SUBMISSION OF COMMENTS ON

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

COMMENTS FROM –THE INTERNATIONAL PLASMA FRACTIONATION ASSOCIATION (IPFA)

GENERAL COMMENTS

This guideline could be organised around the 3 different situations of marketing status of the product (already marketed, new application requiring paediatric indication, new application for a PUMA).

This guideline is globally not very clear, it is really difficult to get a good overview of what needs to be written in which sections (A, B, D).

The guideline contains a complicated procedure which appears difficult to set up; also the date for coming into force is very tight.

Submission time of the PIP should be briefly explained in this guideline.

Date of transmission:

Submit all comments to: by email to peter.arlett@ec.europa.eu in word forma please.
Deadline for comments: <30 March 2007>
These comments and the identity of the sender may be published on the European Commission website unless a specific justified objection is received by the European Commission.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
	INTRODUCTION Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 [1] (hereinafter "the paediatric regulation") entered into force on 26 January 2007. The paediatric regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations. To meet these objectives the paediatric regulation creates a number of requirements on the pharmaceutical industry for when medicinal products are developed and creates rewards for the pharmaceutical industry for when the requirements for studies in children are fully complied with. The paediatric regulation creates a new type of marketing authorisation, the paediatric use marketing authorisation (PUMA) as an incentive for the development of off patent medicines for children. The paediatric regulation also creates support measures to manage the operation of the paediatric regulation including the paediatric committee within the European Medicines Agency (hereinafter "the	

	Agency"). This guideline provides the detailed arrangements concerning the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers and deferrals. The guideline also provides advice on the operation of the compliance check referred to in Articles 23 and 28(3) of the paediatric regulation2. Finally, the guideline provides the assessment criteria for the significance of studies started before and completed after the entry into force of the paediatric regulation. Definitions relevant to this guideline are provided in Directive 2001/83/EC, Directive 2001/20/EC, Regulation No (EC) 141/2000 as well as the paediatric regulation. In addition, the following terms and definitions are used in this guideline: (a) **Condition**: any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome). (b) **Paediatric investigation plan indication:** the proposed indication(s) in the paediatric population for the purpose of a paediatric investigation plan, and at the time of paediatric investigation plan submission. It should specify if the medicinal product is intended for diagnosis, prevention or treatment of a condition. (c) **Proposed Therapeutic Indication:** The therapeutic indication in adults and/or paediatric populations as proposed by the paediatric investigation plan applicant at the time of submission of a paediatric investigation plan. (d) **Granted Therapeutic Indication:** The therapeutic indication in adults and/or paediatric populations that is included in the marketing authorisation. This will be the result of the assessment of the quality, safety and efficacy data submitted with the marketing authorisation application. (e) **Measures:** as used in Article 15(2) of the paediatric regulation	These 2 sentences are contradictory: either a MA has been granted or is submitted to an application. This confusion exists all along the text.

	includes all studies, trials, data and pharmaceutical development necessary in a paediatric investigation plan to obtain a paediatric indication with an age appropriate formulation in all subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan. **SECTION 1: FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS AND DEFERRALS** **1.1: GENERAL PRINCIPLES AND FORMAT** The same application form (see the Annex to this guideline) should be used whether requesting agreement to a paediatric investigation plan, a waiver, a deferral or a combination thereof. Different parts (Part A to Part F) of the application are provided to fulfil the different types of request. Applications should cover all subsets of the paediatric population as required by Article 7(2) of the paediatric regulation. Applications for products falling within the scope of Article 8 of the paediatric regulation should also cover the existing and the new indications, pharmaceutical forms and routes of administration. In the latter case or when an applicant intends to develop several indications simultaneously, only one comprehensive paediatric investigation plan should be included in the application. The paediatric population means the part of the population aged between birth and 18 years (up to but not including 18-years). The paediatric population encompasses several subsets defined in ICH guideline E11[4]: the pre term and term neonate from 0 to 27 days, the infant from 1 month to 23 months, the child from 2 years to 11 years and the adolescent from 12 up to 18 years. However, in some conditions, the use of different subsets may be more appropriate and when different subsets are used they should be	It is not quite clear which “different subsets” are meant here (different from the above?) Should each of the subset be documented separately ?

	explained and justified. When drafting paediatric investigation plans for paediatric use marketing authorisations, applicants are encouraged to consider whether there may be a therapeutic need for the medicinal product in each paediatric subset. If a paediatric investigation plan is included in the application submitted in accordance with this guideline it should focus on studies that will allow labelling the product for appropriate use in all relevant paediatric subsets, as well as the development of appropriate formulations, if applicable. All information relevant to the evaluation of the paediatric investigation plan, as well as requests for deferrals or waivers should be included in the application whether favourable or unfavourable to the product. In particular, all relevant details should be given of any incomplete or discontinued pharmaco-toxicological test or clinical study or trial relating to the medicinal product, and/or completed trials concerning indications not covered by the application. When assessing the significant therapeutic benefit and/or the fulfilment of therapeutic needsin the paediatric population, the paediatric committee may take into consideration in addition to the proposed adult indication other relevant information such as the target and mechanism of action of the medicinal product concerned. Following an Agency decision on an request for a waiver or a paediatric investigation plan or a deferral, if new information becomes available which may have an impact on the decision of the Agency, this should be submitted to the Agency without delay with a proposal to modifythe paediatric investigation plan together with a request for a waiver or deferral asappropriate.	

	1.2 PART A: ADMINISTRATIVE AND PRODUCT INFORMATION It is acknowledged that at an early stage of product development it may not be possible to provide comprehensive answers to all sections of the application. However, applicants should always complete all sections of Part A using the forms annexed to this guideline and where information is not available, this should be stated. ***A.1 Name or corporate name and address of the applicant and contact person*** The name and address of the applicant should be provided. The applicant may be an individual or a company. A contract research organisation may submit an application. Where the applicant is not the person or company responsible for the research and development ofthe medicinal product, details of the person or company responsible should be provided. The person authorised to communicate with the Agency on behalf of the applicant during the procedure, and after the Agency decision, if different, should be provided. In view of the fact that Agency decisions will be made public, the applicant is encouraged to provide a contact point (telephone/fax/e-mail) for enquiries from interested parties that the Agency will then make public with the decisions. ***A.2 Name of the manufacturer of the active substance and medicinal product*** The name(s) and address(es) of the manufacturer(s) and site(s) of manufacture of the active substance(s) and of the medicinal product (if available) should be provided.	Why is it not possible for paragraph *A.1* to *A.5* to use the same content as the application for clinical trial authorization ?

	A.3 Name of the active substance The active substance should be stated by its recommended International Non-proprietary Name (INN), accompanied by its salt or hydrate form if relevant. If the 'recommended' INN is not available the 'proposed' INN should be provided. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances not having an exact scientific designation should be described by a statement of how and from what they were prepared, supplemented where appropriate by any relevant details. A company or laboratory code should not be used. Where the active ingredient is of herbal origin, the Note for Guidance on *Quality of Herbal Medicinal Products* should be taken into consideration for its description. Considering the timing for submission of applications, only preliminary names of the active substance might be provided. In this situation and in the event that the application is resubmitted (e.g. for modification of a paediatric investigation plan) it is suggested to record all successive name changes in the document. ***A.4 Type of product*** The applicant should specify what type of product the application is for (e.g. a new chemical entity, a new biological product, a vaccine, a gene therapy product, somatic cell therapy medicinal product etc). In addition, the applicant should specify the target and mechanism of action. ***A.5 Details of the medicinal product*** If available, the proposed invented name, strength, pharmaceutical form and route of administration should be provided.	

	A.6 Regulatory status of the product inside the Community A description of the Community regulatory status of the medicinal product in both adult and paediatric populations should be provided. This should include: • marketing authorisation status (including refused applications) in individual EU Member States, or through the centralised procedure • 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 scientific advice from the Agency of any national competent authority • details of any regulatory to restrict the use of the medicinal product in any EEA country. ***A.7 Regulatory status of the product outside the Community*** A summary of the worldwide regulatory status and marketing history of the medicinal product in both adult and paediatric populations should be provided. This includes marketing authorisation application status (including refused applications), details of the indications for which the medicinal product is approved in third countries, and regulatory information on clinical trials and any actions taken against the medicinal product in any country. The applicant should provide the paediatric committee with any decisions, opinions or advice (including scientific advice) given by competent authorities of third countries on the paediatric development of the medicinal product. A copy of any relevant documents should be included in Part F.	

	A.8 Conditions to be treated, diagnosed or prevented. For products not yet authorised in the Community or, for authorised products where a new indication is proposed for development, the condition(s), whether in adults or children, that the medicinal product is intended to diagnose, prevent or treat, as envisaged at the time of submission, should be stated, following an agreed classification system, such as the World Health Organisation International Classification of Diseases (ICD-10). ***A.9 Proposed therapeutic indication and pharmacotherapeutic group*** The applicant should provide the proposed therapeutic indication which may cover the adult and/or paediatric population. Where a pharmacotherapeutic group and ATC code have been assigned, these should be included. If there are authorised medicinal products belonging to that class should be stated. **1.3 PART B: OVERALL DEVELOPMENT OF THE MEDICINAL PRODUCT INCLUDING INFORMATION ON THE TARGET DISEASES / CONDITIONS** For medicinal products being developed for applications that will fall under the requirements of Articles 7 and 8 of the paediatric regulation Part B should list for each indication and each subset of the paediatric population, how the requirements of Articles 7 and 8 will be met. This part should also include details on the diseases/conditions in the paediatric population including their similarity between adult and paediatric populations and within the different paediatric subsets, prevalence, incidence, diagnosis and treatment methods, and alternative treatments. This information can be provided in tabulated format for ease of reference.	

	B.1 Discussion on similarities and differences of the disease/condition between populations For each disease or condition already authorised, as well as for each disease or condition which is the subject of new development (i.e. for new medicinal products or new indications for authorised medicinal products) the applicant should state whether the paediatric population is affected. The applicant should provide a description of the diseases or conditions, with a view to discuss any potential differences or similarities: • between the adult and the paediatric populations; • between the different paediatric subsets; Emphasis should put on the seriousness of the disease, aetiology, clinical manifestations and prognosis, and variability in terms of genetic background, in the paediatric subsets. This may be based on published references, or standard textbooks.	This section *B.1* should deal only with the disease/condition The marked wording can therefore be deleted
	B.2 Discussion of anticipated similarities and differences of the effect of the product on the disease/condition The anticipated differences and similarities of the effect of the product on the diseases /conditions should be described focussing on a comparison: • between the adult and the paediatric population; • between the different paediatric subsets. • 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). o The need for specific studies in certain age groups • Pharmacokinetic studies: o The possibility to extrapolate efficacy and safety from adult or older age group based on pharmacokinetics.	This section B.2 should be placed just before section B.5 It appear more appropriated to mention these items in this section B.2 than in the section D.4 because these items deal with differences between adult and paediatric population.

	o The possibility to support pharmacokinetics in certain age groups using information, or to extrapolate pharmacokinetics from other populations. o Discussion of age groups where more extensive studies are needed e.g. due to expected high kinetic variability. o The possibility to extrapolate interactions, organ function impairment and effects of pharmacogenetics, and the need for specific studies. ***B.3 Prevalence and incidence in the paediatric population*** The applicant should provide information of the prevalence and incidence of the diseases/conditions in the Community (and in the different Member States) if available. If possible, this could be broken down by paediatric subsets. Information on the earliest age of onset of the diseases/conditions or the age range concerned should be provided, especially if the applicant intends to apply for a product specific waiver covering specific paediatric subsets. ***B.4 Current methods of diagnosis, prevention or treatment in paediatric populations*** For each treatment of the disease or condition already authorised, as well as for each disease or condition which is the subject of new development (i.e. for new medicinal products or new indications for authorised medicinal products) the applicant should identify the diagnosis, prevention and treatment methods available in the Community, making reference to scientific and medical literature or other relevant information. This should include unauthorised treatment methods if they represent the standard of care. If no methods exist, this should be stated. Of the available treatments identified, in the case of authorised medicinal products, the list should include those authorised	This section deals with treatment of the disease or condition.

	nationally in at least one Member State and by the Community. This can be presented as an overview table containing the invented names(s), active substance, Member State(s) where authorised, holder of the authorisation, and the authorised indication, if applicable. 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. For medical devices, the invented name (s) and the approved use(s) should be provided. For medical devices which fall within the scope of Directive 93/42/EEC, the list should include all devices placed on the market according to this Directive, and in the case of active implantable devices which fall within the scope of Directive 90/385/EEC, those placed on the market or put into service in accordance with this Directive. ***B.5 Significant therapeutic benefit / fulfilment of therapeutic need*** Whether the use of the medicinal product either through use as an authorised product or through the conduct of clinical trials in the paediatric population is expected to be of significant therapeutic benefit to the paediatric population or fulfil a therapeutic need in the paediatric population should be judged by the paediatric committee and will determine whether a paediatric investigation plan receives a positive opinion or whether a waiver is granted. To enable the paediatric committee to make its assessment the applicant should provide a comparison of the medicinal product which is the subject of the application with the current standard of care for the treatment, diagnosis or prevention of the diseases / conditions that are the subject of the intended indication in children. Established treatment methods in the paediatric population (including non-pharmacological treatment methods, medical devices, prevention methods) if they exist in the EU	Text should be harmonised by replacing “children” with “the paediatric population”.

	should also be discussed. Methods of treatment, diagnosis or prevention which are not subject to marketing authorisation might be considered as standard of care if there is sufficient scientific evidence and consensus between experts in the field concerned, as to the value of such methods. Significant therapeutic benefit might also be present because existing treatments are not satisfactory and alternative methods with an improved expected benefit risk balance are needed. When considering significant therapeutic benefit the paediatric committee will take into account the nature of the condition to be treated (diagnosed or prevented) and the available data on the medicinal product concerned. On this basis, significant therapeutic benefit could be based on: a) Expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned. b) Expected substantial improvement in safety in relation to either adverse events or potential medication errors. c) Improved dosing scheme or method of administration (number of doses per day, oral compared to intravenous administration, reduced treatment duration, pain reduction) leading to improved safety, efficacy or compliance. d) Availability of a new clinically relevant age-appropriate formulation. e) 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. f) Different mechanism of action with potential advantage for the paediatric population(s) in terms of improved efficacy or safety. As experience with the use of the medicinal product in the paediatric population might not be available or might be very limited at an early stage of the development of a medicinal	The notion of pain reduction is an important issue in children This item f) seems to be a repetition of a) and b)

	product, significant therapeutic benefit might also be based on well-justified and plausible assumptions. In order to allow the paediatric committee to make its assessment the applicant should explore these assumptions based on reasoned arguments and relevant literature. If significant therapeutic benefit cannot be fully justified at that early stage of the development of a medicinal product, the paediatric committee may consider a waiver or deferral, as appropriate. 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. Particularly early in product development when data to substantiate significant therapeutic benefit may be scarce, studies in children may be justified on the basis that there is a therapeutic need of the paediatric population which may be fulfilled either through inclusion of children in clinical trials or through the availability of the medicine as an authorised medicinal product. If the therapeutic need is included in the inventory of therapeutic needs established by the paediatric committee, the applicant should refer to the inventory. Where the applicant considers the proposed paediatric development to fulfil a therapeutic need and this therapeutic need is not yet included in the inventory as established by the paediatric committee, sufficient information to explain this assumption should be provided. **1.4 PART C: APPLICATIONS FOR PRODUCT SPECIFIC**	

	WAIVERS ***C.1 The scope of a product specific waiver*** A waiver may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both (Article 11(2) of the paediatric regulation). Requests for product specific waivers should clearly define their scope in terms of paediatric subset and indication. As waivers may subsequently be used to satisfy, either in part or in full the requirements of Article 8 of the paediatric regulation, applicants should specify the route of administration and pharmaceutical form. It should be noted that the Agency will make public class waivers in accordance with Article 12 and 25(7) of the paediatric regulation. Depending on the precise scope of any relevant class waiver, no product specific waiver may be necessary to satisfy the requirements of Article 7 and 8 of the paediatric regulation. Where the requirements of Articles 7 and 8 of the paediatric regulation are partially covered by class waiver but a product specific waiver is necessary to satisfy the requirements, the class waivers should be referred to when specifying the scope of the product specific waiver. ***C.2 Grounds for a product specific waiver*** The grounds for a waiver are defined in Article 11 of the paediatric regulation. *C.2.1 Grounds based on efficacy or safety* In accordance with Article 11(1)(a) of the paediatric regulation a request for a waiver based on lack of efficacy in the paediatric population(s) should take account, for the different paediatric subsets, of the seriousness of the condition/disease and the availability of other methods as stated in Part B. All available data should be submitted to support the lack of efficacy in the	

	paediatric population as a whole or in subsets, as applicable. The justification should be based on effects observed in non clinical models, studies and trials, when available. The paediatric committee may take into consideration established inefficacy for products of the same class as the basis for a waiver. The safety profile of a medicinal product is usually only fully characterised after a product has been placed on the market. The justification for a waiver based on safety will therefore differ depending on the existing experience with the product. Justification may include the pharmacological properties of the product or class of product, results from non-clinical studies, clinical trials or post-marketing data. Whether a safety issue is known or suspected should be discussed. At an early stage of development, the absence of any available data on the safety or efficacy in the paediatric population will not be accepted as the sole as justification for a waiver. *C.2.2 Grounds based on the disease or condition only occurring in adults* In accordance with Article 11(1)(b) of the paediatric regulation justification may be based on detailed information on the incidence or prevalence of the disease in different populations. For waivers covering the totality of the paediatric population the justification should particularly focus on the earliest age of onset of the condition/disease. For waivers for specific subsets the justification should focus on the incidence or prevalence in the different paediatric subsets delineated in Part B. *C.2.3 Grounds based on lack of significant therapeutic benefit* In accordance with Article 11(1)(c) of the paediatric regulation applications for waivers may be based on a lack of significant therapeutic benefit. See section 1.3 Part B5.	Please, clarify that the requirement of non-clinical model is additional in this context to the documentation presented in part B.

	1.5 PART D: PAEDIATRIC INVESTIGATION PLAN ***D.1 OVERALL STRATEGY PROPOSED BY THE APPLICANT FOR THE PAEDIATRIC DEVELOPMENT*** *D.1.1 Paediatric Investigation Plan indication* The applicant should state the proposed indication(s) in the paediatric population for the purpose of a paediatric investigation plan, covering part of or all subsets, as appropriate. This part should specify whether the medicinal product is intended for the diagnosis, prevention or treatment of the diseases / conditions in question. *D.1.2 Selected age group(s)* The paediatric investigation plan should cover all subsets of the paediatric population, including neonates, which are not covered by a waiver. The age ranges to be studied should be justified and may vary depending on the pharmacology of the product, the manifestation of the condition in various age groups and other factors. The applicant may refer to the age classification of ICH/CHMP guideline E11. However, these age classes are wide and may include different maturation levels. In addition to age, the classification of the paediatric population may be based on other variables such as gestational age, pubertal stage(s), and renal function. *D.1.3 Outline of the quality, non-clinical and clinical data.* The applicant should outline the development of the medicinal product which is relevant for paediatric development and its results when available. An outline of the planned studies in adults should also be provided. This could take the form of an "investigator brochure" style summary. The full study reports of non-clinical and clinical studies undertaken need not be provided	It is not clear that PIP is only part 1.5 ? What about sections 1.1 to 1.4 ? Maybe the subtitles should be changed

	but should be made available upon request. *D.1.4 Extrapolation and interrelation between development in adult and paediatric populations* The applicant should discuss possible extrapolation from adult data to paediatric patients, as well as from older age groups to younger ones. The interrelation (in terms of common studies, data and timelines) between development in adults and paediatric populations should be highlighted. *D.1.5 Existing paediatric information* The applicant should include a review of any information on the product in the paediatric population, making reference to scientific and medical literature or other relevant information, such as reports from off label or unlicensed use, or accidental exposures, as well as known class effects. *D.1.6 Significant therapeutic benefit / fulfilment of therapeutic need* Information and discussion of significant therapeutic benefit or fulfilment of therapeutic need should be included in section 1.3 Part B5. ***D.2 STRATEGY IN RELATION TO QUALITY ASPECTS*** This section should address the chemical, pharmaceutical and biological aspects related to the administration of the product in paediatric subsets. The discussion will take into account the pharmaceutical development of the product and should address critical issues such as: • Need for a specific formulation or dosage form in relation to the chosen age group(s) and discussion of the benefit of the chosen formulation or dosage form • Availability / timeframe for the development of an age appropriate dosage form • Potential issues in relation to the formulation (e.g.	This information is already described in sections B4 and B5.

	appropriateness of excipients for the paediatric population) • Administration of the medicine to paediatric subsets (e.g. use of specific administration devices, ability to mix with food, taking into consideration different European food cultures, anticipated container closure systems etc.). 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 tablet of a new strength, because the existing pharmaceutical form may be unsuitable for use in all or part of the paediatric population. This means that the suitability of existing pharmaceutical forms should always be discussed in the paediatric investigation plan. ***D.3 STRATEGY IN RELATION TO NON-CLINICAL ASPECTS*** This section should discuss the strategy for the non-clinical development, which is needed in addition to standard non clinical development or to already existing data. The following elements should be addressed: • Pharmacology: o The need for proof of concept for the use in paediatric populations, for example using non-clinical in-vitro and / or in-vivo models. o The need for pharmacodynamic studies (e.g. to establish a dose relationship for a pharmacodynamic endpoint, if there is a reliable animal model to justify the choice of the most relevant species for potential juvenile animal studies). o Safety pharmacology (studies using non-clinical in-vitro and / or invivo models to investigate specific function of the physiological system) • Pharmacokinetics: o Specific studies justifying the most relevant species for potential	

	juvenile animal studies. • Toxicology: o The need for specific toxicity studies including toxicokinetics in juvenile animals. o The need for toxicity study to address specific endpoints e.g. neurotoxicity, immunotoxicity or nephrotoxicity at a particular developmental phase. o The need for additional local tolerance studies e.g. for topical application dosage forms. ***D.4 STRATEGY IN RELATION TO CLINICAL ASPECTS*** This section should discuss and justify the strategy for the clinical paediatric development, in relation to the standard development (including that in adults and in relation to existing data). This section should present the overall clinical approach to support the product development in the paediatric investigation plan indications and age subset(s). This should include critical aspects of study design, and should present the strengths and limitations of the proposed clinical development. It should address the appropriateness of endpoints according to age (the actual design of each individual study should be described in section D5). Details of the formulation to be used should be given and plans for bridging between the different formulations should be addressed. The applicant should address the rationale to support dosing and route of administration. The discussion should reflect which data are needed in order to conduct the studies so that bridging to the timing of the studies in the overall development plan can be made. The applicant should justify that the subjects intended for inclusion in the trials are representative of the population in which the product will be used. The following aspects should be addressed: • Pharmacodynamic studies: o Pharmacodynamic differences between adult and paediatric populations (e.g. influence of maturation of receptors and/or systems).	We believe that the marked items in this section D4 should be deleted here; they should be addressed in section B.2

	o Extrapolation from different populations (from adult and/or for older paediatric age groups). o The need for specific studies in certain age groups o Discussion of any biomarkers for pharmacokinetics /pharmacodynamics. • Pharmacokinetic studies: o The possibility to extrapolate efficacy and safety from adult or older age group based on pharmacokinetics. o The use of pharmacokinetics / pharmacodynamics studies to bridge efficacy and safety in adults or older age group. o The possibility to support pharmacokinetics in certain age groups using information, or to extrapolate pharmacokinetics from other populations. o Discussion of age groups where more extensive studies are needed e.g. due to expected high kinetic variability. o Use of population pharmacokinetics. • Efficacy and safety studies: o The possibility to extrapolate interactions, organ function impairment and effects of pharmacogenetics, and the need for specific studies. o Discussion of the need for specific dose-finding studies. o Discussion of issues of the relevance across the proposed studies, such as age appropriateness of endpoints, use of surrogate markers, use of alternative study design and analysis, potential need for short term and long term safety and potential risks by age group. o Discussion of the proposed studies in the post-authorisation phase and the impact on the risk management system (some of the elements of the risk management system, for instance requests for long-term safety studies may however not be part of the agreed paediatric investigation plan but will be evaluated at the time of the submission of the application for marketing authorisation and may be part of the conditions of the marketing authorisation).	

	Finally the measures proposed to protect the paediatric population during development for example the use of less invasive methods, use of a data and safety monitoring board for certain studies, and issues related to the feasibility of the proposed studies (e.g. recruitment, accessibility to assurance for the paediatric population) should be discussed. ***D.5 PLANNED MEASURES FOR THE PAEDIATRIC DEVELOPMENT*** *D.5.1 Overall Summary Table of all non-clinical and clinical studies* A table should be included providing an overview of all measures planned or performed by the applicant. *D.5.2 Outline of each of the planned or performed studies and steps in the pharmaceutical development* The studies which should be outlined here are strongly dependent upon the proposed strategy mentioned in Section D.2 therefore the examples given below are not exhaustive. • If the basis of the paediatric product is an authorised adult product with a simple reduction in content of active substance, or reduced amount administered, then pharmaceutical development studies may be minimal in the context of a paediatric investigation plan. Otherwise, if the strategy is to create a new pharmaceutical form (e.g. new dosage form, or new route of administration) then the necessary pharmaceutical development studies may need to be more extensive[4]. Proposed studies of particular relevance to the development of paediatric products may include: • Compatibility and stability in the presence of relevant common foods and drinks. • Compatibility with administration systems e.g. medical devices. • Taste-masking or palatability.	The problem of specific insurance for the paediatric population should also be discussed.

	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: • Type of Study • Objective (s) • Test system/species • Method of Administration • Duration of Dosing	
	D.5.4 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: • Type of study • Study design • Type of control (placebo or active control with dose to be used) • Location (regions) • Test(s) products; Dosage regimen; Route of administration • Objective(s) of the study • Number of subjects (M/F), ages, number per ICH age groups or other relevant age group • Duration of treatment • Main inclusion/ exclusion criteria • Parameters or endpoints (primary, secondary) • Sample size (more or less detailed as appropriate) • Power calculation: describe effect size expected • Options in case of recruitment issues, interim analyses and stopping rules • Statistical methods (Statistical methods used to compare groups for primary outcome, and for additional analyses if relevant)	This item doesn't appear realistic, not all the information can be provided so early for the different studies included in the development plan This information should not be provided in this section : a synopsis is not a protocol
	D.6 TIMELINE OF MEASURES IN THE PAEDIATRIC	

	INVESTIGATION PLAN The section should present the detailed timelines of the measured included in the paediatric investigation plan. Particular emphasis should be placed on the timing of the measures in the paediatric investigation plan compared to the development for adults, as expressed for example in ICH/CHMP guideline (E11). The predicted timing of applications which fall under Articles 7 and 8 of the paediatric regulation should be provided and the timing of the measures in the paediatric investigation plan should refer to these applications. The applicant should propose timelines for initiation and completion of each measure, including specific dates. The applicant should include in its proposal a reasonable amount of time for unforeseen circumstances to complete, analyse and report the studies to be included in the application. **1.6 PART E: APPLICATIONS FOR DEFERRALS** The paediatric regulation allows for deferral of the initiation or completion of the measures included in a paediatric investigation plan. Any request for deferrals of the start or the completion of measures should be justified by indication, route of administration and pharmaceutical form. When requesting a deferral, the applicant should specify the age group to which it applies. Requests for deferrals should be justified on scientific and technical grounds or on grounds related to public health (Article 20(1) of the paediatric regulation) and justifications might include the following: • It is considered appropriate to conduct studies in adults prior to initiating studies in the paediatric population; • When studies in the paediatric population will take longer to conduct than studies in adults; • Additional non-clinical data are considered necessary; • Major quality problems prevent development of the relevant formulation(s).	

	1.7 PART F: ANNEXES The annexes should include the following documents, as appropriate: • References (i.e. published literature); • Investigator brochure; • Opinions and decisions given by Competent Authorities, including those from third countries; • Scientific advice given by Competent Authorities, including those from third countries; • Latest approved product information (SPC, PL, Labelling) for a product already authorised; **1.8 MODIFICATION OF AN AGREED PAEDIATRIC INVESTIGATION PLAN** In the case of an application for modification of a paediatric investigation plan, the application form annexed to this guideline should be used. The content of the application should follow the same structure as for an initial paediatric investigation plan request for agreement (Part D) but only relevant sections supporting the change should be completed. The application should provide the reference of the previous paediatric investigation plan decision. **SECTION 2: OPERATION OF THE COMPLIANCE CHECK** The requirements of Articles 7 and 8 of the paediatric regulation as well as applications for paediatric use marketing authorisations are the subject of compliance checks by the competent authorities as described in Articles 23 and 24 of the paediatric regulation. Article 23 of the paediatric regulation provides for the opinion of the paediatric committee on compliance and clarifies when and by whom this opinion can be requested. Non-compliance with the requirements of Articles 7 and 8 of the paediatric regulation results in applications falling within the	

	scope of those Articles being invalid. 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; compliance is one of the prerequisites to obtaining the rewards and incentives provided for in Articles 26 to 38 of the paediatric regulation. Checking of compliance by the competent authorities (based on the opinion of the paediatric committee if requested) can be seen as a two step process with non-compliance leading to non-validation of applications falling under Articles 7 and 8 of the paediatric regulation, and for validated application, non-inclusion in the marketing authorisation of the compliance statement referred to in Article 28(3) leading to ineligibility for the rewards and incentives. The determination of compliance 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, and • for medicinal products with an agreed paediatric investigation plan, whether all of the measures in that plan (studies, trials and timelines) proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population concerned, including any measure to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population have been carried out in accordance with the paediatric investigation plan decision. If only some of the measures included in paediatric investigation plan decision have been completed the compliance statement referred to in Article 28(3) of the paediatric regulation will not be	

	included as this requires completion of all the measures in the paediatric investigation plan. At the time of the assessment of compliance, measures and timeline included in the paediatric investigation plan decision cannot be re-negotiated. Any modification of the paediatric investigation plan and potential amendments should have taken place before the start of the compliance check and should be included in the paediatric investigation plan decision. 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. Compliance may be judged only if full study reports are provided. The confirmation of compliance is not linked to the assessment of the data i.e., compliance is not linked to the scientific judgement on the quality, safety and efficacy of the medicinal product based on data generated as a result of the agreed paediatric investigation plan. If at the time of the evaluation of the data generated as a result of an agreed paediatric investigation plan, it is shown that the studies have not been conducted in accordance with the paediatric investigation plan decision compliance will not be confirmed and the compliance statement referred to in Article 28(3) of the paediatric regulation will not be included in the marketing authorisation. To facilitate the work of competent authorities and paediatric committee in reaching an opinion on compliance, the applicant is encouraged to present a compliance report at the time of the submission of the application. If the paediatric committee opinion is sought by the applicant under Article 23(2)(a), prior to the application a copy of this opinion will be annexed to the application as provided for by Article 23(2) last subparagraph. For medicinal products that fall under the scope of Articles 7 or 8 have been met, the compliance report should indicate in the form of a table how each subset of the paediatric population and for	

	applications falling under Article 8 of the paediatric regulation, how each of the existing and new indications, pharmaceutical forms and routes of administration have been covered by the documents referred to in Article 7(1) of the paediatric regulation. A separate table should be included covering the decision on the paediatric investigation plan, the applicant's position on compliance with the key elements, and a cross-reference for each key element of the paediatric investigation plan to the location within the submitted relevant module in the marketing authorisation application. In case of modifications to a paediatric investigation plan, the table should be based on the latest decision of the Agency. *Points to consider:* • The relevant Competent Authority will perform a detailed check of each key element requested in the paediatric investigation plan against what has actually been submitted. • Because the decision on the paediatric investigation plan will include the minimum critical elements for each of the measures, the applicant will need to comply with each item. • If the paediatric investigation plan included measures using conditional language such as "could", or "such as" then the compliance may be confirmed even if these measures were not followed as suggested. • In the case of a paediatric committee opinion on compliance under Article 23 of the paediatric regulation, the grounds for accepting or denying compliance will be clearly stated in the opinion. **The statement of compliance referred to in Article 28(3) of the paediatric regulation will be the following: This medicinal product has complied will all measures in the paediatric investigation plan [reference number].** **Where studies fall under the provisions of Article 45(3) of the paediatric regulation the statement of compliance referred to in Article 28(3) of the paediatric regulation will be the**	In the paediatric regulation, differences between 28(3) and 45(3) are not clear, this aspect should be explained in this guideline.

	following: This medicinal product has complied will all measures in the paediatric investigation plan [reference number] and includes significant studies. **SECTION 3: ASSESSMENT CRITERIA FOR THE SIGNIFICANCE OF STUDIES STARTED BEFORE AND COMPLETED AFTER THE ENTRY INTO FORCE OF THE PAEDIATRIC REGULATION** *3.1 Background* For studies started before the entry into force of the paediatric regulation to be the basis of granting the rewards of Articles 36, 37 and 38 of the paediatric regulation they need to be completed after the entry into force and to be judged significant (Article 45(3) of the paediatric regulation). The statement of compliance referred to in Article 28(3) of the paediatric regulation will indicate whether the studies included in the paediatric investigation plan which were initiated prior to and were completed after the entry into force of the regulation are considered significant in the meaning of Article 45(3) of the paediatric regulation. *3.2 Assessment Criteria* In general, it is the quality rather than the quantity of the studies, as well as the clinical relevance of data for the paediatric indication, which will determine the significance of studies. In exceptional cases, a set of non-significant studies might be considered as significant if the results taken together are expected to provide important and clinically relevant information. To qualify for the rewards of Articles 36, 37 and 38 significant studies need to be completed after the entry into force of the paediatric regulation. 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) and falls after the date of entry into force of the	

	paediatric regulation. Open extensions of studies consisting of treatment maintenance for patients included, will not be considered as continuing after the entry into force if this was not part of the protocol submitted to the relevant competent authorities. The Agency or competent authorities will assess the significance of each study proposed in a paediatric investigation plan on a case-by-case basis. However, the examples below are provided as a guide to the assessment of the significance of studies. The following study types will normally be considered as significant: 1. Comparative efficacy studies (randomised / active control or placebo); 2. Dose-finding studies; 3. 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; 4. Studies to obtain a new age-appropriate formulation, if the formulation is expected to be of clinical relevance for the safe and effective use of the medicinal product in the paediatric population. In order to be considered as significant, the studies should normally cover all paediatric subsets affected by the condition where sufficient data are not available. However, exceptionally, studies conducted in a single subset of the paediatric population will be considered as significant if carried out a subset considered particularly difficult to study, for example neonates. Where sufficient data for one or more of the paediatric subsets are already available, duplication of studies should be avoided and therefore unnecessary studies will not be considered as significant.	