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Guideline on allergen products development for immunotherapy and allergy diagnosis in moderate to low-sized study populations

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Executive summary

The main aim of the guideline is to address general guidance on the development of medicinal products for the diagnosis and immunotherapy of allergies, where only moderate to low-sized study populations are available in product development.

An allergy is an immune reaction of the body to non-infectious foreign substances (antigens or allergens). The body reacts with signs of inflammation, formation of antibodies in Type I allergy and T-cell activation in Type IV allergy. Depending on the type of allergy, the symptoms vary and can occur predominantly immediately after contact with the allergen, as in Type I allergy, IgE-mediated allergy, or only after a few hours or days, as in Type IV allergy, delayed-type allergy. Management for Type I allergies may involve avoidance of the allergen, medications to relieve symptoms, or allergen immunotherapy (AIT) to desensitise the immune system to the allergen. Regarding Type IV allergy, allergen avoidance is the only measure as there is – to date – no causal therapy available.

This guideline should be read in conjunction with other EMA and ICH guidelines, which may apply to these conditions and patient populations.

In this document, guidance and adaptations of requirements for the available study population are provided on criteria and standards for patient selection, quality and non-clinical aspects, and possible indications concerning products for AIT and *in vivo* diagnosis of allergies. Recommendations are made on the clinical development, potential study designs and safety considerations for allergen products within the scope of the guideline. However, evidence should generally be generated at the highest level of confidence.

1. Introduction (background)

Allergy is a common condition with a large variety of different allergen sources causing allergy and the number of sensitised patients varying strongly for the respective allergen sources. The two types of allergy addressed in this guideline are Type I and Type IV. The pathophysiology is similar for all Type I allergies. The symptoms are mainly IgE-mediated, and the clinical conditions may manifest differently as rhinitis/rhinoconjunctivitis, bronchial asthma, urticaria, pruritus, eczema, gastrointestinal symptoms and/or severe anaphylactic reactions. Anaphylaxis is a rapid systemic and unpredictable disorder that is life-threatening. The disorder often occurs after exposure to certain allergens, which in most cases are insect venom, food, or medications. However, severe anaphylactic reactions can be caused by any allergen regardless of the prevalence of a respective allergy, mono- or polysensitisation and thus in principle in any patient suffering from allergies.

In Type IV hypersensitivity, there is activation of T cells and of macrophages that interact and secrete various cytokines ultimately resulting in delayed skin reactions almost exclusively at the site of contact with the allergenic substance.

While allergen immunotherapy is the only known disease modifying therapy for Type I allergies, there is no such treatment available for Type IV allergies. Allergen extracts for diagnosis and therapy are needed to manage patients with Type I allergies, while for patients with Type IV allergies allergen products are currently only used for diagnosis of Type IV allergies and treatment of these allergies involves allergen avoidance.

Several guidelines applicable for allergen products are available (see section 3) and provide advice on quality and clinical development according to the current knowledge. Generally, the overall principles from the current guidelines are also valid here. However, for the evaluation according to these guidelines, a sufficient number of patients is needed to be included in the clinical trials which cannot be

achieved in case of allergies where a severely limited number of patients is available to study and/or where clinical co-allergies are common. While for AIT in general, collection of evidence on efficacy is complicated by factors such as varying exposure to allergens in field studies and substantial placebo effects, difficulties become more pronounced with reduced patient populations.

There is an unmet medical need for effective diagnosis and treatment by AIT for patients suffering from these allergies, as in most Member States only few products with marketing authorisation are available and further products currently being placed on the market are based on prescriptions for individual patients, so-called named patient products (NPPs). For such NPPs, generally insufficient evidence on quality, safety and efficacy is available and they are in most cases not independently assessed by regulatory authorities.

Guidance is provided herewith regarding the data on quality, non-clinical, safety and efficacy for test and therapy allergens to provide sufficient scientific evidence for the approval of such allergen products, where adequate data according to existing guidelines cannot be reasonably obtained because the number of patients available for the required clinical trials is too low. Within this guideline, low and moderate size study populations are defined as a population for which a standard development program with the usual statistical rigor (or significance levels) on (a) clinically relevant endpoint(s) is not feasible, necessitating alternative strategies to collect the data required for regulatory decision making. This guideline aims to outline such strategies.

2. Scope

This guideline is intended to clarify EU regulatory expectations on the data for allergen products being developed with the goal of obtaining marketing authorisation in case of moderate or low-sized study target populations. The following categories of allergen products are covered:

- Diagnostic allergens for test *in vivo*: Type I (prick test, provocation test, intradermal/intracutaneous test) and Type IV (epicutaneous patch test)
- Allergen Immunotherapies - AIT (inhalant allergens, insect venom allergens, food allergens).

This guideline covers allergen products for allergen immunotherapy of Type I allergies and diagnosis of Type I and Type IV allergies, regardless of the affected organ system (e.g. upper and lower airways, eyes, skin, multi organ affection (systemic reaction)), the allergen source (e.g. pollen, mites, animal dander, moulds, insect venoms, food, chemicals), the allergen product (e.g. extracts, purified allergens, modified allergens, adsorbed allergens) or the route of administration (e.g. subcutaneous, sublingual, oral, percutaneous).

However, this guideline does not cover the indication of atopic dermatitis or asthma as these conditions will require separate clinical trials (e.g. different study designs, endpoints) (see section 6).

In addition, the guideline does not cover medicinal allergen products manufactured using recombinant DNA technology, synthetic peptides, DNA or RNA constructs and/or cell preparations as they differ substantially to the allergen products as discussed above.

Overall, this guideline will not be applicable for any common clinically relevant allergen of Type I allergy (diagnostic or AIT), as defined in the current Annex I of *Recommendations on common regulatory approaches for allergen products* (CMDh/399/2019). In addition, for the present guideline to be pertinent, the applicant should soundly justify that deviation from current guidelines concerning AIT (CHMP/EWP/18504/2006) or diagnostic products (CPMP/EWP/1119/98/Rev. 1) are appropriate due to the reduced population of interest, considering EU epidemiology data (presence of allergen in the environment, rate of sensitisation, clinical allergy prevalence) and other relevant factors. It is

recommended to request scientific advice by competent authorities on a case-by-case basis for principal deviations from current guidelines and for the topics not covered by the present guidance.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles and part of the Annex I to Directive 2001/83 (as amended) and relevant CHMP and ICH guidelines, among them in particular:

- Guideline on clinical trials in small populations - CHMP/EWP/83561/2005
- Guideline on Missing Data in Confirmatory Clinical Trials - EMA/CPMP/EWP/1776/99 Rev. 1
- Guideline on adjustment for baseline covariates in clinical trials - EMA/CHMP/295050/2013
- Note for guidance on statistical principles for clinical trials - CPMP/ICH/363/96
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials - EMA/CHMP/ICH/436221/2017
- Note for guidance on choice of control group in clinical trials - CPMP/ICH/364/96
- Guideline on clinical evaluation of diagnostic agents - CPMP/EWP/1119/98/Rev. 1
- Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases - CHMP/EWP/18504/2006
- Guideline on Allergen Products: Production and Quality Issues - EMEA/CHMP/BWP/304831/2007
- Guideline on process validation for finished products - information and data to be provided in regulatory submissions - EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1
- Recommendations on common regulatory approaches for allergen products - CMDh/399/2019

4. Quality aspects

In general, for all allergen products and their intermediates manufactured by a method involving an industrial process as defined by Directive 2001/83/EC, as amended, a full set of data on quality is expected. These data should include specific manufacturing and quality control aspects on allergen products and intermediates as requested by current pharmaceutical legislation and according to guidelines and the European Pharmacopoeia. There should typically not be any major difference in the expectations on the quality documentation for allergen products within the scope of this guideline, as the quality requirements are mainly independent of the prevalence of the respective allergy.

In any case, the available data should allow a reasonable understanding of the product and the process, with sufficient control to allow the safe and effective use in humans.

4.1. Type I allergy quality aspects

For allergen products for therapeutic use, a validated assay measuring the potency (total allergenic activity, determination of individual allergens or any other justified tests) must be applied if technically possible. For this, commercial availability of assays and options for in-house assay development should be taken into consideration. However, for particular allergies, a sufficient number of patients might not

be available to establish an appropriate sera pool (EMEA/CHMP/BWP/304831/2007) for potency testing of diagnostic or therapeutic products as required or scientific knowledge regarding extract characterisation (e.g. verified major allergens) may be considerably limited. If, correspondingly, IgE-dependent assays cannot be performed, a justification must be provided. In these cases, a justified combination of suitable alternative qualitative and quantitative control tests such as determination of an antigen profile, protein profile, content of total protein or content of relevant individual allergens should be applied. Generally, the concept of homologous groups (EMEA/CHMP/BWP/304831/2007) is applicable for AIT and *in vivo* diagnostics. In view of the high number of allergen products for *in vivo* diagnosis, extrapolation approaches (based on prior knowledge) apart from the concept of homologous groups may be justified for manufacturing process validation. According to the Guideline on Process Validation for Finished Products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1), process validation data should be generated for all products to demonstrate the adequacy of the manufacturing process. In cases where the manufacturing process of allergen extracts not belonging to the same homologous group and of the finished product is highly similar for different products and the type of source material is of similar origin, i.e. has comparable physicochemical and biological properties and where a full set of process validation data are available for one of these products (representative product), produced at the same manufacturing site, it may be justifiable that only a reduced validation program is performed for the other product or that the validation data are extrapolated from the representative product. For a reduced validation program, general manufacturing steps (e.g. filtration steps) that have been validated for other products would not necessarily need validation for each individual product. In any case, a reduced validation should include all relevant manufacturing process steps that are considered product specific. The extent of the validation program should be justified on a case-by-case basis. The selection of a representative product must be based on a comprehensive concept allowing for valid extrapolation. Guidance available on related concepts should be taken into consideration for such approaches (e.g. the Toolbox guidance for PRIME (1)).

Where in accordance with the previous section, full data on the validation of the manufacturing process is not provided, accordingly a full batch analysis and stability data set on several batches manufactured at commercial scale may also not be available at the time of marketing authorisation application. While batch analysis data from at least one batch manufactured at commercial scale should be provided (including corresponding stability studies), it may be acceptable to provide data from batches manufactured at pilot-scale or batches that had been used in clinical trials, to support a full evaluation of the manufacturing process. The transferability of such data to the commercial manufacturing process should be justified by the applicant. A commitment should then be provided to submit additional data on batch analysis and/or stability studies obtained from the next batches produced after marketing authorisation.

4.2. Type IV allergy quality aspects

In case of epicutaneous patch test preparations, characteristically source materials of the active substance do not comply with GMP-standards as they are typically manufactured for use in other settings (e.g. hair dyes, cosmetics). Respective requirements (e.g. as requested by Directive 2001/83/EC) apply once the source material is introduced into the manufacturing process for the medicinal product. Technical data sheets for such source materials should be provided. If an atypical manufacturer for source materials does not provide technical data sheets, the finished product manufacturer should develop relevant internal analytical procedures to ensure batch to batch consistency.

It is regarded acceptable to replace the audit of active ingredient and packaging materials suppliers with a robust alternative process. This process shall include a supplier qualification questionnaire for

the initial qualification and continuous evaluation of the supplier performance. The qualified person declaration shall clearly state the quality of the allergen and clarify, which substances are not guaranteed to be manufactured according to GMP and how the required quality is ensured.

It is regarded acceptable to group products into suitable process categories (matrix approach) for validation of the manufacturing process. Such categories can be based on a combination of main characteristics, such as dosage forms (suspension ointments, emulsion ointments, liquids), batch sizes (or batch size range) and drug substance concentrations (e.g. 0.1% to 1%). Notably, the manufacturing process of each product in a category has to be identical. It is possible to perform the process validation exemplarily on a justified number of representative products for each category, considering e.g. active substance characteristics, low and high drug substance concentration etc. In any case, at least three batches of each representative product should be included for process validation. Reducing the frequency to periodic testing is regarded acceptable based on a risk based approach of the allergen or group of allergens. For marketing authorisation, long-term stability data for the finished product must be provided for at least one batch covering the intended shelf life. A commitment to provide data for at least two additional batches may be acceptable.

For multi-dose products, in-use stability of at least one batch should be presented.

Photostability data are required for at least one batch in each pack size unless the allergen must be stored in a refrigerator or if the applicant can demonstrate that the packaging has sufficient light protective properties.

5. Non-Clinical data

5.1. Allergen immunotherapy products

The data required for non-clinical development will depend on the product for which a marketing authorisation is intended. As a minimum requirement the following data must be provided:

Products containing natural allergen extracts

Allergens in the form in which they occur in nature are basically considered non-toxic and harmless for non-allergic individuals.

For natural allergen extracts, a detailed expert statement is considered acceptable. If relevant bibliographic data on pharmacodynamics, pharmacokinetics, and/or toxicity from research studies or human use are available, they should also be provided. The expert statement should include a discussion of the general safety profile and risks of product administration, treatment, and a risk benefit conclusion.

Furthermore, in case a treatment continuation during pregnancy is planned the applicant would need to provide a justification for non-performance of embryo-foetal development studies. This will not be necessary in case pregnancy is considered an absolute contraindication for the product.

Modified allergen extracts

For all modified allergen extracts (allergoids) a minimum set of non-clinical data will be necessary.

In general, repeat-dose toxicity including local tolerance is to be tested for all modified extracts. However, in case the allergen product has been previously marketed as NPP, the need to perform repeat-dose toxicity studies in animals should be evaluated under consideration of available data. Therefore, all available safety data (e.g. from pharmacovigilance reports) should be provided.

Genotoxicity should be tested *in vitro* - by one bacterial test (usually AMES Test) and one cellular test (usually mouse lymphoma assay). In the case that from both tests there are no concerns, no *in-vivo* test would become necessary. Only if minimum one test shows a positive result and reasonable aspects such as e.g. impurities can be excluded, an *in-vivo* test becomes mandatory.

Reproductive and developmental toxicity should be studied within the mandatory repeated toxicity study. Investigations of embryo-foetal development are not necessary if sufficient data from exposure in pregnant women are available.

5.2. Diagnostic allergen products (Type I allergy)

Products for *in vivo* diagnosis contain natural allergen extracts. Therefore, as described for AIT products, bibliographic data and an expert statement is considered acceptable. The expert statement should include a discussion of the general risks of product application and a risk benefit conclusion.

5.3. Products for epicutaneous diagnosis of contact allergies (Type IV allergy)

Products for epicutaneous diagnosis of contact allergies contain predominantly chemical substances. Therefore, normally data are available from technical data sheets and literature, thus for compiling the non-clinical data, bibliographic data are sufficient. This compilation of data should always include data on acute toxicity (whereby data for other routes of application are also suitable, especially as other routes of application are mostly more critical than the epidermal route) and data on the sensitisation potential. Wherever possible, data on sensitisation potential should have been determined in animal tests. If such data are not available, *in vitro* data can be sufficient where justified. Moreover, data on the potential to provoke unspecific local (irritative) reactions should be included. Where available, data on absorption, metabolism and excretion should be provided. Data on pharmacodynamic/-kinetic and genotoxicity are not regarded as necessary with exemption of substances which are listed as carcinogenic, mutagenic and toxic to reproduction (CMR-substances). However, for these substances the data published in the official document for CMR-substances are sufficient.

In cases were data for the substance in question is sparse or lacking, data regarding metabolites or closely related products may be supportive.

In general, special care must be given on the objective persuasiveness of the non-clinical data package if clinical data are limited.

6. Clinical development: Possible indications/treatment goals

Allergy immunotherapy products

While the aspects discussed in this section are primarily relevant to inhalant allergens, the guideline is also applicable to non-inhalant allergens (i.e. food and venom allergens). For inhalant allergens, it is expected that the majority of clinical trials will investigate the product for the treatment of allergic rhinitis/rhinoconjunctivitis with controlled or without allergic asthma. Treatment of allergic asthma is considered a different indication and would require a separate clinical trial.

In accordance with the EMA Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (CHMP/EWP/18504/2006), different efficacy claims may be requested depending on the duration of the conducted studies. Given the limited data sets anticipated from moderate- to small-sized populations, it is expected that the claim for the

"treatment of allergic symptoms" will often be pursued. However, other claims may also be acceptable if adequately supported by data.

Diagnostic allergen products (Type I allergy)

A possible target indication is diagnosis of Type I hypersensitivity (immediate-type allergy) by prick, intracutaneous or provocation testing. Provocation tests may be developed for conjunctival, nasal and/or bronchial provocation.

Products for epicutaneous diagnosis of contact allergies (Type IV allergy)

A possible target indication is diagnosis of Type IV hypersensitivity (delayed-type allergy/contact allergy) by epicutaneous testing.

7. Clinical development: Criteria and standards for patient selection

Considering the wide scope of this guideline, the specific issues of patient selection will depend on the type of allergen product (diagnostic or therapeutic), on the type of allergy (IgE-mediated or Type IV allergy) as well as on the category of allergen (inhalant allergen, food allergen, hymenoptera venom or haptens).

7.1. Allergen Immunotherapy products

While the most principles of the current guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (CHMP/EWP/18504/2006), including the selection of patients, are applicable also for trials with allergen products for moderate to low-sized study populations, there may be a limitation in recruiting a sufficient number of patients for an adequate sample size. Here, some general approaches to more effectively select the study population are discussed.

Environmental exposure chambers (EECs) with inhalant allergens could be considered to enhance patient selection for phase II or phase III studies.

Co-sensitisation is a major issue also for field studies of common allergens and all recommendations (e.g. limited number of allergens, causal role of allergen, excluding clinical relevance of other allergens) from the Guideline on clinical development of AIT (CHMP/EWP/18504/2006) are valid here as well.

Within moderate to low-sized study populations, it is even more difficult to find monosensitised patients. Provocation tests may be utilised for patient selection if available. If provocation data are also used to support the efficacy assessment, the provocation test method and product must remain consistent throughout the study.

Inhalant allergens

For the indication of rhinitis / rhinoconjuctivitis the following is requested:

- documented comprehensive clinical history of IgE-mediated (skin prick test and/or provocation test and allergen-specific IgE) seasonal (intermittent)/perennial (persistent) allergic rhinitis/rhino-conjunctivitis (needing symptom-relieving medication) with controlled allergic bronchial asthma or without asthma (see section 2).
- appropriate minimum level of symptoms (moderate/severe), according to international criteria, e.g. ARIA classification (2), and sufficient duration prior to randomisation.

Exclusion criteria mentioned in current guideline (CHMP/EWP/18504/2006) are applicable.

Insect venom allergens

Hymenoptera venom immunotherapy is generally indicated following systemic allergic reaction (graded by an established grading system) exceeding generalised skin symptoms with a documented sensitisation to the venom of culprit insect with skin tests (prick and/or intradermal) and/or specific IgE tests and/or basophil activation test in selected cases, according to the diagnostic flow charts as recommended by current scientific guidelines. In case of positivity to more than one hymenoptera venom, the cross-reactivity should be distinguished from the primary sensitivity. The patients should be screened for mastocytosis due to a higher risk of anaphylactic reactions to insect venom immunotherapy and insect stings.

Food allergens

Specific food allergen administration to patients with food allergies carries a high risk of provoking allergic reactions, such as severe systemic allergic reactions including anaphylactic reactions. The patients to be enrolled in the study should have comprehensive clinical history of IgE-mediated allergic reactions after ingestion and positive double-blind, placebo-controlled food challenge (DBPCFC) and evidence of allergic sensitisation (SPT and/or sIgE).

7.2. Diagnostic allergen products

Products for Prick/Provocation tests (IgE-mediated Type I allergy)

These products require a biological standardisation of the respective allergen extracts (e.g. according to the Nordic guidelines or method by Turkeltaub). Based on the chosen standardisation procedure, the patients are selected in order to investigate different allergen concentrations. At least 20 patients are needed that have positive clinical history, with a positive reaction to a prick test containing standardised extract and/or specific IgE. However, in rare cases it is possible that for some allergens no previously standardised prick test is available and/or no specific IgE testing is obtainable. In the absence of both, a comprehensive clinical history as a main pillar of inclusion criteria could be considered sufficient to select the patients. In exceptional cases of food allergens, a prick-by-prick technique could be an option.

For efficacy (sensitivity/specificity) studies, the enrolment of both allergic and non-allergic patients is needed.

Products for epicutaneous diagnosis of contact allergies (Type IV allergy)

In cases when a sensitivity/specificity study is not feasible, the effort should be made to perform studies determining other parameters such as positivity ratio (PR) and reaction index (RI) as alternative endpoints (3-5) (see section 10). The patients to be included in the clinical study should at least have a comprehensive clinical history of contact dermatitis after exposure to the specific hapten to show the potential of the hapten to sensitise and provoke an allergic reaction of clinical relevance in patients.

8. Clinical development of products for AIT: Study design, efficacy and safety

In general, the clinical development should be performed according to current guidelines. The EMA Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (CHMP/EWP/18504/2006) is considered especially relevant and this guideline should be followed wherever possible. If parts of it are not feasible for a limited patient population regarding a

specific allergy, the applicant needs to provide an individual and profound justification why it is considered a moderate to low-sized study population in this case and the reason for the choice of study design and endpoints. The respective choice should always cover the highest evidence level possible for the concerned allergen. The applicant is recommended to submit the clinical development plan to the competent authority within the framework of a scientific advice to discuss and agree whether the chosen level is considered acceptable. Choices for trial design, data collection and statistical analysis should be aligned to the scientific question of interest that is posed by the trial objective. This would require a specification of the estimand (the "target of estimation"), including the specification of strategies to handle each of the relevant events that occur after randomisation and that would affect the interpretation of an outcome variable or preclude its observation (intercurrent events). Intake of rescue medication (an intercurrent event as per ICH E9(R1)) has an impact on symptom severity and is recommended to be integrated in the primary endpoint for phase III trials, which would equate to use a 'composite' strategy (as per ICH E9(R1)) to handle this IE.

8.1. Phase II dose-finding studies

A phase II dose-finding study is generally considered necessary as a starting point for successful clinical development of AIT products. The investigational product should be tested at different doses to gain sufficient data on safety and tolerability to establish the maximum tolerated dose and a suitable dose escalation scheme, if necessary. Dose escalation may be different depending on the route of administration and the active substance of the product (e.g. native allergen versus allergoid). Placebo-control is a prerequisite for each dose-finding study. Sufficient safety surveillance measures should be in place considering that a new product is tested in humans for the first time.

Clinical surrogate parameters accepted as endpoints in dose-finding trials so far are the use of EEC or the performance of provocation testing (nasal, conjunctival). To date, there is not sufficient scientific evidence for a general conclusion that additional surrogate parameters like intracutaneous testing (ICT) (early phase reaction/late phase reaction), allergen specific IgG4 and ratio IgG4/IgE are reliable tools to replace clinical, end-organ related endpoints. Only if no other option is feasible and if sufficiently justified, alternative surrogate endpoints (e.g. ICT, IgG4, IgG4/IgE) might be acceptable for dose-finding.

However, regarding EEC and provocation testing it is known that only limited or no allergen substances are available for testing and EECs are normally only validated for common allergens. When no provocation test substances are available it could be considered if within one clinical trial both medicinal products (provocation test allergen and product for AIT) can be investigated. Patients with a positive history and allergen-specific IgE-antibodies should be included in the trial. The trial may consist of two parts: In the first part of the trial, patients are tested with the investigational provocation test allergen according to the requirements for provocation test allergens (see section 8). If the test allergen is concluded suitable for provocation testing, this allergen product may then be used to determine the primary endpoint in the second part of the study (dose-finding for AIT). In this part of the study, only those patients who had previously reacted positive to the provocation test should be included. The detailed design and suitability for marketing authorisation should be discussed with in a scientific advice.

In any case, a sufficient amount of safety data must be generated in the first-in-human study. Generally, it is expected that safety data are collected from a phase II dose-finding trial in a limited population before the allergen product can be tested in a larger group of subjects.

In exceptional cases and only based on a robust justification, a dose-finding trial may be skipped. Rationales for skipping a phase II dose-finding trial might be that sufficient other meaningful data are

available allowing conclusions on the dose selection for further efficacy development (e.g. from product usage as NPP or based on the content of major allergen) or that a combined phase II/III dose-finding and efficacy study will be performed. It is recommended to discuss such scenarios within a scientific advice. To ensure patient safety, the tolerability of the product should have been demonstrated for the chosen dose. If tolerability data are not available, in the combined phase II/III trial, different doses should be investigated before selecting one or more doses for efficacy testing in the confirmatory part of the study and/or a staggered design for the confirmatory part of the study should be planned.

8.2. Phase III confirmatory efficacy trial

Placebo-control is a prerequisite for every efficacy trial for products for AIT. It is possible to randomise a higher number of patients to active treatment compared to placebo, however, statistical aspects should be considered. As mentioned above, a suitable dose should be defined by a phase II study (or in exceptional cases from other data) or alternatively a combined phase II/III trial has to be performed. In any case, the clinical trial design has to ensure the safety of the study subjects, taking into consideration the knowledge available on the specific product, by means of e.g. strict individual withdrawal criteria, stopping rules for groups or the entire clinical trial and a data safety managing board.

Study subjects will need to fulfil adequate inclusion and exclusion criteria including a documented comprehensive clinical history of IgE mediated allergic disease and a positive allergy testing via specific serum IgE and/or a positive skin prick test (SPT). For further details see section 7.

The value of observational data for supporting efficacy or to demonstrate efficacy is yet unclear and is not considered sufficient as the principal evidence for efficacy. This type of data may be submitted as supportive evidence. The current regulatory guidance and recommendations should be taken into account.

8.3. Considerations on endpoints for clinical trials for AIT with inhalant allergens for the treatment of allergic rhinitis/rhinoconjunctivitis

The most relevant clinical endpoint should always be chosen as primary endpoint. This will ideally be a combined symptom medication score as outlined in the EMA Guideline CHMP/EWP/18504/2006. If this endpoint will be investigated, in case of seasonal allergies for which pollen counts are obtainable, the exposure to the relevant allergens should be documented and the minimum pollen level determined to define the evaluation period should be outlined in the study protocol.

In exceptional cases in which the combined symptom medication score cannot be used for the conduct of the phase III trial due to low patient numbers, the applicant has to provide a comprehensive justification including a statistical rational and could consider a clinical trial with a different endpoint. In the order of decreasing evidence levels this might be the usage of an EEC or other allergen provocation testing (nasal or conjunctival provocation). Other endpoints, such as intracutaneous tests and surrogate parameters as allergen-specific serum immunoglobulin levels (IgG or IgG/IgE ratio) are considered unsuitable for a phase III trial.

Data from sources with a lower level of evidence (e.g. from named patient use, uncontrolled studies, quality of life data, case reports) can be provided as supportive data. This might be especially useful if an acceptable surrogate parameter is used as the primary endpoint. It is recommended to discuss such scenarios within a scientific advice.

8.4. Considerations on endpoints for clinical trials for AIT for the treatment of food allergy

A double-blind placebo-controlled food challenge test is the gold standard for determination of the allergen level tolerated (e.g. as mg of protein) for food allergy. Therefore, the determination of tolerated allergen level is also the primary endpoint for studies regarding treatment of food allergy and is required also for allergens in moderate to low-sized study populations.

8.5. Considerations on endpoints for clinical trials for AIT for the treatment of Hymenoptera venom allergy

Hymenoptera venom allergy may cause severe reactions and even fatalities. The most common allergies are induced by stings of insects belonging to the genus Vespula or Apis. However, other insects belonging to the families of Vespidae and Apoidea may also cause severe allergies but in a limited number of patients. Even though these venoms are in part cross reactive to Vespula and Apis venoms, patients may benefit more from treatment with a specific venom immunotherapy instead of using the common Vespula or Apis AIT products. As venom immunotherapy (VIT) is in general highly effective, it is considered unethical to use placebo in the control group in clinical trials. Due to the partial cross reactivity, common hymenoptera authorised products may be used as comparator. It is expected that it will be difficult to show superiority over such products, thus non-inferiority study design could be used. Efficacy can be evaluated by a controlled sting provocation (6). If sting provocation is not possible, exceptionally the comparison of the severity of reactions after the most recent sting (pre-VIT) and after field re-stings (during VIT) can be used. The grading of reactions should follow an established grading system.

9. Clinical development of diagnostic allergen products (Type I allergy): Study design, efficacy and safety aspects

In general, the clinical development of test allergens should be performed according to the EMA Guideline on the clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev 1). This guideline should be followed wherever possible. If parts of it are not feasible for a considerably limited patient population, the applicant needs to provide an individual and profound justification why it is considered a low-sized population and the reason for the choice of study design and endpoints. The respective choice should always cover the highest evidence level possible for the concerned allergen from the point of feasibility. As for AIT products, the value of observational data for supporting the clinical documentation of allergen products for *in vivo* diagnosis is unclear. Principles as discussed above also apply here.

9.1. Dose-finding

A dose-finding is generally considered necessary as a starting point for successful clinical development of medicinal products. Clinical trials for biological standardisation of allergen extracts (e.g. according to the Nordic guidelines or the ID_{50}EAL method by Turkeltaub (7-8)) have been found suitable to determine a useful concentration for test allergens. The Nordic method compares the wheal size with a histamine dose-response curve and determine histamine equivalent prick (HEP) units or Biological Units (BU). A strength according to 10 HEP or 10.000 BU (same wheal size in a median sensitive patient with a wheal provoked by a positive reference solution consisting of histamine 54.3 mmol/l (e.g. histamine dihydrochloride 10 mg/ml)) may be a useful concentration. In Europe, mostly this method is performed. The ID_{50}EAL method measures the erythema response to determine the ID_{50} value (intradermal dilution for 50 mm sum of erythema) in BU and is used especially in the USA but is

also accepted in Europe. The investigational product should be tested in approximately 20 patients with a 3- to 5-fold dilution series.

If sufficient other data are available to support the dose selection for further efficacy development e.g. from product usage as NPP, from evidence of suitable dosages of other preparations or based on the content of major allergen, a dose-finding may be skipped. For these options the applicant has to provide a justification.

9.2. Phase III confirmatory efficacy trial

Wherever possible, a clinical trial to determine sensitivity and specificity of the product should be performed. For this purpose, clinical trials combining several allergens can be conducted. For example, 10 different allergen products can be investigated in one study. Patients allergic to at least one of the investigational allergens should be included based on their history and allergen-specific IgE. Patients allergic to different allergens can then serve vice versa as negative controls.

In general, sensitivity and specificity of the product should be determined. However, in moderate or low sized study populations it might be difficult to include enough patients to determine sensitivity and specificity. In these cases, it should be justified, why it is not possible to include more patients. The following alternatives may then be used.

Where possible, data from NPP use or from registries should be submitted. Data can be compiled for example, by performing retrospective studies. In these retrospective compilations at least data of the characterisation of patients (age, gender, ethnicity, anamnesis, wheal sizes of the allergen under investigation) as well as positive and negative controls should be included. Regarding anamnesis, wherever possible IgE data should be provided, at least in a sub-population of patients. If no IgE data can be provided, this has to be justified by the applicant. For such retrospective compilations dose-finding data may not be available. This is considered acceptable as the retrospective clinical data should show that the product is able to provoke an allergic reaction and thus has a suitable concentration.

In exceptional cases, data of biological standardisation may be the only data available. This might be sufficient for marketing authorisation, if it can be justified that no further clinical data can be provided.

10. Clinical development of products for epicutaneous diagnosis of contact allergies (Type IV allergy)

Due to a lack of a standard of truth or even a surrogate standard of truth or comparator preventing the determination of sensitivity and specificity, the Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1) is often not applicable for the investigation of new epicutaneous patch tests independently of the size of the patient population.

When feasible, sensitivity and specificity of the product should be assessed. Besides sensitivity and specificity, which often cannot be determined, data for the clinical assessment of epicutaneous test allergens on the positivity ratio (PR) and the reaction index (RI) (1,3) should, wherever possible, be provided. It is recommended to submit data from controlled clinical trials. However, if already relevant data are available from registries a compilation of these data may be used instead. Moreover, there should always be data on the sensitisation potential of the substance.

10.1. Dose-finding studies

A dose-finding is generally considered necessary as a starting point for successful clinical development of medicinal products. For the development of new medicinal products or a change in the existing formulation, it is considered acceptable to conduct a single study that combines dose finding and efficacy assessment. However, for epicutaneous test allergen products, classical dose-finding studies with regard to tolerability and efficacy may not be feasible.

Epidemiological studies may be useful to determine the need for a substance to be provided as epicutaneous patch-test product. However, such studies are per definition not intended to investigate the characteristics of the substance and thus can only be submitted as supportive data. Case Reports e.g. of reactions in certain occupation groups may be another source of data documenting medical need and sensitisation potential. Regarding dose-finding, concentrations used e.g. in cosmetics may be helpful to estimate a suitable dose. In some cases, published threshold values which should not be exceeded may be available and could support the choice of dosage.

Wherever available, data from expert associations regarding suitable concentrations for patch testing can be used. Alternatively, literature data suitable for choosing an appropriate concentration could be submitted.

10.2. Phase III confirmatory efficacy trial

If sensitivity and specificity of the product could not be assessed, wherever possible clinical studies should be performed in a sufficient number of patients allowing determination of the positivity ratio (PR) and reaction index (RI). As described for products for diagnosis of Type I allergies, several substances can be tested in a single study and patients not sensitised to some tested allergens can be used as control for nonspecific local (irritative) reactions for other allergens included in the study panel. If studies to determine PR and RI values of the product are not considered possible to conduct due to low patient numbers, an adequate justification has to be provided. In such cases data from named patient use, monitor series or bibliographic data from other manufacturers should be submitted wherever available in addition to limited data from clinical studies. Reactions in certain occupation groups may be another source of data documenting sensitisation potential and thereby the medical need to develop a patch test product.

11. Safety aspects

11.1. Specific effects

Many adverse reactions or contraindications are class effects of specific immunotherapy/diagnostic tests. These events can be supported by bibliographic data and reported as such without specific frequencies calculated from clinical studies.

12. Studies in special populations

Due to the very low number of patients affected by allergies with limited patient population, the conduct of separate clinical trials for special populations such as paediatrics and elderly are generally considered not feasible. Extrapolation of dose-finding, efficacy and/or safety to the paediatric population may be justified on the basis of a detailed extrapolation plan. Applicable legal requirements concerning medicinal product development in paediatric populations (Paediatric Regulation EC 1901/2006) need to be taken into consideration. Extrapolation of data from the studied population to

other populations not represented or underrepresented in the clinical trial may also be possible but pending adequate justification.

Further, the inclusion of patients belonging to a special population might be possible within the main pivotal trial. This possibility may depend on several factors, such as the allergen and the allergen product, previous data (especially for safety) and study design (e.g. staggered design (first in adults, then in paediatrics)). In particular cases (e.g. food allergy) the studies could be conducted initially in children, based on an agreed paediatric investigation plan, considering the relevance and/or potentially higher efficacy of the specific AIT in paediatric population as compared to adults.

13. References

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14. Abbreviations

AIT	Allergen Immunotherapy
ARIA	Allergic Rhinitis and its Impact on Asthma
BU	Biological Units
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
DBPCF	Double-Blind, Placebo-Controlled Food Challenge
DNA	DeoxyriboNucleic Acid
EEC	Environmental Exposure Chamber
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
HEP	Histamine Equivalent Prick
ICH	International Council for Harmonisation
ICT	Intracutaneous test
$ID_{50}EAL$	Intradermal Dilution for 50 mm sum of erythema diameters determines the allergy unit
IgE	Immunoglobulin E
IgG	Immunoglobulin G
NPP	Named Patient Product
PDCO	Paediatric Committee
PR	Positivity Ratio
RI	Reaction Index
RNA	Ribonucleic acid
SPT	Skin prick test
VIT	Venom Immunotherapy