II

(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS AND BODIES

COMMISSION

Communication from the 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

(2008/C 243/01)

1. 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 fully complying with the requirements for studies in children. 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 a framework to manage the operation of the paediatric regulation including the paediatric committee within the European Medicines Agency (hereinafter 'the Agency').

Pursuant to Article 10 of the paediatric regulation, 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 lays down the arrangements for the operation of the compliance check referred to in Articles 23 and 28(3) of the paediatric regulation ([2]). Finally, pursuant to Article 45(4) of the paediatric regulation the guideline provides the assessment criteria for the significance of studies started before and completed after the entry into force of the paediatric regulation ([3]).

Definitions relevant to this guideline are provided in Directive 2001/83/EC, Directive 2001/20/EC, Regulation (EC) No 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;

([1]) OJ L 378, 27.12.2006, p. 1.

([2]) Article 10 of the paediatric regulation states: 'In consultation with the Member States, the Agency and other interested parties, the Commission shall draw up the detailed arrangements concerning the format and content which applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals must follow in order to be considered valid and concerning the operation of the compliance check referred to in Articles 23 and 28(3)'.

([3]) Article 45(4) of the paediatric regulation states: 'In consultation with the Agency, the Commission shall draw up guidelines to establish assessment criteria for the significance of studies for the purposes of applying paragraph 3'.

(c) **proposed therapeutic indication**: the therapeutic indication in adults and/or paediatric populations as proposed in the paediatric investigation plan 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 includes studies, trials, data and pharmaceutical development proposed to generate new scientific information aiming at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population including the development of age appropriate formulation in all subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan.

2. SECTION 1: FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS AND DEFERRALS

2.1. General principles and format

It is acknowledged that the amount of information available relevant to applications for agreement or modification of a paediatric investigation plan and requests for waivers and deferrals will differ substantially depending on whether a medicinal product is in early clinical development or already has a marketing authorisation and is being investigated for new or extended uses. Because the same format for applications for paediatric investigation plans, waivers and deferrals should be used whatever the stage of product development, it will not always be possible to provide comprehensive information in some Sections of the application. In this situation an absence of data or information should be indicated in the relevant Section. However, when available, 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. This includes details 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.

The same application format should be used whether requesting agreement to a paediatric investigation plan, a waiver, a deferral or a combination thereof. Different parts of the application are provided to fulfil the different types of request, as follows:

— Part A: Administrative and product information,

— Part B: Overall development of the medicinal product including information on the conditions,

— Part C: Applications for product specific waivers,

— Part D: Paediatric investigation plan,

— Part E: Applications for deferrals,

— Part F: Annexes.

Because the same application format is used some Sections of the application will not be applicable to specific types of application.

One single application should cover all subsets of the paediatric population as required by Article 7(2) of the paediatric regulation with either a waiver or a paediatric investigation plan (with or without a deferral). Applications for products falling within the scope of Article 8 of the paediatric regulation should cover the existing and the new indications, pharmaceutical forms and routes of administration. In this case one comprehensive paediatric investigation plan should be included in the application. Similarly, when it is intended to develop several indications simultaneously, only one comprehensive paediatric investigation plan should be included in the application.

The paediatric population is defined in Article 2 of the paediatric regulation as 'that part of the population aged between birth and 18 years'. This is understood to mean up to but not including 18 years. The paediatric population encompasses several subsets defined for example in international guidelines ([1]): 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, when it is considered to be more appropriate, to use different subsets this may be acceptable but the choice of subsets should be explained and justified.

When drafting paediatric investigation plans for paediatric use marketing authorisations, those drafting are encouraged to consider whether there may be a therapeutic need for the medicinal product in each paediatric subset.

To facilitate the practical submission of applications the European Medicines Agency (EMEA) has made available online forms that follow the structure of this guideline (available at: http://www.emea.europa.eu/htms/human/paediatrics/pips.htm).

2.2. 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 Part A of the application. However, all Sections of Part A should be completed and where information is not available, this should be stated.

2.2.1. *A.1: Name or corporate name and address of the applicant and contact person*

The name and address of the applicant for the Paediatric Investigation Plan, Waiver or Deferral should be provided. The applicant may be any legal or natural person or a company established within the European Economic Area. 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.

([1]) ICH Guideline E11 available at: www.ich.org

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.

It should be stated whether or not the applicant qualifies under Commission Regulation (EC) No 2049/2005 [1] as a micro, small or medium sized enterprise.

2.2.2. *A.2: 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 yet 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 European 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 cannot be used as the sole identifier of the active substance.

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.

2.2.3. *A.3: Type of product*

The type of product for which the application is for (e.g. a chemical entity, a biological product, a vaccine, a gene therapy product, somatic cell therapy medicinal product etc) should be specified. In addition, where possible t the pharmacological target and mechanism of action should be specified. Where a pharmacotherapeutic group and Anatomical Therapeutic Chemical (ATC) code have been assigned, these should be included. 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).

2.2.4. *A.4: Details of the medicinal product*

The precise information to be provided will depend on whether the application relates to:

1. Article 7 of the paediatric regulation, a medicinal product not yet authorised in the Community (EEA);
2. Article 8 of the paediatric regulation, a medicinal product authorised in the Community (EEA) and covered by a supplementary protection certificate or a patent which qualifies for the grating of the supplementary protection certificate; or
3. Article 30 of the paediatric regulation, a product being developed for a paediatric use marketing authorisation.

For medicinal products that will be caught by Article 7 or 8 of the paediatric regulation information on all different formulations under development irrespective of future use in the paediatric population should be provided. In addition, for applications relating to products that will be caught by Article 8, information on authorised strength(s), pharmaceutical form/route(s) of administration should be provided in Section A.6. For products being developed for paediatric use marketing authorisations information on the proposed strength(s), pharmaceutical form(s), and route(s) of administration should be provided.

2.2.5. *A.5: Regulatory information on clinical trials related to the condition and to the development in the paediatric population*

In this Section regulatory information on clinical trials related to the condition and to the development in the paediatric population should be provided in a tabular format. For clinical trials conducted inside the EEA, please provide a table of clinical trials relevant to the condition in children, and in adults if relevant to the development in the paediatric population. For clinical trials conducted outside the EEA, please provide a table of clinical trials performed in children only and relevant to the condition.

The information provided, whether relating to studies conducted in the EEA or outside the EEA should include a statement on whether each clinical trial was conducted according to Good Clinical Practice (GCP).

2.2.6. *A.6: Marketing authorisation status of the medicinal product*

Information of the marketing authorisation status of the medicinal product should be provided in a tabular format.

For medicinal products not yet authorised which will subsequently be caught by the requirements of Article 7 of the paediatric regulation, the marketing authorisation status outside the EEA should be provided.

For medicinal products on the market and covered by a supplementary protection certificate or a patent which qualifies for the grating of the supplementary protection certificate, which will subsequently be caught by Article 8 of the paediatric regulation, the marketing authorisation status in the EEA should be provided and regarding authorisation status outside the EEA only information on authorisations in children should be included.

[1] OJ L 329, 16.12.2005, p. 4.

For products being developed for paediatric use marketing authorisations information should be provided on authorised medicinal products in the EEA containing the same active substance.

Details of any regulatory action to restrict for safety reasons the use of the medicinal product outside the EEA should be provided. This will include any product withdrawal, restriction of indication or new contraindication for the medicinal product.

2.2.7. *A.7: Advice from any regulatory authority relevant to the development in the paediatric population*

The paediatric committee should be provided with any decisions, opinions or advice (including scientific advice) given by competent authorities, including those of third countries, on the paediatric development of the medicinal product. This should include any written request for paediatric information issues by a regulatory body. A copy of any relevant documents should be included in Part A.10 of the application.

2.2.8. *A.8: Orphan drug status in the EEA*

It should be clear whether the medicinal product has been designated an orphan medicinal product by the European Commission's decision. For orphan designated products the number in the Community Register of Orphan Medicinal Products should be provided. If orphan designation is being sought this should be indicated and for pending applications the EMEA Orphan Designation Procedure Number should be provided.

2.2.9. *A.9: Planned application for marketing authorisation/line extensions/variation*

The planned submission date for the marketing authorisation or variation application, as appropriate, should be provided together with an indication of whether the application can be expected via the centralised or mutual recognition/decentralised route. For medicinal products not yet authorised which will subsequently be caught by the requirements of Article 7 of the paediatric regulation, the date of completion of adult pharmacokinetic studies should be provided.

2.2.10. *A.10: Annexed documentation where appropriate*

The following documents, if available, should be annexed in this Section:

— a letter of authorisation for the person authorised to communicate on behalf of the Applicant,

— a copy of any Scientific Advice given by the EMEA Committee on Human Medicinal products (CHMP),

— a copy of any Scientific Advice given by any EEA National competent authorities,

— a copy of United States Food and Drug Administration (FDA) written request and/or of any advice/opinion/decision relating to paediatric information given by a regulatory agency outside the EEA,

— a copy of any Commission Decision on Orphan Designation,

— a copy of any previous EMEA decision on a Paediatric Investigation Plans or a negative opinion of the paediatric committee on such plans,

— a copy of a representative Summary of Product Characteristics recently granted in the EEA.

2.2.11. *A.11: Table of translations of the EMEA decision*

If the EMEA Decision is requested in an official EU language other than English then the name of the active substance, the condition, the pharmaceutical form and route of administration should be provided in that language.

2.3. **Part B: Overall development of the medicinal product including information on the 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.

Where the medicinal product is developed for use in children only some of the information requested in Part B may not be available and this should be clearly indicated.

2.3.1. *B.1: Discussion on similarities and differences of the disease/condition between populations*

For each disease or condition already the subject of an authorised indication, 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 application should state whether they occur in the paediatric population. A description of the diseases or conditions should be provided, 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, epidemiology, clinical manifestations and prognosis, and pathophysiology in the paediatric subsets. This may be based on published references, or textbooks.

Information on the earliest age of onset of the diseases/conditions or the age range concerned should be provided, as well as, if possible, incidence and/or prevalence in the Community, especially if it is intended to apply for a product specific waiver covering specific paediatric subsets. This information can be based on published references if available.

A brief description of the pharmacological properties and mechanism of action should be provided. Any anticipated differences and similarities of the safety and efficacy profile (known or expected) of the product should be described focussing on a comparison:

— between the adult and the paediatric population,

— between the different paediatric subsets.

2.3.2. *B.2: Current methods of diagnosis, prevention or treatment in paediatric 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 diagnosis, prevention and treatment interventions available in the Community should be identified, making reference to scientific and medical literature or other relevant information. This should include unauthorised treatment methods if they represent the standard of care, for example, if they are mentioned in internationally recognised treatment guidelines. This should be presented in tabulated format for ease of reference.

Of the available treatments identified, in the case of authorised medicinal products, when the information is accessible the list should include those authorised by the national authorities in at least one Member State and those authorised in the framework of centralised procedure in accordance with Regulation (EC) No 726/2004. This can be presented as an overview table. In order that the paediatric committee has an overview over the existing diagnosis, prevention or treatment of the condition, 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, should be indicated. In this context, 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.

If methods for diagnosis, prevention or treatment of the condition in question have been included in the inventory of therapeutic needs established pursuant to Article 43 of the paediatric regulation then this information should be highlighted.

2.3.3. *B.3: Significant therapeutic benefit and/or fulfilment of therapeutic need*

On the basis of Article 6(2) ([1]), 11(1)(c) ([2]) and 17(1) ([3]) of the paediatric regulation, whether the use of the medicinal product either through use as an authorised product or through the conduct of clinical trials in children is expected to be of significant therapeutic benefit to children and/or fulfil a therapeutic need in children will be assessed by the paediatric committee and this assessment will be pivotal in determining 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 application should include a comparison of the medicinal product which is the subject of the application with the current methods of diagnosis, prevention or treatment of the diseases/conditions that are the subject of the intended indications in children, referred to in Section B.2.

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 one or more of the following:

(a) 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;

(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 improvement in safety in relation to either adverse reactions or potential medication errors in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned;

(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;

([1]) Article 6(2) of the paediatric regulation provides that 'When carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population'.

([2]) Article 11(1)(c) provides a ground for granting a waiver 'that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients'.

([3]) Article 17(1) provides that the opinion on a paediatric investigation plan '… as to whether or not the expected therapeutic benefits justify the studies proposed'.

(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) different mechanism of action with potential advantage for the paediatric population(s) in terms of improved efficacy or safety;

(h) existing treatments are not satisfactory and alternative methods with an improved expected benefit-risk balance are needed;

(i) expected improvement in the quality of life of the child.

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 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 application should explore these assumptions based on reasoned arguments and relevant literature. If significant therapeutic benefit cannot be justified at that early stage of the development of a medicinal product, the paediatric committee will consider a waiver or deferral, as appropriate.

If the therapeutic need is included in the inventory of therapeutic needs established by the paediatric committee pursuant to Article 43 of the paediatric regulation, the application should refer to the inventory ([1]). 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.

2.4. **Part C: Applications product specific waivers**

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 the second subparagraph of Article 8 of the paediatric regulation, the route of administration and pharmaceutical form should be specified.

2.4.1. *C.1: Class waiver*

No product specific waiver may be necessary to satisfy the requirements of Article 7 and 8 of the paediatric regulation if the therapeutic indication and the subset of the paediatric population are already covered by a class waiver ([2]). 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.

Companies are encouraged to inform the paediatric committee when new information becomes available which suggests that a class or product specific waiver should be reviewed in accordance with Article 14(2) of paediatric regulation.

2.4.2. *C.2: Grounds for a product specific waiver*

The grounds for a waiver are defined in Article 11 of the paediatric regulation.

2.4.2.1. C.2.1: The specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population

Article 11(1)(a) of the paediatric regulation provides a specific ground for granting a waiver as 'that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population'. On this basis a request for a waiver may be based on evidence of lack of efficacy in the paediatric population(s). The application 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 evidence should be submitted (cross-referring to the information in Part B) describing 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 justification for a waiver based on evidence that the product is unsafe may differ depending on the existing experience with the product as the full characterisation of the safety profile of a medicinal product usually only occurs after a product has been placed on the market. Justification for a waiver on these grounds may include the pharmacological properties of the product or class of product, results from non-clinical studies, clinical trials or post-marketing data. The applicant should specify whether a specific safety issue is known or suspected.

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.

([1]) Article 43 of the paediatric regulation provides that the inventory be published by the EMEA by 26 January 2010 at the latest.

([2]) Class waivers will be made public on the EMEA website in accordance with Article 12 and 25(7) of the paediatric regulation.

2.4.2.2. C.2.2: The disease or condition for which the specific medicinal product or class is intended occurs only in adult populations

Article 11(1)(b) of the paediatric regulation provides a specific ground for granting a waiver as 'the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations'. On this basis justification may be based on detailed justification 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.

2.4.2.3. C.2.3: The specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients

Article 11(1)(c) of the paediatric regulation provides a specific ground for granting a waiver as 'that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients'. On this basis justification for a waiver may be based on a lack of significant therapeutic benefit.

Where a waiver based on a lack of significant therapeutic benefit is requested, particularly 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.

2.5. **Part D: Paediatric investigation plan**

2.5.1. *D.1: Overall strategy proposed for the paediatric development*

Whereas Part B relates to the overall development of the medicinal product including development work relating to the adult population as well as information on the medical conditions, Part D should focus specifically on the development of the medicinal product for the paediatric population.

2.5.1.1. D.1.1: Paediatric investigation plan indication

The proposed indication(s) should be stated 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.

2.5.1.2. D.1.2: Selected age group(s)

The paediatric investigation plan should cover all subsets of the paediatric population 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. Unless otherwise justified the application should 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.

2.5.1.3. D.1.3: Information on the quality, non-clinical and clinical data

The application should outline the development of the medicinal product, including the pharmaceutical development 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 but should be made available upon request. The application should take into account any existing scientific guidance/advice and justify any deviation for the development.

In addition the application 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.

2.5.2. *D.2: Strategy in relation to quality aspects*

This Section should address the chemical, pharmaceutical, biological and biopharmaceutical aspects related to the administration of the product to the relevant paediatric subsets. The discussion will take into account the pharmaceutical development of the product and, in addition to the normal requirements for the pharmaceutical development, should address critical issues such as:

— need for specific formulations or dosage forms in relation to the chosen age group(s) and discussion of the benefit of the chosen formulation or dosage form,

— qualitative and quantitative composition if available,

— availability/timeframe for the development of an age appropriate dosage form,

— potential issues in relation to the formulation (e.g. 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, anticipated container closure systems etc.),

— the acceptability of the formulation (including palatability) — i.e. its 'fitness for purpose', justified from a physico-chemical, biological and physiological point of view. In case it is not possible to develop a formulation which is relevant and acceptable for paediatric use on an industrial scale, the application should state how it intends to facilitate the extemporaneous magistral preparation of an individual ready-for-use paediatric formulation.

The addition of a paediatric indication may result in the need for a new pharmaceutical form or new strength, for example a liquid rather than a tablet, or a tablet of a new dose strength, because the existing pharmaceutical form or strength may be unsuitable for use in all or part of the relevant paediatric populations. This means that the suitability of existing pharmaceutical forms/strengths should always be discussed in the paediatric investigation plan. Consideration should be given to any ethnic or cultural difference in route of administration, acceptable dosage forms and excipients.

2.5.3. *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 classical non-clinical development or to 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 should be considered, taking into consideration existing scientific guidance:

— pharmacology:

  — the need for proof of concept for the use in paediatric populations, for example using non-clinical *in vitro* and/or *in vivo* models,

  — 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),

  — the need for safety pharmacology (studies using non-clinical *in vitro* and/or *in vivo* models to investigate specific function of the physiological system),

— pharmacokinetics:

  — the need for specific studies justifying the most relevant species for potential juvenile animal studies,

— toxicology:

  — the need for specific toxicity studies including toxicokinetics in juvenile animals,

  — the need for toxicity studies to address specific endpoints e.g. neurotoxicity, immunotoxicity or nephrotoxicity at a particular developmental phase,

  — the need for additional local tolerance studies e.g. for topical application dosage forms.

2.5.4. *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 D.5). Details of the formulation to be used should be given and plans for bridging between the different formulations should be addressed.

In its strategy, the application 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 explained.

The application should address the rationale to support dosing, formulation(s) and route(s) 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 application should justify that the subjects intended for inclusion in the trials are representative of the population in which the product will be used. Trials should be performed in the least vulnerable groups whenever possible (i.e in adults rather than in children, in older children rather than younger ones). If results cannot be extrapolated to younger groups, this should be justified.

The following aspects should be considered, where relevant:

— pharmacodynamic studies:

  — pharmacodynamic differences between adult and paediatric populations (e.g. influence of maturation of receptors and/or systems),

  — extrapolation from different populations (from adult and/or for older paediatric age groups) including, where appropriate, the use of pharmacodynamic modelling,

  — the need for specific studies in certain age groups,

  — discussion of any biomarkers for pharmacokinetics/pharmacodynamics,

  — use of the pharmacodynamic approach, particularly when pharmacokinetics cannot be measured,

— pharmacokinetic studies:

  — the possibility to extrapolate efficacy and safety from adult or older age group based on pharmacokinetics,

  — the possibility to use sparse pharmacokinetic sampling,

  — the use of pharmacokinetics/pharmacodynamics studies to bridge efficacy and safety in adults or older age group,

  — the possibility to support pharmacokinetics in certain age groups using information, or to extrapolate pharmacokinetics from other populations,

  — discussion of age groups where more extensive studies are needed e.g. due to expected high kinetic variability,

  — use of population pharmacokinetics,

  — the possibility to extrapolate interactions, organ function impairment and effects of pharmacogenetics, and the need for specific studies,

— efficacy and safety studies:

  — discussion of the need for specific dose-finding studies,

  — discussion of issues of relevance across the proposed studies, such as the use of placebo or active control, 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,

  — if there is an approved EU-risk management plan for a product which is already authorised for use in the adult population, any risk minimisation activities appropriate for the paediatric population should be taken into account in developing the paediatric investigation plan. If there are pharmacovigilance studies in the EU-risk management plan which involve a paediatric population, they should also be cross-referred to in the paediatric investigation plan.

The need for long-term safety studies in the paediatric population should always be discussed in the paediatric investigation plan. If such studies are considered necessary, the details should also be provided in the EU-risk management plan, or its update, submitted at the time of the application for marketing authorisation, but in principle would not form part of the agreed paediatric investigation plan.

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 or quantity of blood sampling compared to blood volume) should be discussed.

2.5.5. *D.5: Measures for the development in paediatric population*

It should be noted that this Section, together with Section D.5.1 and Part E is critical to the development of the paediatric committee opinion and subsequently the EMEA Decision on the paediatric investigation plan.

2.5.5.1. D.5.1: Overall Summary Table of all planned and/or ongoing non-clinical and clinical studies

While it is acknowledged that the proposed timing of measures in a paediatric investigation plan will be estimates, particularly for medicinal products in early development, it should be noted that this Section is critical to the development of the paediatric committee opinion and subsequently the EMEA Decision on the paediatric investigation plan.

A table should be included providing an overview of all measures planned and/or ongoing by the application in the paediatric population.

This table should present the timelines of the measures 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 marketing authorisation applications which fall under Articles 7, 8 and 30 of the paediatric regulation should be provided and the timing of the measures in the paediatric investigation plan should refer to these applications. The application should propose timelines for initiation and completion of each measure, including specific dates. The application 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.

2.5.5.2. D.5.2: Outline of each of the planned and/or ongoing 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. In any case, the full range of pharmaceutical development studies to confirm process and product uniformity and stability would be required at the stage of application for Marketing Authorisation. Agency guidelines in this area are available should be consulted to decide which studies could be relevant within the strategy proposed in Section D.2.

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 particularly if food is used to facilitate administration of the dosage form,

— compatibility with administration systems e.g. medical devices,

— taste-masking or palatability.

2.5.5.3. D.5.3: Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies

Sufficient information to adequately describe the study should be detailed as relevant, for example:

— type of study,

— objective(s),

— test system/species,

— method of administration,

— duration of dosing.

2.5.5.4. D.5.4: Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies or trials

The following should be detailed as relevant according to the study and as appropriate to the phase of product development:

— type of study,

— study design,

— type of control (placebo or active control with dose to be used) and justification,

— 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 including the duration of post-treatment observation,

— 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).

2.6. **Part E: Applications deferrals**

Pursuant to Article 20(1) of the paediatric regulation, at the same time as the paediatric investigation plan is submitted, a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan.

With reference to the timelines stated in Section D.5.1, any request for deferrals of the start or the completion of measures should make clear to which indication, route of administration and pharmaceutical form the deferred timeline relates to. When requesting a deferral, the application should specify the age group to which it applies. For timelines, specific months and years should be given, and timelines may also be expressed in relation to the development in adults.

Requests for deferrals should be justified on scientific and technical grounds or on grounds related to public health and the paediatric regulation requires that a deferral be granted when:

— it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population,

— studies in the paediatric population will take longer to conduct than studies in adults.

Other examples of scientific and technical justification for a deferral may include when additional non-clinical data are considered necessary or when major quality problems currently prevent development of the relevant formulation(s).

2.7. **Part F: Annexes**

The annexes to the application should include the following documents, if available:

— references (i.e. published literature),

— investigator brochure,

— latest approved EU-risk management plan for a product already authorised.

2.8. **Modification of an agreed paediatric investigation plan**

Paediatric investigation plans should be submitted early during product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing authorisation applications are submitted. Such early submission of a paediatric investigation plan will ensure early dialogue between the applicant and the Paediatric Committee. As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, provision is made in Article 22 of the paediatric regulation for modifying an agreed plan where necessary ([1]).

([1]) Article 22 of the paediatric regulation states 'If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee. […]'.

Submission of an application to propose changes to the paediatric investigation plan, or a request for deferral or a waiver will be particularly important if the new information may have an impact on nature or timing of one of the key measures explicitly highlighted in the EMEA decision on the paediatric investigation plan.

In the case of an application for modification of a paediatric investigation plan, the content of the application should follow the same structure as for an initial paediatric investigation plan request for agreement only relevant Sections supporting the change should be completed. The application should provide the reference of the previous paediatric investigation plan decision.

3. 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 (provided for in Article 30 of the paediatric regulation) are the subject of compliance checks by the competent authorities. These compliance checks are described in Articles 23 and 24 of the paediatric regulation. Article 23 provides for the timing of the compliance check, for the possibility of an opinion of the paediatric committee on compliance and clarifies when and by whom this opinion can be requested. Pursuant to Article 23(3) second subparagraph, Member States shall take account of the opinion of the paediatric committee. Article 23 does not provide for re-examination of the paediatric committee opinion on compliance.

One compliance standard is checked by the competent authorities in a two step process:

— step one, pursuant to Article 23, compliance is checked at validation for applications under Article 7, 8 and 30 of the paediatric regulation. Non-compliance of these applications will lead to non-validation of the application,

— step two, pursuant to Article 24 of the paediatric regulation, detection of non-compliance during the scientific assessment of a valid application will result in non-inclusion in the marketing authorisation of the compliance statement referred to in Article 28(3) and the product shall not be eligible for the rewards and incentives provides for in Articles 36, 37 and 38 of the paediatric regulation.

The determination of compliance in both steps described above will 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.

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. Any modification of the paediatric investigation plan should have taken place before the submission of the marketing authorisation application.

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.

Compliance can be judged only if full study reports are provided. To facilitate the work of competent authorities and, when appropriate, the paediatric committee in reaching an opinion on compliance, presentation of a compliance report at the time of the submission of the application is encouraged. If the paediatric committee opinion is sought by the applicant for a marketing authorisation or variation 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, 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 marketing authorisation or variation applicant's position on compliance with the key elements, and, when submitted with the marketing authorisation application, a cross-reference for each key element of the paediatric investigation plan to the location within the relevant module in that marketing authorisation application. In case of modifications to a paediatric investigation plan, the table should be based on the latest decision of the Agency.

It should be noted that:

— the relevant Competent Authority or the Agency will perform a detailed check of each key element of the EMEA decision on 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 marketing authorisation or variation applicant will need to comply with each item,

— if the EMEA Decision on the paediatric investigation plan includes 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.

Where a paediatric investigation plan contains no study completed before the entry into force of Regulation (EC) No 1901/2006, the statement of compliance referred to in Article 28(3) of the paediatric regulation will be the following: 'The development of this product has complied with all measures in the agreed paediatric investigation plan [reference number]. For the purpose of the application of Article 45(3) of Regulation (EC) No 1901/2006, all studies in the agreed paediatric investigation plan [reference number] were completed after the entry into force of that Regualtion'.

Where a paediatric investigation plan contains some studies completed before the entry into force of Regulation (EC) No 1901/2006,the statement of compliance referred to in Article 28(3) of the paediatric regulation will be the following: 'The development of this product has complied with all measures in the agreed paediatric investigation plan [reference number]. For the purpose of the application of Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation'.

4. SECTION 3: ASSESSMENT CRITERIA FOR THE SIGNIFICANCE OF STUDIES STARTED BEFORE AND COMPLETED AFTER THE ENTRY INTO FORCE OF THE PAEDIATRIC REGULATION

4.1. Background

For studies started before the entry into force of the paediatric regulation ([1]) to be the basis of granting the rewards and incentives 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.

4.2. Assessment criteria

In general, the significance of studies is determined by the clinical relevance of data generated for the paediatric population rather than by the number 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 and incentives 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 generally 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 (this includes studies on growth and development);
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;
5. PK/PD studies: well founded pharmacokinetic/pharmacodynamic clinical studies if they are likely to 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.

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, unless a waiver has been granted. However, on a case by case basis, studies conducted in a single subset of the paediatric population could 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. 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.

([1]) The 26 January 2007.