EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products — authorisations, EMA

COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR PAEDIATRIC INVESTIGATION PLANS

(ARTICLE 10 OF REGULATION (EC) NO 1901/2006)

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Deadline for public consultation: 18 December 2013

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary draft. The suggestions contained in this document do not prejudge the form and content of any future proposal made by the Commission.

Contact:

Responses should be sent preferably by email to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to the Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels.
The subject of the letter/email should refer to 'PCPIP/13/01 — Public consultation on PIP guideline'.

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I. ABOUT THE CONSULTATION

A. INTRODUCTION

In accordance with Article 10 of the Paediatric Regulation (Regulation (EC) No 1901/2006), in consultation with the Member States, the Agency and other interested parties, the Commission has to draw up detailed arrangements concerning the format and content which applications for agreement on 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.

In September 2008 the Commission published the relevant guideline[1]. It has been in use for the last five years. In its recent report on the Paediatric Regulation[2], the Commission undertook to review the guideline in order to take into account the experience gained, including the considerable number of requests to modify paediatric investigation plans.

The Commission therefore requested the European Medicines Agency and its Paediatric Committee to suggest amendments to the current guideline which they considered appropriate. This document is based on but not identical to those suggestions, for which the Commission is grateful. At the same time this means, however, that the present document does not necessarily represent the Commission's position on all the issues. Instead, it is a tool to explore the views of interested parties on a preliminary proposal.

In discussing suggestions for a revised version of the guideline, the Agency took the following approach:

- The Agency considered that the guideline could benefit from some improvement and adaptation to current implementation, but that its general structure and content did not require substantial changes.
- It deleted unnecessary or repetitive details, and simplified the language and style used where possible.
- It added new concepts: definitions of key elements and extrapolation, and the request for an 'Application Summary' to be attached to the application's scientific documents (parts B-E).
- It updated other definitions, such as that of condition.
- It clarified the difference between condition and indication and the respective roles.
- It mentioned explicitly rather than implicitly the possibility of having multiple paediatric investigation plans for the same product.

The purpose of this concept paper is to support the Commission in further exploring which parts of the current guideline should be updated. For the sake of clarity changes are, however, not tracked in the document.

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1 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, OJ C 243, 24.9.2008, p. 1.

2 Better medicines for children — From concept to reality, COM(2013) 443 final.

The concept paper is now being put out for public consultation. Replies or comments should be submitted by 18 December 2013 at the latest.

B. CONSULTATION TOPICS

The consultation text is supplemented by a number of specific consultation items in boxed text raising questions on which the Commission seeks input from interested parties.

Respondents are invited to address those points specifically. Comments on any other part or aspect are also welcome.

C. HOW CAN I CONTRIBUTE?

Stakeholders are invited to comment on this concept paper, and on the boxed text in particular, by 18 December 2013 at the latest. Responses should be sent (preferably by email) to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to the Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels. The subject line of the letter or email should refer to 'PCPIP/13/01 — Public consultation on PIP guideline'.

When you submit your comments and responses, please state your affiliation or whether you submit your comments as a private individual. If you represent an association, please indicate clearly what type of association it is (patients, health professionals, manufacturers, marketing authorisation holders, etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

An acknowledgement of receipt will be issued for each contribution received.

The contributions received and the identity of the contributors will be made publicly available on the 'Public health' website[3], unless the contributor objects to the publication of his or her personal data on the grounds that it would harm his or her legitimate interests. In that case the contribution may be published in anonymous form. Otherwise the contribution will not be published, nor will its content normally be taken into account. For more information on the processing of your personal data in the context of this consultation, you should read the specific Privacy Statement available on the Public health website.

Professional organisations are invited to register in the EU's Register of Interest Representatives (http://europa.eu/transparency-register/index_en.htm) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structure of interest representatives.

D. WHAT WILL HAPPEN NEXT?

All contributions will be carefully analysed. Any subsequent Commission proposal will build on the consultation.

[3] http://ec.europa.eu/health/human-use/index_en.htm.

II. THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

1. INTRODUCTION

In accordance with Article 10 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use[4] (hereinafter 'the Paediatric Regulation'), this guideline sets out the detailed arrangements concerning the format and content of applications for agreement on 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 Article 23 and Article 28(3) of the Paediatric Regulation. Finally, pursuant to Article 45(4) of the Paediatric Regulation, the guideline spells out the criteria for assessing the significance of studies started before and completed after the entry into force of the Paediatric Regulation. This guideline replaces the previous version from 2008[5].

For the purpose of this guideline the following definitions should apply:

(a) condition: any deviation 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; a condition may also be represented by a specific use during specialised therapeutic or diagnostic procedures (e.g. use in bone marrow transplantation, contraception). As the medicines development is different, diagnosis, prevention and treatment of a condition will be considered as separate;

(b) paediatric investigation plan indication: proposed indication in the paediatric population for the purpose of a paediatric investigation plan, and at the time of submission of the paediatric investigation plan, within a specific condition;

(c) proposed indication: the indication for use in adults (and/or in specified paediatric subsets), as submitted by an applicant. In case of a completed or ongoing adult development, this is the starting point to identify the condition for potential paediatric use;

(d) measures: any studies, trials, data and pharmaceutical form and formulation development proposed to generate new scientific information, with a view to ensuring that in accordance with Article 15(2) of the Paediatric Regulation the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

(e) key elements: each measure in a paediatric investigation plan may contain one or more specific key elements, as specified in the annex to this guideline;

(f) extrapolation: extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related

[4] Regulation (EC) No 1901/2006 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, OJ L 378, 27.12.2006, p. 1.

[5] OJ C 243, 24.9.2008, p. 1.

conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, condition or medicinal product.

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

2.1. General principles and format

The particulars and documents accompanying an application for agreement on or modification of a paediatric investigation plan or a request for waiver or deferral should be presented in accordance with this guideline. The application should consist of the following sections:

- Part A: Administrative and product information
- Part B: Overall development of the medicinal product, including information on the conditions
- Part C: Application for a product-specific waiver
- Part D: Paediatric investigation plan
- Part E: Request for deferral
- Part F: Annexes.

The same application format should be used, whether requesting agreement on a paediatric investigation plan, a waiver, a deferral, or a combination thereof. Sections and/or subsections which are not relevant for the specific application can be left empty.

The application should be based on all available information relevant to the evaluation, whether favourable or unfavourable to the product and its development. 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.

It is acknowledged that the amount of available information relevant to applications 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.

An application falling under the requirements of Article 7 or 8 of the Paediatric Regulation should cover all subsets of the paediatric population with a condition unless there are grounds for a waiver. 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[6]: the pre-term and term neonate from 0 to 27 days, the infant or toddler 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 more appropriate to use different subsets (e.g. based on sex or pubertal development) this may be acceptable but the choice of subsets should be explained and justified.

A paediatric investigation plan for a paediatric use marketing authorisation may be limited to certain paediatric subsets.

All conditions that will be part of a single regulatory submission should be covered by the application. Applications for products falling within the scope of Article 8 of the Paediatric Regulation should cover both 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.

The application may include a request for a product-specific waiver either in all subsets of the given condition, or in some of them. Additionally, a paediatric investigation plan may include a request for deferring some or all of the measures, in some or all subsets.

The European Medicines Agency (hereinafter 'the Agency') may publish templates or online forms that follow the structure of this guideline. Procedural advice is available on the Agency's website (www.ema.europa.eu). Prospective applicants may also request presubmission meetings, to facilitate successive validation and assessment of the application.

2.2. Part A: Administrative and product information

All sections of Part A should be completed; where information is not available, this should be stated.

2.2.1. Name or corporate name and address of the applicant and contact person

The name and address of the applicant should be provided, together with the person authorised to communicate with the Agency on behalf of the applicant.

In view of the fact that Agency decisions will be made public, the applicant is encouraged to provide a contact point (telephone and email) for enquiries from interested parties that the Agency will then make public with its decisions. Personal email addresses should be avoided.

Where the applicant qualifies as a micro, small or medium-sized enterprise within the meaning of Commission Recommendation 2003/361/EC[7] this should be stated.

2.2.2. 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 no recommended INN exists, the European Pharmacopoeia name should be provided or, if the substance is not in the European Pharmacopoeia, the usual common name should be provided. In the absence of a common name, the exact scientific designation should be given. Substances not having an

[6] ICH Guideline E11 available at: www.ich.org.
[7] OJ L 124, 20.5.2003, p. 36.

exact scientific designation should be described by a statement of how and from what they were prepared, supplemented where appropriate by any relevant details.

In addition to the common name or scientific designation, the applicant may also submit the company or laboratory code.

Considering the timing for submission of applications, only preliminary names of the active substance might be provided.

The full scientific designation may be considered commercially confidential. In this case, the applicant can propose an abridged name in the form of 'a derivative of parent compound [X]', to be used in any published information or decision concerning the application.

2.2.3. Type of product

The type of product for which the application is made (e.g. a chemical entity, a biological product, a vaccine, a gene therapy product, a somatic cell therapy medicinal product) should be specified. In addition, where possible 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 European Union, or for authorised products where a new indication is proposed for development, the condition, 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 named by the applicant, following an agreed classification system, such as MedDRA.

2.2.4. Details of the medicinal product

Information on all different pharmaceutical forms and formulations under development, irrespective of future use in the paediatric population, should be provided. For products being developed for paediatric use marketing authorisations, information on the proposed strength, pharmaceutical form and route of administration should be provided.

2.2.5. Marketing authorisation status of the medicinal product

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

For medicinal products authorised in the EU the marketing authorisation status including information on all authorised indications, strengths, pharmaceutical forms and routes of administration should be provided and, regarding the authorisation status outside the EU, only information on authorisations in children should be included.

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

For medicinal products not yet authorised in the EU the marketing authorisation status outside the EU should be provided.

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

2.2.6. Advice from any regulatory authority relevant to the development in the paediatric population

The Agency should be provided with any decisions, opinions or advice (including scientific advice) given by competent authorities, including those of non-EU countries, on the paediatric development of the medicinal product. This should include any written request for paediatric information issued by a regulatory body. A copy of any relevant documents should be annexed to the application.

2.2.7. Orphan medicine status in the EU

For orphan designated products, the number in the European Union Register of Orphan Medicinal Products should be provided. If orphan designation is being sought this should be indicated, and for pending applications the EMA Orphan Designation Procedure Number should be provided.

2.2.8. Planned application for marketing authorisation/line extensions/variation

The planned submission date for the marketing authorisation (or variation/extension application, as appropriate) should be provided, together with an indication of whether the application is planned to be submitted via the centralised procedure or the procedures provided for by Directive 2001/83/EC[8].

For medicinal products not yet authorised, which will fall under the requirements of Article 7 of the Paediatric Regulation, the date of completion of adult pharmacokinetic studies should be provided. When an application is submitted later than upon completion of the human pharmacokinetic studies in adults, a justification should be provided in this section.

2.2.9. Application summary

Applications for paediatric investigation plans or waivers should contain an application summary, not longer than 750 words, written in accordance with a template made available by the Agency.

2.2.10. Table of translations of the Agency decision

If the Agency 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 existing indication and proposed condition/indication, and each subset of the paediatric population, how the requirements of Articles 7 and 8 will be met.

Applicants should provide a general justification of the application submitted, including the methodology chosen to identify potential conditions of paediatric need.

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[8] OJ L 311, 28.11.2001, p. 67.

This part should also include a description of the condition 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. For common, well-described paediatric conditions, reference can be made to paediatrics textbooks without submitting detailed information. Furthermore, detailed information on the condition in adults need not be provided.

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. Discussion on similarities and differences in the condition between populations, and pharmacological rationale

Similarities and differences in the condition. The application should briefly discuss any potential differences or similarities in the condition between the adult and the paediatric populations and/or between the different paediatric subsets.

This should be discussed with a view to extrapolation of efficacy and/or pharmacokinetics, between adults and children, and the various paediatric subsets. Differences in aetiology, severity, symptoms, evolution, prognosis and response to therapy should be addressed where applicable.

Pharmacological rationale and explanation. A sufficiently detailed description of the pharmacological properties and of the known or suspected mechanism of action should be provided. The potential paediatric use of the product, based on the characteristics of the product, should be discussed by the applicant in the therapeutic area of the proposed indication in adults, and particularly in the relevant conditions. In addition, data/assumptions and a discussion of the impact of maturation aspects of pharmacokinetics should be provided where applicable.

2.3.2. Current methods of diagnosis, prevention or treatment in paediatric populations

For each condition covered by the application, the diagnosis, prevention and treatment interventions that are available in the EU should be identified, making reference to scientific 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 tabular format for ease of reference.

Of the available treatments identified, in the case of authorised medicinal products, the list should include those authorised by the national authorities and those authorised under the centralised procedure. This can be presented as an overview table. Information on generic medicinal products need not be provided.

For medical devices, the invented name and the approved use should be provided if placed on the market in the EU.

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. Significant therapeutic benefit and/or fulfilment of therapeutic need

The Paediatric Committee will assess whether the specific medicinal product is expected to be of significant therapeutic benefit to children and/or to fulfil a therapeutic need in children. 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 conditions that are the subject of the intended indications in children.

When considering significant therapeutic benefit the Paediatric Committee will take into account the nature and the seriousness of the condition to be treated (or diagnosed or prevented) and the available data on the medicinal product concerned. Significant therapeutic benefit could be based on one or more of the following:

(a) reasonable expectation of 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;

(d) improved dosing scheme or method of administration (e.g. 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 or pharmaceutical form;

(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 in terms of improved efficacy or safety;

(h) unsatisfactory nature of existing treatments and need for alternative methods with an improved expected benefit-risk balance;

(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 the time of submission of the application, significant therapeutic benefit might also be based on well-justified and plausible assumptions. The application should explore these assumptions based on reasoned arguments and relevant literature.

If the therapeutic need is included in the inventory of therapeutic needs pursuant to Article 43 of the Paediatric Regulation, the application should refer to the inventory.

2.4. Part C: Applications for product-specific waivers

2.4.1. Overview of the waiver request

A waiver may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified conditions, or to a combination of both. Requests for product-specific waivers should clearly define their scope in terms of paediatric subset and indication.

A product-specific waiver may not be required if the proposed indication falls within a condition (and subset of the paediatric population) already covered by a class waiver. Where the submission is only 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 may request the Agency to give advance confirmation of the applicability of a class waiver to a proposed development of a medicinal product in one or more adult conditions.

2.4.2. Justification for a product-specific waiver

2.4.2.1. Applications based on a likely lack of safety or efficacy in part or all of the paediatric population

In accordance with Article 11(1)(a) of the Paediatric Regulation a waiver may be granted if '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 a pharmaceutical rationale or (preliminary) data suggesting lack of efficacy or safety in the paediatric population. The application should take account, for the different paediatric subsets, of the seriousness of the condition and the availability of other methods as stated in Part B. All available evidence should be submitted 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. Justification for a waiver on these grounds may include the pharmacological properties of the product or class of product, results of 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 justification for a waiver.

2.4.2.2. Applications based on the disease or condition not occurring in the specified paediatric subset

In accordance with Article 11(1)(b) of the Paediatric Regulation a waiver may be granted if 'the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations'. On this basis, a justification for a waiver may be based on a detailed description of the incidence or prevalence of the condition 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. For waivers for specific subsets

of the paediatric population, the justification should focus on the incidence or prevalence in the different paediatric subsets delineated in Part B.

2.4.2.3. Applications based on lack of significant therapeutic benefit

In accordance with Article 11(1)(c) of the Paediatric Regulation a waiver may be granted if 'the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients'. On this basis, the 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, justification for such a waiver should be based on a detailed discussion of the existing treatment methods. Reference can be made to the discussion under point 2.3.3.

In particular, when existing medicinal products are authorised for use in children, applicants intending to request a waiver on this ground should justify in detail why the new product would be devoid of significant benefit over the existing treatments.

If applicants intend to claim a lack of significant benefit due to non-feasibility of measures, appropriate and detailed justification should be provided to support the claim.

2.5. Part D: Paediatric investigation plan

Part D should focus specifically on the development of the medicinal product for the paediatric population. While applicants can discuss possible choices, there is no need to propose separate alternative developments in the application.

2.5.1. Existing data and overall strategy proposed for the paediatric development

2.5.1.1. Paediatric investigation plan indication

The proposed indication should be established for the paediatric subsets included in the paediatric investigation plan. This part should specify whether the medicinal product is intended for the diagnosis, prevention or treatment of the conditions in question.

2.5.1.2. Selected paediatric subsets

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. In addition to age, the classification of the paediatric population may be based on other variables, such as gestational age, pubertal stages, gender and renal function.

2.5.1.3. 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, completed clinical studies in adults and the results when available. A brief outline of the planned studies in adults should also be provided. This information may be provided in tabular format.

The full study reports of completed non-clinical and clinical studies do not need to be provided; a summary of the results and a discussion of the implications for paediatric development should be sufficient. Full reports should be made available upon request. The

application should take into account any existing scientific guidance/advice and standard paediatric investigation plans published by the Agency and justify any deviation for the paediatric 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 on use outside the terms of a marketing authorisation, medication errors, accidental exposures, or known class effects.

2.5.2. Paediatric formulation development

2.5.2.1. General strategy

This section should address selected aspects related to the administration of the product to the relevant paediatric subsets.

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

The discussion will take into account the existing or proposed pharmaceutical development of the product and should address critical issues, such as:

- the need for specific formulations or pharmaceutical forms in relation to the chosen paediatric subsets/age groups, and discussion of the benefit of the chosen formulation or form;
- potential issues in relation to excipients to be used in the paediatric population;
- administration of the medicine to paediatric subsets (e.g. palatability, use of specific administration devices, ability to mix with food);
- precision of dose delivery in the case of solid dosage forms, when breakable tablets are proposed for paediatric use;
- timeframe for the development of an age-appropriate formulation/pharmaceutical form, where required.

If it is not possible, based on scientific justifications, to develop a formulation/pharmaceutical form which is relevant and acceptable for paediatric use on an industrial scale, the applicant should state how it intends to facilitate the industry-verified or extemporaneous preparation of an individual ready-for-use paediatric formulation.

2.5.2.2. Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development

The application should contain in tabular format a list of planned and/or ongoing measures intended to address the issues discussed under point 2.5.2.1. This list should consist of the proposed key elements in accordance with the annex to this guideline.

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. Agency guidelines in this area should be consulted to decide which measures could be relevant within the strategy proposed.

Proposed measures of particular relevance to the development of paediatric products include:

- compatibility with paediatric administration systems, e.g. medical devices;
- taste-masking and palatability.

2.5.3. Non-clinical studies

2.5.3.1. General strategy

This section should discuss the strategy for the non-clinical development which is needed to support paediatric use 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 standard non-clinical development should not be submitted or discussed unless it brings relevant information to the paediatric development and is not covered elsewhere in the application package (i.e. the investigator brochure).

The following aspects should be discussed, taking into consideration existing scientific guidance:

(a) 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 in children (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 paediatric safety pharmacology (studies using non-clinical *in vitro* and/or *in vivo* models to investigate specific functions of the physiological system);

(b) toxicology:

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

2.5.3.2. Summary of each of the planned and/or ongoing non-clinical studies

A tabular list should be provided, with the proposed non-clinical measures. This list should consist of the proposed key elements for the non-clinical measures in accordance with the annex to this guideline.

2.5.4. Paediatric clinical studies

2.5.4.1. General aspects

This section should discuss and justify the strategy for the clinical paediatric development, in relation to the development in adults where applicable and in relation to existing data and the potential to extrapolate. This should include critical aspects of study design and should present the strengths, advantages and disadvantages of the proposed clinical development.

In this section, the application should also discuss possible complete or partial extrapolation from adult data to paediatric patients and between paediatric subsets. The interrelation in terms of common studies, data and timelines between development in adults and paediatric populations should be explained. If extrapolation is a substantial component of the proposed development, a specific extrapolation protocol should be described in the list of measures. 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.

A discussion on how dosing in very young and young children is determined and verified should be included where necessary.

2.5.4.2. Paediatric pharmacokinetic/pharmacodynamics studies

The following aspects should be considered, where relevant:

(a) pharmacodynamic studies:

- pharmacodynamic differences between adult and paediatric populations (e.g. influence of maturation of receptors and/or systems);
- use of pharmacodynamic modelling;
- discussion of any biomarkers for pharmacokinetics/pharmacodynamics;
- use of the pharmacodynamic approach, particularly when pharmacokinetics cannot be measured;

(b) pharmacokinetic studies:

- possibility to use sparse pharmacokinetic sampling;
- use of population pharmacokinetics;
- discussion of age groups where more extensive studies are needed, e.g. due to expected high kinetic variability;

- pharmacogenetics.

2.5.4.3. Clinical efficacy and safety studies

The following aspects should be considered, where relevant:

- discussion of the need for specific dose-finding studies;
- discussion of the selected efficacy and/or safety endpoints (primary or secondary), in each of the relevant paediatric subsets;
- discussion of issues of relevance across the proposed studies, such as 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 studies and differential risks by age group.

Any potential concern for the long-term safety or efficacy in the paediatric population should always be discussed in the paediatric investigation plan application. If such studies are considered necessary, the details should be provided in the risk management plan, but would not normally form part of the agreed paediatric investigation plan.

Finally, specific measures proposed to protect the paediatric population involved in development, for example the use of less invasive methods, should be discussed where relevant.

Issues related to the feasibility of the proposed studies (e.g. recruitment capacity) should be presented and discussed.

2.5.4.4. Summary table of all planned and/or ongoing clinical studies in the paediatric population

A tabular list should be provided, with the proposed clinical measures. This list should consist of the proposed key elements for clinical studies in accordance with the annex to this guideline.

The table should propose timelines for initiation and completion of each measure, including specific dates (month and year) or ranges of up to six months, and should specify whether a deferral is being requested for the initiation and/or completion of each measure. Timelines for initiation may also be linked to the completion of a study in adults ('x months after completion of study y') or a measure in the paediatric investigation plan.

As completion of a measure (trial) is understood as the date of the last visit of the last subject included, the timelines should include a reasonable amount of time to complete, analyse and report the studies to be included in the marketing authorisation application, since the final (complete) study report is necessary for the operation of the compliance check.

2.5.4.5. Details of the planned and/or ongoing clinical studies

In order to help the Paediatric Committee to understand the proposed measures, the applicant may in addition provide more detailed information, such as a full study protocol.

Additional information, as appropriate to the stage of product development and in addition to the proposed key elements, may be provided:

- justification of type of study, study design and methodology;
- main objective of the study;
- justification of the dose of the proposed product and its regimen, and of the type of control (e.g. placebo or active control, with dose to be used);
- information on the location of the study (where scientifically justified);
- description of the sample size/power calculation (as appropriate; with expected effect size in children) used to determine the proposed number of subjects (M/F). This discussion should include, whenever possible, a sensitivity analysis (a tabulation with varying assumptions and statistical parameters, and the resulting sample sizes);
- justification of the relevant age groups or subsets included in the study (and of staggered inclusion where applicable);
- justification of the proposed duration of treatment (and duration of post-treatment observation if included in the study);
- proposed main inclusion/exclusion criteria;
- justification of the choice of outcome parameters/endpoints (primary, secondary);
- justification and, if needed, a more detailed description of statistical methods than the one contained in the key elements;
- discussion of options in the event of recruitment issues.

2.6. Part E: Request for deferral

With reference to the timelines stated in Part D, any request for deferral of the start or the completion of measures should make clear the indication, route of administration and pharmaceutical form to which the deferred timeline relates. When requesting a deferral, the application should also 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. 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.

Particular emphasis should be placed on the timing of the measures compared to the development for adults, as expressed for example in the ICH guideline (E11).

2.7. Part F: Annexes

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

- references (i.e. published literature);
- the investigator brochure (latest version), or full protocols of the proposed studies;
- the latest approved summary of product characteristics and risk management plan for a product already authorised;
- a letter of authorisation for the person authorised to communicate on behalf of the applicant;
- a copy of any scientific advice given by the EMA Committee on Human Medicinal Products;
- a copy of any scientific advice given by any EU national competent authority;
- a copy of any written request by the United States Food and Drug Administration and/or of any advice/opinion/decision relating to paediatric information given by a regulatory agency outside the EU;
- a copy of any Commission decision on orphan designation;
- the reference number or a copy of any previous EMA decision on paediatric investigation plans or a negative opinion of the Paediatric Committee on such plans.

2.8. Modification of an agreed paediatric investigation plan

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. Those modifications are required where key elements of the paediatric investigation plan are unworkable or no longer appropriate.

Submission of an application to modify 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 the nature or timing for completion of one of the key elements in the Agency 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, but only relevant sections supporting the change should be completed. The application should provide the reference of the previous paediatric investigation plan decision.

Consultation item No 1: Do you have any comments on the format and content of applications for agreement on or modification of a paediatric investigation plan and requests for waivers or deferrals?

3. OPERATION OF THE COMPLIANCE CHECK

Compliance with the requirements of Articles 7 and 8 of the Paediatric Regulation and the compliance of applications for paediatric use marketing authorisations are checked by the competent authorities. These compliance checks are described in Articles 23 and 24 of the Paediatric Regulation. Article 23 specifies the timing of the compliance check, provides 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 must take account of the opinion of the Paediatric Committee.

Compliance is checked by the competent authorities as follows:

- pursuant to Article 23 of the Paediatric Regulation, compliance is checked at validation for applications for marketing authorisation or variation. Non-compliance of these applications will lead to non-validation of the application;

- 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); the medicinal product will not be eligible for the rewards and incentives provided for in Articles 36, 37 and 38 of the Paediatric Regulation.

The determination of compliance 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

- whether all of the measures in an agreed paediatric investigation plan have been carried out in accordance with the key elements specified in the decision approving the paediatric investigation plan. The measures checked for compliance are those that are part of the condition covering an indication for which an application for marketing authorisation is made and that are not deferred.

Any necessary modification of the paediatric investigation plan should take place before the submission of the application for marketing authorisation or variation.

Compliance can be judged only if final study reports are provided. To facilitate the work of the 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.

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 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. If a paediatric investigation plan has been modified, 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 on each key element of the Agency decision on the paediatric investigation plan against what has actually been submitted;

- because the decision on the paediatric investigation plan will include the key elements for each of the measures, the applicant for marketing authorisation or variation will need to comply with each item;

- when conditional language such as 'could', or 'such as' is used in the opinion, then compliance may be confirmed even if these measures were not followed as suggested.

When only some measures referred to in the Agency decision had to be completed, the Paediatric Committee will adopt a letter confirming or denying (interim) compliance with those measures. In all cases, the grounds for accepting or denying compliance will be detailed in a report adopted by the Committee.

Where the measures in a paediatric investigation plan contain no study completed before the entry into force of Regulation (EC) No 1901/2006 (26 January 2007), 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]. All studies were completed after the entry into force of Regulation (EC) No 1901/2006'.

Where the measures in a paediatric investigation plan contain 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 were completed after the entry into force of that Regulation'.

The statement of compliance must be included in the marketing authorisation together with other technical information that forms part of the marketing authorisation ('technical dossier'). For reasons of legal certainty, the competent authorities in the Member States or, in the case of centralised marketing authorisations, the Agency must provide the marketing authorisation holder with confirmation that the compliance statement is included in the technical dossier of the marketing authorisation.

Consultation item No 2: Do you have any comments on the operation of the compliance check and/or the compliance statement?

4. CRITERIA FOR ASSESSING 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 to qualify for the rewards and incentives provided for in Articles 36, 37 and 38 of the Regulation, they need to be completed after the entry into force of the Regulation 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 those studies are considered significant within the meaning of Article 45(3) of the 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.

A study will be considered as completed after the entry into force of the Paediatric Regulation when the last visit of the last patient has occurred, as planned in the latest version of the protocol (as submitted to the 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 the 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: pharmacokinetic/pharmacodynamic clinical studies if they are likely to provide meaningful data that 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 several 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.

Consultation item No 3: Do you have any comments on the assessment criteria for significant studies?

672 **ANNEX**

673 *Key elements*

674 1. Paediatric formulation development

675 (a) Pharmaceutical form proposed for development for paediatric use

676 (b) Objectives for pharmaceutical development

677 (c) Timelines for completion

678 2. Non-clinical studies

679 (a) Type of study

680 (b) Objectives

681 (c) Test system/species

682 (d) Route of administration and doses

683 (e) Duration of dosing

684 (f) Timelines for completion

685 3. Paediatric clinical studies:

686 3.1 Paediatric pharmacokinetic/pharmacodynamic studies

687 (a) Type of study

688 (b) Objectives of study

689 (c) Study design

690 (d) Age group and population in which the study will be conducted

691 (e) Paediatric formulation(s) used in the study

692 (f) Dose ranges to be used in the PK studies

693 (g) Endpoints

694 (h) Modelling/simulation

695 (i) Sample size

696 (j) Timelines for completion

697 3.2 Efficacy and safety studies

698 (a) Type of study

(b) Objectives of the study

(c) Study design

(d) Age group and population in which the study will be conducted (including minimum number of paediatric participants)

(e) Inclusion and exclusion criteria

(f) Endpoints (primary and main secondary)

(g) Timing of endpoint assessment

(h) Safety assessments (including timing)

(i) Statistical approach

(j) Timelines for completion

For deferred studies, time-limits for initiation are also part of the key elements.

Consultation item No 4: Do you have any comments on the key elements of a paediatric investigation plan? Is it appropriate to list key elements in this guideline or should key elements only be specified in the individual decision of the Agency agreeing a specific paediatric investigation plan?

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Consultation item No 5: Please feel free to raise any other issues or make any comments which have not been addressed in the consultation items above.