and of medical relevance at a Community level. It should not be an exhaustive list, but only be limited to key treatments. Ultimately, we believe that the overview table of the authorisation status of all available treatments should not be required from the applicant. This information will be available through EudraPharm.	~~represented by an overview table containing the invented name(s), active substance, Member Stae(s) where authorised, holder of the authorisation, and the authorised indication, if applicable.~~'
Section B4 Last paragraph p. 8/19	Since medical devices are regulated by means that differ from the ones for medicines, clarity should be provided on the Paediatric Committee's role in the CE marking process. Unless the device includes a substance with ancillary action, it is classified as a medical device and it therefore not clear why this information should be provided as part of the PIP.	
Section B5 General p. 8-9/19	This section should make it clear that the source of the information is likely to be from the literature, for example comparative trials (para 2) on new products are unlikely to be available at the time a PIP is submitted.	Add an introductory sentence: "This section is expected to be completed by evaluation of available information from the literature."
Section B5 General p. 8-9/19	The guidance should allow for quality of life improvements (demonstrated in adult studies) or compliance benefits (demonstrated in adult studies) to be included as a therapeutic benefit. Improved compliance should translate to improved disease outcome. Improved quality of life will translate into improved compliance.	Add wording to allow inclusion of quality of life improvements or compliance benefits from adult studies when available
Section B5 General p. 8-9/19	Concerning the inventory of therapeutic needs established by the Paediatric Committee, it would be useful that it is published as soon as possible. The Paediatric Regulation mentions in its Article 43 "*at the earliest by 26 January 2009 and at the latest by 26 January 2010"*. Although not required as part of this guidance, clarifications of the process for the establishment of this inventory and its updates are needed. This is important because when an indication is not included in the inventory, the potential for significant therapeutic benefit is debatable and may lead, at a minimum, to a deferral. Conversely, when the indication is included in the inventory, the potential for significant therapeutic benefit is obvious, and the information to provide in this section will be limited to a reference to the official list	

	of paediatric needs. The term "inventory of therapeutic needs" should be added to the list of definitions in INTRODUCTION.	
Section B5 General p. 8-9/19	The “significant therapeutic benefit” should also be applicable for those medicinal products which are used for preventive purposes (such as vaccines, oral contraceptives, immunosuppressants and specific diagnostics for body functions) rather than therapeutic purposes.	
Section B5 Paragraph 2 3rd sentence p. 8/19	We believe that a significant therapeutic benefit should exist if the product would represent a significant improvement of the treatment, diagnosis or prevention of a disease <u>compared with marketed products adequately labelled</u> for that use in paediatrics. We object to making comparison of medicinal products under paediatrics development with products, which have never been authorised for the target indication. In our view it is unethical to conduct such research.	Please delete the 3rd sentence: ‘~~Methods of treatment, diagnosis or prevention … , as to the value of such methods.~~’
Section B5 Paragraph 2 p. 8/19	‘ The applicant should provide a comparison of the medicinal product … with the current standard of care.’ If a PIP is to be filed during early clinical development, 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.	Amend as follows: ‘… the applicant should provide a comparison of the medicinal product … with the current standard of care … that are the subject of the intended indication in children. <u>Where a proposed PIP is submitted at an early stage of development then the comparison should be based on the anticipated use of the medicinal product.</u>
Section B5 Paragraph 2 p. 8/19	When discussing significant therapeutic benefit/fulfilment of therapeutic need, the statement “to provide a comparison of the medical product” should be clarified to allow the use of historical data/guidelines/published data be used as reference. A definitive requirement for a comparative arm may impact the sample size and therefore could affect the intent to minimize the number of paediatric patients exposed during a clinical trial. Also, for paediatric oncology studies in certain indications this approach may be rather difficult to follow.	Amend the sentence as follows: ‘…the applicant should provide a ~~comparison~~ <u>discussion comparing</u> the medicinal product which is the subject of the application with the current standard of care…’
Section B5	There are very few therapeutic classes for which one drug is universally effective and safe, and therapeutic alternatives are	

Paragraph 5 p. 9/19	needed. The guidance should also consider these cases, where another therapeutic option may be an important consideration for the child who has failed treatment with the other limited options available.	
Section B5 Paragraph 5 p. 9/19	EFPIA in principal supports the list of criteria on which to judge "significant therapeutic benefit" according to Article 6.2 of the Regulation. However, we would like to propose a few amendments. Moreover, we are proposing additional criteria, which in our opinion, is missing although fully in line with Article 6(2) of the Regulation and section B5 of the draft as it relates to the situation where no authorised standard of care exists in the paediatric population. Finally, the last criteria has been modified to better reflect the situation where a different mechanism of action may lead to a different indication in the paediatric population, for the same product such as with aspirin (depending on the mechanism of action can either be an analgesic or a platelet anti aggregating agent) or for different product classes such as beta-blockers and calcium-antagonists for hypertension. There is no explicit mention of changed PK properties. The fact of introducing a NME for the same medical condition could be an advantage overall for the population by increasing the therapeutic choice but this is not mentioned. It is also important to consider that a large proportion of products currently used in paediatric patients have never been formally evaluated or authorized for use in this population. Significant therapeutic benefit should therefore be defined comparative to existing treatments and in absolute terms.	"On this basis, significant therapeutic benefit could be based on <u>any one of the following or a combination thereof</u>: a) <u>Reasonable expectation for safety and efficacy for a marketed or new medication to treat a paediatric condition where no authorised paediatric medicinal product is on the market ("unmet medical need")</u>. b) Expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned. c) Expected ~~substantial~~ improvement in safety in relation to either adverse events or potential medication errors. d) Improved dosing scheme or method of administration (number of doses per day, oral compared to intravenous administration, reduced treatment duration) leading to improved safety, efficacy or compliance. e) Availability of a ~~new~~ clinically relevant age-appropriate formulation. f) Availability of clinically relevant ~~and new~~ therapeutic knowledge for the use of the medicinal product in the paediatric population leading to improved efficacy or safety of the medicinal product in the paediatric population. g) <u>Different mechanism of action for the same product or compared to authorised standard of care with potential advantage for the paediatric population(s) in terms of improved efficacy or safety.</u> h) <u>Introducing an NME for the same medical condition could be an advantage overall for the population by increasing the therapeutic choice</u> i) <u>The development of more appropriate formulations</u> Add the following at the end of the paragraph: "<u>However, unauthorised methods of treatment, diagnosis or prevention shall not be taken into account for the assessment of a PIP.</u>"

Section B5 Paragraph 8 p. 9/19	For the sake of clarity, it would be better to delete a part of the sentence.	Where the applicant is requesting a waiver based on a lack of significant therapeutic benefit ~~and where applications are submitted before clinical trial data are available~~, justification for a waiver could be based on a detailed discussion of the existing treatment methods, as well as extrapolations from non-clinical or adult clinical data if available.
Section B5 Last paragraph p. 9/19	Significant Benefit. It might be difficult to draw conclusions at early stage of developments. The Applicant is asked to make assessments based on assumptions	Change the word assumptions to hypotheses
SECTION 1.4 PART C: APPLICATIONS FOR PRODUCT SPECIFIC WAIVERS		
Section C1 p. 9-10/19	Information that is needed for requesting a waiver should be simplified. There is absolutely no scientific justification to provide a detailed Part B for obvious disease waivers (such as "smoking cessation in the neonate", "surfactant disease in children other than neonates"…).	Only very simplified parts A and C should be requested.
Section C1 Paragraph 3 p. 9-10/19	It would be appreciated if some guidance could be included as to how the applicant would determine if the product belongs to a class waiver. It is suggested that it would be valuable to generate class waivers in the sense of 'disorder waivers', for the following reasons: • When the initial PIP/waiver/deferral application is submitted the compound may be being investigated across several disease areas i.e. a metabolic pathway inhibitor for Parkinson's, COPD, CV – hence it would be very difficult for a 'class' in early development to be granted a waiver in any subset of the paediatric population • It relies on the PDCO being fully aware of the R&D behind new drug classes and all their potential targets. Would industry have to apply for any new class of drug to feature on this list? Without 'disorder exemption lists' industry will have to generate	A process for determining class waivers and which products belong to these classes should be established by the EMEA through consultation with stakeholders. Furthermore, it should be clarified if the class waiver covers all paediatric subsets. The guidance should include the format of a statement that would be issued by the Paediatric Committee on request (without a PIP) for products where the requirements of Articles 7 and 8 are fully covered by a class waiver.

	applications addressing section A, B and C.2.2 for conditions that are recognised to only occur in adults ie. Alzheimer's. It would improve efficiency and reduce resource burden for the PDCO and industry if no application was required for such disorders. On the other hand the disease/condition may occur in adults as stated in the title of C 2.2, but may also occur in paediatric subpopulation: waiver for smoking cessation in neonates + PIP in adolescent; PIP for neonate surfactant disease + waivers for other children groups.	
Section C2.1 Last paragraph p. 10/19	We understand the motivation of the Commission to include such a statement in the guideline; however, we believe that it is unnecessary to highlight these cases. Article 11 is clear enough to avoid such situations. Instead we would recommend that a statement is included to allow the paediatric committee to adopt pragmatic views in some cases when paediatric programs could be difficult or impractical due to very small patient populations or difficult formulation development. If the adult formulation is not suitable for use in children, a company should show it has taken reasonable efforts to develop a paediatric formulation. However, if it proves not practically possible to develop a paediatric formulation, it may then be appropriate to justify a waiver based on grounds that the product is likely to be ineffective in the paediatric population (Article 11.1 (a)) due to the unavailability of an appropriate formulation, or unsafe to use the adult formulation in the absence of the ability to develop an alternative. The intention of the Orphan legislation could easily be jeopardised by the Paediatric Regulation, if the additional paediatric requirements for Orphan drug development become too onerous. Individual cases need careful discussion and granting waivers for products or populations where clinical studies are impossible or impractical to conduct or for products that are not likely to be used in a substantial number of patients, should be considered in the EU framework. Such waiver requests could be based on the ground that the product is likely not to provide significant therapeutic benefit over existing treatments, or unsafe based on assessment of anticipated risk/benefit in paediatric patients. A low level of risk is required if efficacy can only be defined by very limited information. Efficacy cannot be	Please add:" <u>In some cases, paediatric programs could be difficult or impractical due to very small patient populations or difficult formulation development.</u> <u>If the adult formulation is not suitable for use in children, the applicant should show it has taken reasonable efforts to develop a paediatric formulation. However, if it proves not practically possible to develop a paediatric formulation, it may then be appropriate to justify a waiver based on grounds that the product is likely to be ineffective in the paediatric population (Article 11.1 (a)) due to the unavailability of an appropriate formulation, or unsafe to use the adult formulation in the absence of the ability to develop an alternative.</u> <u>Individual cases, specifically for Orphan medicines, need careful discussion. Granting waivers for products or populations where clinical studies are impossible or impractical to conduct or for products that are not likely to be used in a substantial number of patients, should be considered in the EU framework. Such waiver requests could be based on the ground that the product is likely not to provide significant therapeutic benefit over existing treatments, or unsafe based on assessment of anticipated benefit /risk in paediatric patients. A low level of risk is required if efficacy can only be defined by very limited information. Efficacy cannot be determined if a clinical study cannot properly be designed to ensure the quality and interpretation of the data. Such studies would be recognised to be against established ethical principles. Alternative (or less conventional) designs and/or analyses may be justified only in specific cases based on the requirements of Article 22 of Directive 2001/83/EC as amended.</u>"

	determined if a clinical study cannot properly be designed to ensure the quality and interpretation of the data. Such studies would be recognised to be against established ethical principles. Alternative (or less conventional) designs and/or analyses may be justified only in specific cases based on the requirements of Article 22 of Directive 2001/83/EC as amended.	
Section C2.3 p. 10/19	Clarifications would be appreciated on whether lack of justification for significant therapeutic benefit over the existing therapies and/or fulfilment of a therapeutic benefit will automatically qualify for a waiver.	
SECTION 1.5 PART D: PAEDIATRIC INVESTIGATION PLAN		
Section D1 p. 11/19	These duplicate other sections of the document (D1.1/1.2=A9, D1.4= B2, D 1.3=D 5.2-D 5.4, D1.5 = B3/4/5, D 1.6=B5).	The format needs to be streamlined to avoid this duplication.
Section D1 p. 11/19		Sections D1 and E should be cross-referred.
Section D1.1 p. 11/19	As already outlined, a new formulation may also be an acceptable new therapy option for children.	Please rephrase: " D.1.1 Paediatric Investigation Plan ~~Indication~~ Scope If applicable, the applicant should state the proposed indication(s)…"
Section D1.2 p. 11/19	Remove reference to neonates, there is no reason for any subset to be specifically highlighted.	
Section D1.3 p. 11/19	A reference to the Investigators Brochure should be possible to avoid the provision of redundant information.	Propose adding: “References to the Investigators Brochure can be made where appropriate.”
Section D1.5 p. 11/19	It is very difficult for companies to collect reports from off-label or unlicensed use without elevating the standard of care. We advise the Commission to use caution with regard to the expectations from such reports.	
Section D2 p. 12/19	More details are sought.	Proposed rewording of parts of the section: “This section should address the chemical**, pharmaceutical, biological** and biopharmaceutical aspects related to the administration of the product for the targeted paediatric subsets (age groups).

		The addition of a paediatric indication may result in the need for a new pharmaceutical form for example a liquid rather than a tablet or a new dose strength, because the existing pharmaceutical form may be unsuitable for use in all or part of the targeted paediatric population."
Section D2 p. 12/19	Further guidance is available to support applicants when determining the strategy in relation to quality aspects (i.e. from the EMEA Reflection Paper on 'Formulations of Choice for the Paediatric Population [EMEA/CHMP/PEG/194810/2005]) and it would be useful to include a reference in the document.	Include a cross-reference to the EMEA Reflection Paper on 'Formulations of Choice for the Paediatric Population (EMEA/CHMP/PEG/194810/2005)'.
Section D2 Paragraph 1 Bullet 1 p. 12/19	Different forms can be developed in a single PIP.	"Need for ~~a~~ specific formulation(s) or dosage form(s)…"
Section D2 Paragraph 1 Last bullet p. 12/19	What exactly is meant with 'European food cultures'? If the ability of the drug product to mix with food is assured a variability of different food possibilities should have been addressed already. It seems extremely difficult to assess different European food cultures in 27 countries. At least milk and milk products can be assessed but not specific things in different countries.	It would be helpful to clarify the meaning and expectation of "taking into consideration different food cultures" or delete it.
Section D3 p. 12/19	The elements of the non-clinical strategy that should be addressed require further clarification. For example, a broader discussion on the merits of non-clinical models for proof of concept studies is needed. Many disease models in juvenile animals do not exist or are not as well characterized and understood as adult animal models. Predictability and concordance between juvenile animal models and paediatric populations is questionable. Choosing the most relevant species for potential juvenile animals studies can be dependent on the endpoints to be evaluated (for example, fertility and/or behavioural endpoints like reactivity, motor activity, and learning). Therefore the use of pharmacodynamic and/or pharmacokinetic studies in justifying the choice of the most relevant species should be clarified. Examples should be provided as to how one would use this information to define most relevant species.	Include references to relevant guidelines, including the CHMP Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005).

	The statement of safety pharmacology studies under pharmacology needs further clarification. Does this refer to the standard safety pharmacology studies in adult animals or does this refer to the need for safety pharmacology studies in juvenile animals? If needed in juvenile animals, examples should be provided as to what potential triggers might be.	
Section D3 Paragraph 1 p. 12/19	In general, a medicinal product can be studied in children when adequate pharmacokinetic, pharmacodynamic, and clinical efficacy and safety data are available in adults. This implies, in most cases, the availability of a non-clinical data package in adult animals. At a minimum, results from appropriate repeated dose toxicity studies, the standard battery of genotoxicity test, the core safety pharmacology package and data from reproductive toxicity studies relevant to the age of the patient population under study should be available prior to the initiation of trials in a paediatric population. If human safety data and previous animal studies are considered insufficient for reassurance on the likely safety profile in the intended paediatric age group, juvenile animal studies should be considered. EFPIA recommends including reference text from the ICH M3 guideline to clarify that juvenile animal studies are only required in specific cases.	Please rephrase to read: "This section should discuss the strategy for the non-clinical development, which is needed in addition to standard non-clinical development in adults or already existing data. If human safety data and previous animal studies are considered insufficient for reassurance on the likely safety profile in the intended paediatric age group, juvenile animal studies should be considered on an individual basis. The following elements may ~~should~~ be addressed, if scientifically justified:"
Section D3 Pharmaco bullet Bullet 1 p. 12/19	Proof of concept studies cannot be done in animals and we suggest deleting the first bullet under pharmacology.	Please delete first bullet of Pharmacology section.
Section D3 Pharmaco bullet Bullet 1 p. 12/19	In accordance with the EMEA Note for Guidance (CPMP/SWP/465/95), immunogenicity and safety pharmacology studies on vaccines are conducted in adult animals and the use of juvenile animals is not normally needed for these assessments.	
Section D3	As noted in EMEA Note for Guidance (CPMP/SWP/465/95), pharmacokinetic studies (determining the serum concentrations of	

PK bullet p. 12/19	antigens) are not normally required for vaccines.	
Section D3 Toxico bullet p. 12/19	Toxicity studies on vaccines are conducted in accordance with the EMEA Note for Guidance (CPMP/SWP/465/95). It should be noted that vaccines are generally administered once or twice, and not on a repeated basis for prolonged periods, as may be the case with pharmaceuticals. Since the approach to preclinical toxicity evaluation for vaccines differs from that normally applied to pharmaceuticals, it seems reasonable to expect that such a differentiation should *also* apply to the manner in which the paediatric regulation is applied to vaccines. Regarding the safety of vaccines to the developing foetus and neonate, such assessments are conducted as part of rat pre-, peri-, and post-natal toxicity studies in which pregnant rats are dosed pre-mating and during gestation. Foetal and pup exposure to the vaccine (via the placenta and lactation, respectively) is confirmed via immunogenicity assessments of foetal and pup serum.	
Section D3 Toxico bullet p. 12/19	The choice of the animal species shall be addressed (from a toxicological point of view; not DMPK as above). Also the study outline reflecting the focus of a juvenile toxicity study shall be addressed (e.g. start and duration of dosing in relation to organ assessed) if such information is available at that stage	Add bullet point to Toxicology: • <u>Justification of species and study outline</u>
Section D4 General p. 12-14/19	There is no mention of the use of historical controls in this section or use of non-validated endpoints/assessments/surrogates. It would be particularly helpful for orphan designated products to add this or clarify that a comparator can either be a head to head comparison or a historical control.	
Section D4 General p. 12-14/19	It should be clarified that the bulleted text is a checklist and that only the relevant elements need to be addressed.	
Section D4 General	The whole section is very specific. A detailed clinical plan (as outlined) cannot be generated without knowing anything about PD/efficacy of the compound. It is difficult to extrapolate if we do not even know that the compound works and how. The first PIP	

p. 12-14/19	should contain only information on intent to study, and details will be given later in subsequent PIP updates (see also GENERAL COMMENTS). For early development products details of the formulation to be used are not known. Therefore it is not possible to give plans for bridging between the different formulations should be addressed. Introducing post approval commitments and risk management system issues seems very premature, particularly for early PIPs.	
Section D4 Paragraph 2 p. 13/19	Age appropriate formulations are important and their importance should be highlighted in the section.	"The applicant should address the rationale to support dosing, <u>formulation</u>, and route of administration."
Section D4 Paragraph 3 p. 13/19	The possibility of extrapolating certain data from adults to the paediatric population should be discussed through population pharmacokinetics and pharmacodynamic modelling.	Add the following: • Pharmacodynamic studies: o Pharmacodynamic differences between adult and paediatric populations (e.g. influence of maturation of receptors and/or systems). o Extrapolation from different populations (from adult and/or for older paediatric age groups) <u>through the use of pharmacodynamics modeling</u> o The need for specific studies in certain age groups o Discussion of any biomarkers for pharmacokinetics /pharmacodynamics.
Section D4 Paragraph 3 p. 13/19	The possibility to conduct sparse PK sampling in efficacy trials in paediatric population should be mentioned in either PK studies section or Efficacy/safety study section. See also **Section 3.2**	Add the following: o Pharmacokinetic studies: o The possibility to extrapolate efficacy and safety from adult or older age group based on pharmacokinetics. o <u>The possibility to use sparse PK sampling</u> o The use of pharmacokinetics / pharmacodynamics studies to bridge efficacy and safety in adults or older age group. o …..

Section D4 Paragraph 4 p. 13/19	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 in the scaling exercise, using a PD approach to make dose recommendations. Even when (sparse) PK is measurable, evaluation of the 'full' PD response surface can enhance the paediatric treatment. Examples include: juvenile rheumatoid arthritis, epilepsy, or leukemia, where the population modelling of the PD endpoints justified the recommended paediatric dosing; essentially confirming (or rejecting) pharmacological hypotheses in the most efficient way.	*Adding a bullet under the Heading "Pharmacodynamic Studies" as follows:* • Use pharmacodynamic (PD) approach, particularly when pharmacokinetics cannot easily be measured. Evaluation of the PD response surface may also be useful to refine the paediatric dose even when pharmacokinetic sampling is available.
Section D4 Paragraph 5 p. 13-14/19	The bullet list provides only examples which may be addressed, if scientifically justified.	Please rephrase: " the following aspects <u>may</u> be addressed, <u>if scientifically justified</u>:"
Section D4 Paragraph 5 p. 13-14/19	Logistic issues are not completely considered, e.g., the possibility of exsanguinations due to reduced circulating blood volume in infants.	Please add: "<u>Consider appropriateness of blood volume draws relative to age.</u>"
Sections D5.1 & D5.2 p. 14/19	It would be simpler and clearer to include information on timelines in the summary tables in section D.5.1 and D.5.2. See also comments under section D.6.	Include information on timelines in sections D.5.1 and D.5.2.
Section D5.1 General p. 14/19	We encourage that the "overall summary table" should be part of the EMEA PIP template. A table should be included providing an overview of all measures planned or performed by the applicant. Could the above statement also include all measures <u>available</u> to the applicant and not be limited to measures planned or performed by the applicant.	Please rephrase: "A table should be included providing an overview of all <u>research activities</u> planned, ~~or~~ performed by <u>or available to</u> the applicant."
Section D5.2 General p. 14/19	It would be helpful to indicate that in some circumstances the end-point of pharmaceutical development may be guidance on extemporaneous formulations.	Add the following statement "<u>In some cases there may be a need for guidance on extemporaneous formulations, and if so this should be covered here</u>."
Section D5.2	Section D.5.2 refers to situations where *"…the basis of the paediatric*	

Paragraph 2 p. 14/19	*product is an authorised adult product with a simple reduction in content of active substance..."* This is another example showing that the guideline may not be appropriate/applicable to vaccines, for which the effect is sometimes the opposite, i.e. the dose required may be higher than for adults, and also, tolerability of the product may be better in a paediatric than in an adult population (e.g. in combined DTPw vaccines: a lower D content is required in adults, and Pw contra-indicated in adults).	
Section D5.2 Paragraph 2 p. 14/19	A reference 4 is included at end of paragraph, but reference/footnote is missing.	
Section D5.2 Last paragraph p. 14/19	EFPIA is concerned about the requirement to test various foods if the formulation is blended for dosing and how far such testing would be extended? In addition, we would like to have details on requirement for palatability studies.	We recommend that the CHMP reflection paper on choice of formulations is referenced in the EC guideline and that this paper is revised to include a standard list of test food and elaborate on palatability testing for the application of the PIP requirements.
Section D5.2 Last paragraph Bullet 1 p. 14/19		Add the following: • Compatibility and stability in the presence of relevant common foods and drinks <u>(if food is used to facilitate administration of dosage form).</u>
Section D5.3 General p. 14/19	Information on planned non-clinical studies should be limited to a list of potential studies without specific details as required in this section (already part of D.5.1). Otherwise this would reduce the flexibility in the final implementation of the tests, or will lead to frequent applications of modified PIPs and corresponding procedures because of modified nonclinical testing. The appropriateness of nonclinical tests and results will anyway be assessed by Authorities as part of the Clinical Trial Applications for paediatric studies.	*D.5.3 Synopsis/outline of protocol of each of the planned or performed non-clinical* Studies ~~The following should be detailed as relevant according to the study:~~ <u>Sufficient information to adequately describe the study should be detailed as relevant, for example:</u>
Section D5.4 p. 14-15/19	The level of detail required in this section is not normally available until around 6 months before study start, and is unlikely to be available at the time a deferral may be requested, and especially for an early PIP. Locations of studies, detailed eligibility criteria, all endpoints, sample sizes, power calculations, operational aspects for	*D.5.3 Synopsis/outline of protocol of each of the planned or performed clinical studies or trials.* ~~The following should be detailed as relevant according to the study:~~ <u>Sufficient information to adequately describe the study and relevant to the</u>

	recruitment, and statistics methodology will not be available in detail at the time a PIP needs to be considered. This information is already submitted to agencies in Clinical trial applications.	stage of the study should be detailed for example:
Section D6 p. 15/19	It should be possible to link the timing of paediatric development to results in adults (HVTs or patients), and link in a milestone fashion rather than hard dates, as clinical development plans easily slip several months due to review times for CTAs, delayed initiation because of ethics reviews, slow recruitment etc.	It is suggested to clarify that at early stages of development the PIP timelines should be in milestones manner "The applicant should propose which measures will be included in the application under Art. 7 or Art. 8 and which measures will be made available post approval."
Section D6 p. 15/19	D.6: First sentence has a typo—"the measured included"	Measures
SECTION 1.6 PART E: APPLICATIONS FOR DEFERRALS		
General p. 15-16/19	It may be appropriate to provide additional guidance in relation to the circumstances where it is appropriate to conduct studies in adults prior to children.	Add a statement along the lines of: "The requirement to conduct paediatric studies should never compromise the well-being of paediatric patients participating in clinical trials and it is important to carefully weigh the benefit/risk and the therapeutic need in deciding when to start paediatric studies, bearing in mind that in the majority of cases it will be necessary to have an appropriate background of safety and efficacy data in adults before embarking on studies in children(i.e., if the studied condition is not severe/life-threatening, it is appropriate to defer paediatric studies until extensive adult data are available)."
General p. 15-16/19	For applications covered by this guidance submitted early in development it will be difficult or even impossible to complete much of the information in Part D, particularly the sections on specific measures and strategy. The introductory paragraph to section 1.2 Part A acknowledges that it may not be possible to provide comprehensive answers to all sections of the application. Deferral requests are likely to be the norm in such cases, unless a waiver can be justified. It should therefore be made clear that, for such requests submitted early in development, deferrals will be granted.	We propose to only complete sections A, B, D.1 and E for deferral request.
Paragraph 1 Last	It is unclear what is meant by deferral being "justified by indication, route of administration and pharmaceutical form". This seems to	Should be re-phrased to: "justified ~~by~~ on scientific and technical grounds or on grounds related to public health such as indication, route of

sentence p. 15/19	contradict with the 2nd paragraph regarding justification according to Article 20(1) of the regulation.	administration and pharmaceutical form."
Paragraph 2 Last bullet p. 15/19		Should be a reason for a (partial) waiver and not a deferral (see comments Part C)
SECTION 1.7 PART F: ANNEXES		
General p. 16/19	In the case of already approved products that have been licensed through the national procedure, can the Commission clarify if the product information to be provided is at the discretion of the applicant, bearing in mind that there may be some differences between the approved product information per member state?	
General p. 16/19	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, unless being included in place of specific sections of the request.	Amend as follows: "Investigator brochure**,** if provided in place of other parts of the request"
General p. 16/19	For the opinions and decisions, and scientific advice given by Competent Authorities that should be included in this section, they should concern paediatric indications and developments only. The scope of "any scientific advice" and "third countries" is too wide and should be restricted to advice and countries "as appropriate". Annexes on scientific advice should be limited to paediatric scientific advice or information from other scientific advices that is relevant to the paediatric programme.	Bullets 2 and three should be modified to read as follows: • Opinions and decisions relating to paediatric applications given by Competent Authorities, and if relevant from third countries. • Details of any paediatric scientific advice from the Agency of any national competent authority. Outcomes of other scientific advice may be added at the discretion of the applicant
General p. 16/19	Please confirm that 'Latest approved product information (SPC, PL, Labelling) for a product already authorised' refers to the product information of the exact product for which the paediatric indication is sought (not of other products containing the same active substance)	

SECTION 1.8: MODIFICATION OF AN AGREED PAEDIATRIC INVESTIGATION PLAN		
1.8 p. 16/10	The document is very detailed and there is a danger if too much detail is requested in the plan that unnecessary regulatory burden will result from many successive modifications to update the detail, as the specifics of plans will certainly change during development. This is important in view of the large numbers of PIPs expected to be active (300 submitted in the first year alone). This is not compatible with current initiatives by the Commission to promote better regulation via simplification, and will impact adversely on the workload of the Paediatric Committee. This is especially important with reference to Section 2 – compliance checking, since over-emphasis on small changes could result in failed validation. See also GENERAL COMMENTS. There is clearly a need for pragmatism on the level of detail of changes to the PIP that need to be notified to the agency. PIP updates should concentrate on the key information required for a high quality paediatric clinical, preclinical and formulation development programme. It would be wise to exclude from modifications items that will be subject to change on a regular basis (for example much of the detail in section D). Many relatively minor details of a paediatric clinical trial/programme frequently change either prior to or during the conduct of studies and the need to update the PIP with all these changes could prove very burdensome both for industry and the regulatory agencies. Complete details of clinical programmes are in any case already regulated and documented on an ongoing basis in the Clinical Trial applications submissions made under the Clinical Trials Directive. Information on planned non-clinical studies should be limited to a list of potential studies without specific details. Otherwise this would	The following text to be added under section 1.8 Modification of an agreed paediatric plan: "Changes to the content of the plan should be notified as modifications if they affect the following aspects of the document: 1. Major changes in indication, population, age ranges being studied 2. Timing for completion of the plan 3. The conclusion of the assessment of therapeutic benefit 4. To complete the detailed content of the PIP following an initial early submission 5. Proposed changes to withdrawal or deferral status 6. Important safety aspects 7. Deletion or addition of non-clinical studies 8. Discontinuation of formulation under development or addition of a completely new type of formulation."

	reduce the flexibility in the final implementation of the tests, or will lead to frequent applications for modified PIPs and corresponding procedures because of modified non-clinical testing. Updates to formulation development sections are expected to be required rarely.	
1.8 p. 16/19	Any early initial PIP will be a top-level strategic document and will not be able to cover more than a descriptive review of the indication (some of part B), with possibly an indication of likelihood of deferral, or an application for a waiver. Clear confirmation of the intention that submission of the information will be "phased", and that the guideline represents an ideal "end-point" is needed, and it will be up to companies to decide upon the phasing of submissions dependant on the developing availability of information and the nature of the project concerned (flexibility is needed to accommodate a wide range of differing development projects). For example, Parts D1 to 4 will not be able to be provided until possibly late in phase II, or later and the detailed descriptions of studies that are requested in D5 (especially in relation to clinical data, e.g. appropriateness of end-points) will not be available until phase III. Paediatric trials plans, and their final design will depend on data obtained from other studies at a later point in time. The PIP content described in the guideline assumes availability of the majority of 'non-clinical' data at a relatively late stage in the overall development plan. When PIPs are submitted at an early stage the majority of these data would not be available to allow for a detailed proposal of the non-clinical support of the paediatric plan. It is therefore assumed that the final detailed document is developed from the initial early submission via modifications to increase the level of detail. Multiple modifications submissions should be avoided to save resource both at the PDCO and in companies. Companies should be encouraged to minimise the number of stages at which the PIP is reviewed from the point of view finalising the more	The following text to be added under section 1.8 Modification of an agreed paediatric plan: "It is expected that the plan will be developed in a phased approach, from an initial strategic outline in early development leading eventually to a final plan containing all the relevant parts of this guideline. Companies will wish to consider how the plan should be built up as the product development proceeds. Multiple modifications submissions should be avoided and companies are encouraged to minimise the number of stages at which the PIP is reviewed, from the point of view of developing the detail of the plan. It will be helpful for companies to indicate to the Committee the point at which they consider that the complete plan is finalised so that a final commitment can be clear".

	complete plan. There should also be a clear understanding when the final plan has been reached. Modifications to a PIP should only need to provide justification for the changes and not provide again information already in the original PIP.	
1.8 page 16/19	Please refer to the general section for concerns relating to how multiple and additional indications for products should be managed in the context of the scope of PIPs and SPC-extension incentives.	
SECTION 2: OPERATION OF THE COMPLIANCE CHECK		
General p. 16-18/19	If the Paediatric Committee gives a positive opinion on compliance with the PIP at the applicant's request, it is clear that the applicant provided the results of the studies performed and information collected in compliance with a PIP and thus that Article 7.1 (a) is met. In such a case, the competent regulatory authority no longer has to check whether this provision is complied with.	
General p. 16-18/19	It should be clarified how a situation where the competent authority/ethical committees do not agree with the opinion of the PDCO will be handled.	
General p. 16-18/19	It is stated that operation of compliance check applies to applications under Articles 7 and 8, and also to PUMA. Nevertheless, this section seems applicable to the requirements of Articles 7 and 8 only. Indeed, the two-step process for checking of compliance seems to only apply to applications falling under Articles 7 and 8. Clarification on the compliance process for PUMA is needed.	
General p. 16-18/19	How will compliance at the second step be checked? e.g. if some studies are due at the time of the adult application (for instance for an indication A) and some others deferred (for instance indication B), will the PDCO start assessing data already available or only assess them "globally" (i.e. when all studied are performed).	
General p. 16-18/19	Could an applicant appeal against the PDCO's opinion if the PDCO considers that the paediatric program carried out is not in compliance with the agreed PIP? It seems that such provision has not been clearly taken into account in	The procedure for appealing compliance check decision should be described.

	the regulation, in contrast to other opinions generated by the PDCO (e.g agreement on a PIP, deferral, modification of a PIP...).	
Paragraph 2 p. 16/19	As with other applications, minor deficiencies should not automatically lead to invalidity of the application, and the applicant should be given the opportunity to rectify the deficiencies (see, for instance, Notice to Applicants, Vol.2A, Chapter 2, Section 3.3.2).	Add the following at the end of the paragraph: "In case of minor compliance issues, the applicant will be given the opportunity to rectify the application within a specific, reasonable deadline after he has been notified of the problems."
Paragraph 3 p. 16/19	See line above	The compliance check includes whether all measures agreed in a paediatric investigation plan decision have been conducted in accordance with it including the agreed timelines relative to the development in adults;…
Paragraph 5 p. 16-17/19	The operation of the compliance check is confusing and requires further clarification. The guideline does not clearly distinguish between the check performed to validate a marketing authorisation application and the check to confirm compliance with a PIP. It appears that, when provided, paediatric study results will be checked twice for compliance with the PIP: once to ensure validation and again to evaluate eligibility for rewards and incentives. Such repetition is unnecessary, and could lead to a delay or even refusal of validation, and a consequential delay in assessment and approval of a product for other populations, which is against the principles of the Directive. The check performed at validation of an application under Art.7 or 8 of the paediatric regulation has to be done in accordance with the Notice to Applicants (Chapters 2, 4, and 7). It should be a simple verification that the dossier includes the documents described in Art.7, or that the applicant has already obtained confirmation of compliance under Art.23(2)(a). In addition, as an application for a PIP includes much general and background information, the guideline must be clear about exactly what information is included in the scope of the check with respect to the compliance statement in the MA. Only the specific measures and their timelines described in section D.5 (and D.6, but see comments above) should be included in this check.	Amend as follows: "The determination of compliance with respect to validation will therefore include: • whether or not the documents submitted pursuant to Article 7(1) of the paediatric regulation cover all 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 will be made in accordance with the standard validation procedure specified in the Notice to Applicants. The determination of compliance with respect to 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 described in section D.5 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."
Paragraph 6	The exact meaning of this paragraph is unclear; text offering	Please amend to read: "If only some of the ~~measures~~ research activities included in the EMEA decision on the paediatric investigation plan have

p. 17/19	clarification is proposed (see opposite):	been completed by the time the compliance check in accordance with Articles 7 & 8 of the Regulation is performed, the compliance statement…"
Paragraph 7 p. 17/19	Compliance at Step 1 will be checked while deferrals are probably ongoing and it may happen that extension of those is needed. As a consequence the sentence should be modified. Furthermore, if several indications are developed simultaneously for adults, there is always a risk that not all study results are positive and lead to inclusion of the respective indication in an MAA/Type II variation. Study results are usually available only 3-4 months before submission. Should this occur for the first PIP it would not be enough time to amend the PIP in due time before submission of the MAA/Type II variation. 'When the paediatric development has to stop for example for safety reasons, a modification of the paediatric investigation plan or a request for a waiver should be requested.' If this happens in a late stage of development, having to request a PIP change could potentially delay submission of the adult indication. This is in contrast with what is in the regulation, namely that paediatric development should not delay the adult development/application process.	Amend paragraph 7 as follows: '… measures and timeline included in the paediatric investigation plan decision ~~cannot be renegotiated~~ should be, as far as possible, negotiated sufficiently in advance of compliance check step 1. However, in exceptional cases, it could be possible to modify the paediatric investigation plan even during or after this phase. When the paediatric development plan …'
Paragraph 8 p. 17/19	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 as follows: Compliance may be judged on the basis of submission of study synopses ~~only if full study reports are available.~~
Paragraph 9 p. 17/19	*"If at the time of the evaluation of the data generated as a result of an agreed paediatric it is shown that the studies have not been conducted in accordance with the paediatric investigation plan … of the paediatric regulation will not be included in the marketing authorisation.*" It should be made clear that this requirement applies to the nature and design of the trials, but in any case not to their timelines.	
Paragraph 10	EFPIA would like to ask for clarification what the "compliance	Please develop a specific compliance report template for completion

p. 17/19	report" contains. Will there be a specific template to fill out?	
Paragraph 11 p. 17/19	"*For medicinal products that … on the latest decision of the Agency*." This paragraph is very complex and confused (some words are missing). It will be helpful to simplify it.	
Paragraph 11 p. 17/19	If the compliance check is done before submission of the MAA/Type II variation, the information on location within the dossier is not available.	Amend paragraph 11 as follows: 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.
Paragraph 11 p. 17/19	Linguistic/editorial error	For medicinal products that fall under the scope of Articles 7 or 8 ~~have been met~~,
Paragraph 12 Bullet 1 & 2 p. 18/19	Clarification should be provided on what is meant by "key elements" and "minimum critical elements" referred to in the first and second bullet points, respectively.	
Last paragraph p. 18/19	The wording of the proposed statement of compliance needs to be improved.	Amend 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: The marketing authorisation holder ~~is medicinal product~~ has complied ~~will~~ with all measures in the paediatric investigation plan [reference number] and conducted ~~the studies includes~~ significant studies."
SECTION 3: ASSESSMENT OF CRITERIA FOR THE SIGNIFICANCE OF STUDIES STARTED BEFORE AND COMPLETED AFTER THE ENTRY INTO FORCE OF THE PAEDIATRIC REGULATION		
Section 3.1 Paragraph 1	It would be helpful to clarify that the assessment of significance is a transitional measure that does not apply to studies started after the	Add the following after the 2nd paragraph: "Assessment of significance is limited to studies started before and

p. 18/19	entry into force of the paediatric regulation.	completed after the entry into force of the paediatric regulation and thus is a transitional measure.”
Section 3.1 Added paragraph p. 18/19	In general, it should be clarified that significance of studies is to be assessed in view of all the studies to be conducted under a specific PIP and not in the abstract.	*Add the following as last paragraph:* The significance of a study is determined in view of all the studies to be conducted under the PIP concerned.
Section 3.2 Paragraph 1 p. 19/19	The moment at which a study is considered as completed must be consistent with the European rules on clinical trials. Volume 10 of the Notice to Applicant also refers to the date of the last visit of the last patient undergoing the trial but specified that this is 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). Furthermore, the date of entry into force of Regulation 1901/2006 is not relevant for the definition of the completion of a study.	*Amend the second sentence of the third paragraph as follows:* 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) but exceptions might be possible if justified. ~~and falls after the date of entry into force of the paediatric regulation~~.
Section 3.2 Paragraphs 3 & 4 p. 19/19	The guideline does not contain criteria for assessment of significance, but instead describes a case-by-case analysis and gives examples of significant studies. More general criteria should be set on which the pharmaceutical industry can rely, as required by Regulation 1901/2006. A study should be considered significant if it is necessary to support a paediatric use marketing authorisation.	Amend 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 support an authorisation for use in all or part of the paediatric population. ~~However,~~ ~~t~~The examples below are provided as a guide to the assessment of the significance of studies. One or more of t~~T~~he following study types will normally be considered as significant:
Section 3.2 Paragraph 4 p. 19/19	The criteria for assessment of significant studies for the purposes of gaining the incentive should be broadened in line with ICH E11 recommendations, to cover open label or pharmacokinetic-pharmacodynamic (PK/PD) studies.	Add the following additional points to the list of studies normally considered significant 5 - Open label studies: There are likely to be situations where it is not possible to conduct randomised/active control or placebo controlled comparative efficacy studies in paediatrics because, • there is no appropriate active comparator; • placebo controlled studies are not considered to be ethical;

		• and/or the paediatric population for a particular disease is small. In these circumstances, open label studies or the use of historical controls may be the only way of generating useful data in the population in question and should be considered as significant. 6 - PK/PD studies: well founded pharmacokinetic/pharmacodynamic clinical studies should also be considered as significant if they can provide meaningful data which would avoid the need for a clinical efficacy study and therefore spare the numbers of children who may need to be enrolled in a larger trial.
Section 3.2 Paragraph 4 p. 19/19	If paediatric data already exist for some sub-populations, the applicant may not be aware if they have not been published yet.	Please add:"…will not be considered as significant, provided that such data were published at the time the studies started."
Section 3.2 Paragraph 4 Point 3 p. 19/19	In the assessment section at the end there are statements about the different type of studies. There is no guidance as to whether safety only studies are acceptable as long as the efficacy can be extrapolated from adult data.	Suggest to change point 3 into: Prospective clinical safety studies, if the results are expected to make a major contribution to the safe use of the medicinal product in the paediatric population and/or when efficacy can be extrapolated from the adults population.
Section 3.2 Last paragraph p. 19/19	Studies in a single paediatric sub-set may be sufficiently extensive or make an important contribution to treatment of children and thereby justify the incentive. It is not clear why studies should cover normally all paediatric subsets to be considered as significant. In many instances first the older age groups will be studied before moving into the younger ones because of valid scientific and ethic considerations. If for example a study has been completed in children 6-18 yrs before 26 Jan 07, further studies completed after 26 Jan 07 in toddlers should also qualify as significant.	The following re-wording is proposed: “In order to be considered as significant, the studies should normally cover all paediatric subsets affected by the condition where data are not available unless a waiver has been granted. However, ~~exceptionally~~ on a case-by case basis, studies conducted in a single subset of the paediatric population will be considered as significant if sufficiently extensive or if they make an important contribution to treatment of children or if they are carried out in a subset considered particularly difficult to study, for example neonates”.