



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

EMA/PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy

Revision 4*

Background:

The EU Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use (Paediatric Regulation) mandates that any MA application for a new medicinal product should include either the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP), or an EMA decision on a waiver or on a deferral. While the development in children should not delay the granting of the MA for any age group thanks to the use of deferrals, the PIP still needs to be agreed with the EMA Paediatric Committee before validation of the MAA.

This document defines a standard set of measures that applicants should include in their application for a PIP. This standard set is intended to facilitate the work of all parties; it is not a guideline, nor a complete protocol; it indicates the measures in the PIP that the Paediatric Committee considers necessary for the development in children, i.e. the so-called “key elements” to be included in the Decision. These key elements are those on which compliance check will be performed.

Specific cases may not fit in this template, and justified modifications are always possible. Should applicants diverge from the standard set, this might have consequences on timelines of assessment and/or content of the agreed PIP.

DISCLAIMER:

This document concerns treatment of allergic rhinitis/rhinoconjunctivitis. **Should the long-term data support disease modification with regard to prevention of asthma, this additional indication can also be applied for.**

In case the intended condition is treatment of allergic asthma, a PIP with a specific development plan must be submitted.

This document applies to all allergen products (e.g. allergen extracts, purified allergens, modified allergens, and adsorbed allergens, recombinant allergens and synthetic peptides). As the spectrum of allergens is reduced in allergen products containing recombinant allergens and specific peptides, the Guideline CHMP/EWP/18504/2006 states that applicants have to justify the selected allergens and

* The revised sections are highlighted throughout the text.



have to define and justify the selection of study population in regard to the included allergens. Consequently, enrolled patients must be well characterised with regard to their sensitization profile.

The EMA Paediatric Committee may decide to revise the standard PIP to take account of the evolution of knowledge.

Please note that the principles covered in this template for a Paediatric Investigation Plan are to be read in light of the CHMP/EWP/18504/2006 Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases and the EMEA/CHMP/BWP/304831/2007 Guideline on Allergen Products: Production and Quality Issues.

Please note that competent authorities will assess the data on quality, safety and efficacy generated in accordance with this standard PIP. It is the responsibility of the competent authority to judge, based on the overall assessment of the file, whether the medicinal product is safe, effective and of acceptable quality in relevant age groups.

Introduction

1. Type I Allergies and Specific Immunotherapy (SIT)

The basic pathophysiologic mechanism of type I allergies, be it seasonal or perennial, is not fully understood but is assumed to be identical in the adult and paediatric populations. However, while SIT is expected to act in the same way in children and adults, the magnitude of the effect and the safety profile could differ. Therefore, dedicated studies in children are considered necessary. This is expressed in the EMA/CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases CHMP/EWP/18504/2006.

In addition, children are believed to derive potentially greater benefit from immunotherapy to inhalant allergens, due to the preventive effects of subcutaneous specific immunotherapy (SCIT) on the development of allergic asthma.⁽¹⁾ Applicants, therefore, can opt to add the condition prevention of asthma to a PIP on allergic rhinitis/rhinoconjunctivitis.

2. Homologous groups

The Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007) introduced the concept of homologous groups and predefined the main homologous groups.

The grouping is based on the following criteria:

Comparable physicochemical and biological properties of the source material;

Cross-reactivity/structural homology of allergens;

Identical formulation of the finished product;

Identical production process of the allergen extract and of the finished product

All four criteria have to be fulfilled for group formation.

Predefined homologous groups are:

Birch group: Birch, alder, hazel, hornbeam, oak, chestnut, beech

Grass group: Kentucky bluegrass, timothy, cocksfoot, fescue, sweet vernal, velvet, oat, barley, ryegrass, cultivated rye, wheat

Mite group: House dust mites (*Dermatophagoides pteronyssinus*, *D. farinae*)

One member of a homologous group can be selected as the representative allergen for the purpose of quality, efficacy and safety clinical trials. The choice should be justified, taking into consideration, for example, geographical differences in the sensitisation patterns and other relevant factors.

Up to now there is no evidence that the cross-reactivity of allergens differs between adults and children. Thus the concept of homologous groups is also valid for children with the consequence that clinical studies would be required for one allergen of a homologous group only. These data can then be used for all allergen products belonging to the same homologous group, but not across groups.

It is of note, that one PIP covers only one specific medicinal product. Therefore separate PIPs have to be submitted for each product within one homologous group, cross-referring to the data/studies in the PIP of the representative allergen.

3. General requirements:

- In the PIP application a very brief discussion is sufficient for part B (Overall development of the medicinal product including information on the target diseases / conditions) focusing on B.3 (Significant therapeutic benefit / fulfilment of therapeutic needs), i.e. on those data that are needed to discuss the potential benefit of the MEDICINAL PRODUCT IN QUESTION and to justify and support the proposal in part D.
- Waivers:
The PDCO agreed that a waiver in children less than 5 years is acceptable on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. However, granting a waiver will not prevent enrolment of eligible patients from the age of 3 years.
- Dose-finding studies:
Extrapolation from dose-finding studies in adults should be considered. The inclusion, as well as the absence, of a dose-finding study in the paediatric population should be justified particularly for studies with SLIT.
- Study duration / Long-term efficacy:
The main aim of specific immunotherapy is persistent efficacy due to changes in the immune system, but this can only be demonstrated in long-term studies. This is particularly important for the paediatric population.

Recently, first data on long-term efficacy in adults have been published.⁽²⁾ At present evidence is still lacking to allow a final conclusion whether or not long-term efficacy in children might be extrapolated from adult data.⁽³⁾ Some data, demonstrating long-term clinical effects and the potential for preventing development of asthma in children with allergic rhinoconjunctivitis up to 10 years after a 3-year course of specific immunotherapy (SIT) with standardized allergen extracts support the proposal for extrapolation.⁽¹⁾ Divergent positions argue that at present the exact mechanism of how the immunomodulating effect of SIT is achieved is unknown; therefore extrapolation does not seem appropriate at present. A currently on-going study in more than 800 children with grass pollen-induced allergic rhinoconjunctivitis evaluating the preventive effect on asthma development of a grass allergy immunotherapy tablet is expected to provide more answers.⁽⁴⁾ Until such evidence is available, the

following stepwise approach is proposed to balance scientific requirements, i.e. the need to further elaborate the mechanism of action of SIT with:

- the need to develop a sound standard paediatric development programme which can be fulfilled by several applicants in parallel,
- the paediatric patient population available for recruitment,
- the requirement of the Paediatric Regulation to avoid unnecessary trials.

Applicants have to select one allergen product out of their portfolio which will be evaluated for long-term, **disease modifying** efficacy in adults and children (3 year treatment period and 2 year post-treatment follow-up).

Paediatric trials with the selected product should be initiated as soon as

- a tolerated dose range
- a dose-response relationship for clinical efficacy
- short-term efficacy
- safety data demonstrating no increased risk of anaphylactic reactions from adult trials (possibly including adolescents) are available.

Once long-term efficacy of the selected product has been established in adults and children, development of all other allergen products will depend on the proposed MAA (treatment of allergic symptoms, sustained clinical effect, long-term efficacy / disease modifying effect and curing allergy).

The principles of study design and claims for efficacy, as laid down in Guideline CHMP/EWP/18504/2006, are applicable. Until evidence on long-term efficacy in adults and children is available for the selected allergen product, long-term studies in children have to be proposed in the PIP for all allergen products with a request for a deferral, which may be modified upon evidence of long-term efficacy of the selected product. The deferred trials may be initiated at any time and need not wait until completion of the long-term study with the selected product.

This requirement might be revised with evolution of knowledge.

The PDCO acknowledges that the above step-wise approach is a compromise and will not address the antigenic differences among different extracts.

- Symptom score / medication score:

A standard procedure for assessing symptoms and evaluating the use of rescue medication appears vital in order to draw correct conclusions from a study. The PDCO takes the initiative for obtaining information needed to establish such a balanced and validated scoring system. Therefore the symptom score which is recommended by the EMA Guideline on the Clinical Development of Products for Specific Immunotherapy for the treatment of Allergic Diseases (CHMP/EWP/18504/2006) should be always implemented as secondary endpoint. This score has already been used in successful paediatric trials and gives the opportunity to collect data using one similar score in all studies in addition to the well-defined primary endpoint (taking in account both symptom and medication) proposed by the applicant.

Cooperation with the EAACI to define and validate a primary endpoint is strongly encouraged.

References:

1. Jacobsen L et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007 Aug; 62(8):943-8.
2. Durham S et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010; Vol. 125, pp. 131-138
3. Calderon M et al. Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement. *Pediatr Allergy Immunol* 2012; 23: 300–306
4. Valovirta E et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther.* 2011 Oct; 33(10):1537-46

Treatment of allergic rhinitis / rhino-conjunctivitis

Overview of standard measures to be proposed by applicants

Study identifier	Standard PIP allergen product for subcutaneous specific immunotherapy (SCIT)
Type of study	Randomized, placebo-controlled, double-blind parallel-group study to evaluate efficacy and safety/tolerability.
Study design features	<ul style="list-style-type: none"> • Superiority trial. • The trial to consist of a screening phase and an active treatment phase. • In case of seasonal allergies it is mandatory to document the exposure to the relevant allergens and to define in the study protocol the minimum pollen count which has to be reached to define the evaluation period as well as the baseline period, if performed. <p><Efficacy endpoints should be evaluated and presented in each allergen season; and at least at the end of follow-up.></p> <p><Efficacy endpoints should be evaluated and presented several times during the treatment for perennial allergies; and at least at the end of follow-up.></p> <ul style="list-style-type: none"> • In trials evaluating a mixture of allergens belonging to birch and grass pollen group (as members of different homologous groups): <ul style="list-style-type: none"> - an efficacy / safety study must be performed in patients suffering from both allergies - Efficacy endpoints should be evaluated and presented for each allergen season separately; and at least at the end of follow-up. - Treatment schedule must provide a safe and efficacious treatment for both allergies. - It is mandatory to document the exposure to the relevant allergens and to define in the study protocol the minimum pollen count which has to be reached to define the evaluation period for both seasons.
Main objectives	<p>Primary objectives:</p> <ul style="list-style-type: none"> • to assess the long-term efficacy of test product when compared to placebo on rhinitis/rhinoconjunctivitis symptoms and rescue medication usage. <p>Optional:</p> <ul style="list-style-type: none"> • to evaluate prevention of asthma. <p>Secondary objectives:</p> <ul style="list-style-type: none"> • to evaluate safety and tolerability.
Study population and subset definition	<ul style="list-style-type: none"> • Children and adolescents from 5 years to less than 18 years. Eligible children from 3 years onwards may be included. • Children from 5 to less than 12 years should be assessed separately. • Adolescents aged 12 to less than 18 years may either be included in the paediatric trial or in adult trials which in this case should be included in the PIP. • In combined children/adolescent studies at least 45% of patients must be between 5 and less than 12 years old. • In trials evaluating recombinant allergens: <ul style="list-style-type: none"> - all patients must be well characterised with regard to their sensitization profile.

Study identifier	Standard PIP allergen product for subcutaneous specific immunotherapy (SCIT)
	<p>Selection criteria:</p> <p>If the objective is treatment of allergic rhinitis/rhino-conjunctivitis:</p> <ul style="list-style-type: none"> • Children with a documented clinical history of IgE-mediated <seasonal allergic rhinitis/rhino-conjunctivitis with or without bronchial asthma (GINA I or II), attributable to seasonal pollen allergens.> • <perennial allergic rhinitis/rhino-conjunctivitis with or without bronchial asthma (GINA I or II), attributable to house dust mite or other perennial allergen sources.> • The history of IgE-mediated allergic rhinitis/rhino-conjunctivitis must cover at least 2 consecutive years for seasonal and 1 year for perennial allergy, requiring intake of symptomatic treatment. • Only patients to be enrolled who experience an appropriate minimum level of symptoms prior to randomization, defined as at least moderate level in 2 symptom categories. • In trials evaluating a mixture of allergens belonging to birch and grass pollen group (as members of different homologous groups) <ul style="list-style-type: none"> - patients must have documented allergy to both allergens (in vitro test and clinical history). <p>To be excluded:</p> <ul style="list-style-type: none"> • Asthmatic patients with a forced expiratory volume in the first second (FEV₁) < 80% of predicted value. <p>If the objective is prevention of asthma (as defined per GINA 2014):</p> <ul style="list-style-type: none"> • Only patients with allergic rhinitis/rhino-conjunctivitis without asthma must be enrolled. • The history of IgE-mediated allergic rhinitis/rhino-conjunctivitis must cover at least 2 consecutive years for seasonal and 1 year for perennial allergy, requiring intake of symptomatic treatment. The second consecutive year could occur during the baseline period.
Number of study participants by paediatric subset	<ul style="list-style-type: none"> • The sample size calculation should be sufficient to detect clinically meaningful effect in the proposed primary endpoint(s) with at least 80% power and a (multiple) type I error rate of 0.05 (two-sided). • If co-primary endpoints are selected the power should be at least 80% to reject both of them. • Regardless of the choice of the primary efficacy parameter(s), the applicant should provide a definition of a clinically meaningful effect in the primary endpoint(s) and the basis for choosing this value. The validity of the assumptions on the expected treatment effects and variability used for the sample size calculation should be thoroughly considered and be supported by data and/or literature references. A merely statistical significant effect might not be sufficient.
Dosage, treatment regimen, route of administration	<ul style="list-style-type: none"> • Dose as determined in dose-finding studies. • Treatment schedule must be described.
Duration	<ul style="list-style-type: none"> • 3 year treatment period - <to provide efficacy data in the first/second/third pollen season after start of SIT>

Study identifier	Standard PIP allergen product for subcutaneous specific immunotherapy (SCIT)
	- < to provide efficacy data in perennial allergies after three years of treatment with a minimum duration of treatment evaluation of 2 months. In addition, earlier time points should be evaluated > • <2 year treatment-free, blinded follow-up period>.
Rescue medication	<ul style="list-style-type: none"> • Rescue medication and its use must be standardized and justified by the applicant. • Antihistamine (oral form or eye drops, or nasal spray) and nasal corticosteroid to be dispensed to the patient, oral glucocorticoids to be kept and administered at the study centre. • Any intake of rescue medication has to be documented in the patients' diary.
Control	Placebo.
Primary endpoint with time point of assessment	<p>Efficacy:</p> <p>If the primary objective is long-term/disease modifying effect of allergic rhinitis/rhino-conjunctivitis:</p> <ul style="list-style-type: none"> • The primary endpoint has to reflect both the symptom severity and the intake of rescue medication. This can be achieved by a combined symptom-medication score or by individual symptom and medication scores as co-primary endpoints. A detailed definition and justification of the primary endpoint(s) must be provided. • If a combined symptom-medication score is applied, the method to combine both scores has to be pre-specified and justified. • No validated symptom score exists, but the measurement of symptoms on a 4-point rating scale is generally accepted in adults. This symptom score is valid for children as well if it is ensured that the symptoms are always rated in the same way throughout the study by the parent or the patient depending on the age groups. • The endpoint(s) should be evaluated and presented during each allergen season (in the case of seasonal allergic rhinitis) or several times during the treatment for perennial allergies; and at least at the end of follow-up. • Time points of assessment must be pre-specified. <p>If the primary objective is prevention of asthma (as defined per GINA 2014):</p> <ul style="list-style-type: none"> • The primary endpoint must reflect the primary objective (e.g. proportion of patients with/without asthma at the end of follow-up period; or time to onset of asthma, assessed over the course of the study). • The key secondary endpoint should be the (combined) allergic rhinitis symptom and medication score.
Secondary endpoints	<ul style="list-style-type: none"> • If not used as primary endpoint, the symptom score which is recommended by the EMA Guideline on the Clinical Development of Products for Specific Immunotherapy for the treatment of Allergic Diseases (CHMP/EWP/18504/2006) should be always implemented as secondary endpoint. • Changes in organ related Quality of Life scores (validated questionnaires, e.g. Juniper Paediatric Rhinoconjunctivitis Quality of Life Questionnaire

Study identifier	Standard PIP allergen product for subcutaneous specific immunotherapy (SCIT)
	<p>(PRQLQ) for children less than 12 years old; Adolescent Juniper RQLQ (AdoIRQLQ) for children above 12 years old) and/or validated asthma QoL scores.</p> <ul style="list-style-type: none"> • Percentage of patients free of symptoms/signs and with no use of rescue medication. • Changes in allergen-specific IgG and IgG4 levels. • Safety: According to Guideline CHMP/EWP/18504/2006. <p>Exploratory endpoints may be:</p> <ul style="list-style-type: none"> - regulatory T-cells in sub group of patients
Statistical analysis	<ul style="list-style-type: none"> • Superiority of long-term efficacy versus placebo. • All analyses should be pre-specified. • According to ICH E9 the primary analysis for testing superiority should be based on the intention-to-treat principle including all randomized subjects. Any deviation from the ITT principle has to be defined and justified in advance in the PIP. • A responder analysis with pre-defined responder definition to be performed as sensitivity analysis if it is not the primary analysis. • The rules for futility analyses to be applied as well as the frequency must be agreed upon in the PIP.
Stopping rules	The study has to be discontinued if futility analysis shows a lack of efficacy after 1 year of treatment.
External Data Safety Monitoring Board	Yes.
Plan for specific follow-up	Not determined by the PDCO.
Date of initiation	<p>Paediatric trials to be initiated as soon as results from adult trials (possibly including adolescents) are available including:</p> <ul style="list-style-type: none"> - a tolerated dose range - a dose-response relationship for clinical efficacy - short-term efficacy - safety

Study identifier	Standard PIP allergen product for sublingual immunotherapy (SLIT)
	Use the same elements as for SCIT apart from the following:
Study population and subset definition	<ul style="list-style-type: none"> • Children and adolescents from 5 years to less than 18 years. Children from 3 years onwards may be included. • Children from 5 to less than 12 years should be assessed separately. • Adolescents aged 12 to less than 18 years may either be included in the paediatric trial or in adult trials which in this case should be included in the PIP. • In combined children/ adolescent studies at least 45% of patients must be between 5 and less than 12 years old. <p>Selection criteria:</p> <p>If the objective is treatment of allergic rhinitis/rhino-conjunctivitis:</p> <ul style="list-style-type: none"> • Children with a documented clinical history of IgE-mediated

Study identifier	Standard PIP allergen product for sublingual immunotherapy (SLIT)
	<p><seasonal allergic rhinitis/rhino-conjunctivitis with or without bronchial asthma (GINA I or II), attributable to seasonal pollen allergens>.</p> <p><perennial allergic rhinitis/rhino-conjunctivitis with or without bronchial asthma (GINA I or II), attributable to house dust mite or other perennial allergen sources >.</p> <ul style="list-style-type: none"> • The history of IgE-mediated allergic rhinitis/rhino-conjunctivitis must cover at least 2 consecutive years for seasonal and 1 year for perennial allergy, requiring intake of symptomatic treatment. • Only patients to be enrolled who experience an appropriate minimum level of symptoms prior to randomization, defined as at least moderate level in 2 symptom categories. • In trials evaluating a mixture of allergens belonging to birch and grass pollen group (as members of different homologous groups). <p>- patients must have documented allergy to both allergens (in vitro test and clinical history).</p> <p>To be excluded:</p> <ul style="list-style-type: none"> • Asthmatic patients with a forced expiratory volume in the first second FEV₁ < 80% of predicted value. <p>If the objective is prevention of allergic asthma (as defined per GINA 2014):</p> <ul style="list-style-type: none"> • Only patients with allergic rhinitis/rhino-conjunctivitis without asthma must be enrolled. • The history of IgE-mediated allergic rhinitis/rhino-conjunctivitis must cover at least 2 consecutive years for seasonal and 1 year for perennial allergy, requiring intake of symptomatic treatment. The second consecutive year could occur during the baseline period.

Treatment of insect venom allergy

Overview of standard measures to be proposed by applicants

Study identifier	Standard PIP allergen product for subcutaneous specific immunotherapy (SCIT)
Type of study	Randomized, active-controlled, double-blind study to evaluate efficacy and safety/tolerability.
Study design features	Non-inferiority trial.
Main objectives	Primary objectives: to compare the clinical efficacy of test product versus control for inducing tolerance to <insect> venom. Secondary objectives: to evaluate safety and tolerability.
Study population and subset definition	<ul style="list-style-type: none"> • Children and adolescents from 3 years to less than 18 years. • Children from 3 to less than 12 years should be assessed separately. • Adolescents aged 12 to less than 18 years may either be included in the paediatric trial or in adult trials which in this case should be included in the PIP. • In combined children/adolescent studies at least 45% of patients must be between 3 and less than 12 years old. • Determination of baseline serum tryptase in all patients. • Children with a documented clinical history of severe systemic reaction, including respiratory and cardiovascular symptoms, to <insect> stings. <p>AND</p> <ul style="list-style-type: none"> • Documented sensitization to the respective insect with either skin tests and/or specific serum IgE tests. • The history of insect venom allergy should be based on a detailed description of allergic symptoms after a hymenoptera sting graded by the grading system established by the EAACI.
Number of study participants by paediatric subset	<ul style="list-style-type: none"> • Sample size calculation should be justified in light of expected efficacy: <ul style="list-style-type: none"> - for vespid venom allergy approximately 5% chance for therapeutic failure after a VIT (licensed preparation) is well documented. - for honey bee venom allergy the expected failure rate at treatment with a licensed product is about 15%.
Dosage, treatment regimen, route of administration	<ul style="list-style-type: none"> • The maintenance dose has to be specified and justified. • The maintenance interval has to be duly justified.
Duration	<ul style="list-style-type: none"> • At least 6 months of a well-tolerated double-blind standard maintenance dose (100 mcg) before performing sting challenge. • Open-label extension up to a total duration of maintenance treatment of at least 3 years (provided the product is found to be non-inferior to the comparator).
Rescue medication	<ul style="list-style-type: none"> • Rescue medication has to be standardized and justified by the applicant. • Any intake of rescue medication has to be documented in the patients' diary.
Control	<ul style="list-style-type: none"> • Another product with proven efficacy in paediatric studies as comparator
Primary endpoint with time point of assessment	<ul style="list-style-type: none"> • controlled sting challenge after at least 6 months of a well-tolerated double-blind standard maintenance dose (100 mcg). • Grading to follow the grading system established by the EAACI.
Secondary endpoints	<ul style="list-style-type: none"> • Skin reactivity.

Study identifier	Standard PIP allergen product for subcutaneous specific immunotherapy (SCIT)
	<ul style="list-style-type: none"> • Venom-specific IgG, IgG4 and IgE concentrations.
Statistical analysis	<ul style="list-style-type: none"> • Non-inferiority to comparator. • Special consideration should be given to the handling of missing values.
Plan for specific follow-up	Treatment-free follow-up of three years required.
Stopping rules	The study has to be stopped if non-inferiority of the test product has not been demonstrated. In this case all patients must receive three year maintenance treatment with a product with proven efficacy in paediatric studies.
External Data Safety Monitoring Board	Yes
Date of initiation	Paediatric trials to be initiated after results from adult trials (possibly including adolescents) including: <ul style="list-style-type: none"> - a tolerated dose range; - a dose-response relationship for clinical efficacy; - short-term efficacy; - safety.

2. Potential long-term safety issues in relation to paediatric use for consideration in the Risk Management Plan/Pharmacovigilance activities

It is considered that the following issues are particular causes of concern in children:

- exacerbation of asthma;
- anaphylaxis and immunogenicity.

FINAL NOTES AND PRACTICAL GUIDANCE

Format of the PIP application

PIP applications should follow the standard format of PIP applications. Templates and guidance can be found in the [Application guidance](#) page in the Paediatrics section of the EMA website. In particular, consultation of the [European Commission guideline on format and content of applications for paediatric investigation plans](#) and of the [EMA procedural advice on PIP applications](#) is recommended before applying for a PIP. However, a brief discussion for parts B and C is considered sufficient.

The structure of the application should follow the outline published in the last page of the [Application for PIP / waiver \(part A\)](#) and also shown in the [Template for scientific document \(part B-E\)](#).

A [Key Elements Form](#) should be used to propose key elements for development in children.

Please note that the paediatric clinical trials mentioned in this document only cover part D.IV of the application.

For all questions pertaining to this standard PIP, applicants may contact the Paediatric Section at paediatrics@ema.europa.eu.

Deadlines and procedure for agreement of the PIP

For PIP applications which follow the above guidance and do not raise additional issues, an opinion will be adopted at day 60 of the procedure. If there is a need for interaction with the applicant, the PDCO will request the applicant to propose modifications to the plan at day 60. In this case, the procedure will be suspended until such proposed modifications are submitted by the applicant; the PDCO will then adopt an opinion on day 120.

One member of a homologous group can be selected as the representative allergen for the purpose of quality, efficacy and safety clinical trials. Nevertheless, separate PIPs have to be submitted for every individual product within one homologous group, cross referring to the data/studies in the PIP of the representative species.

Applicants, when submitting several PIP applications with products within one homologous group, must identify the one which will serve as the "representative PIP". In the application form, the section on information on related applications should be duly completed. In related applications, the information in the scientific parts (Part B to E) will be the same as in the "representative PIP". Applicants must confirm that the scientific information provided is identical to the information in the "representative PIP".