EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/251023/2018
Rheumatology / Immunology Working Party (RIWP)

Concept paper on a Guideline for allergen products development in moderate to low-sized study populations

Agreed by RIWP	September 2018
Adopted by CHMP for release for consultation	13 December 2018
Start of public consultation	21 December 2018
End of consultation (deadline for comments)	30 June 2019

Comments should be provided using this template. The completed comments form should be sent to RIWPSecretariat@ema.europa.eu

Keywords	allergen product, diagnosis, treatment, clinical development programme, quality control, guidance, moderate population, low-sized population

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1. Introduction

This concept paper proposes the development of a scientific guideline for 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 and for which there is no distinct regulatory guidance currently available within the EU.

2. Problem statement

Several guidelines applicable for allergen products are available (1–4) and provide advice on quality and clinical development according to the current knowledge. However, for the evaluation according to these guidelines, a sufficient number of patients are needed for clinical trials which cannot be achieved in case of allergies of low prevalence or where clinical co-allergies are common. There is an unmet medical need for effective diagnosis and disease modifying treatment by allergen immunotherapy (AIT) for patients suffering from these allergies, in contrast to allergies of high prevalence for which currently defined test and therapy allergens are available.

Thus, it has become clear that there is a need to clarify the EU regulatory expectations with regard to the data on quality, safety and efficacy for test and therapy allergens to provide sufficient scientific evidence for the approval of such allergen products.

3. Discussion (on the problem statement)

Allergy as such is a common condition. A large variety of different allergen sources can cause allergy and the number of sensitized patients varies strongly for the respective allergen sources. The allergen should cause an immune response to the host when exposed and it should be clinically warranted to have appropriate diagnostics available and/or develop a therapy to alleviate the effect caused.
Allergens are currently available in medicinal products such as

- AIT of IgE mediated allergic diseases (type I allergies) that are of biological origin (allergen extracts derived from natural source materials),
- *in vivo* diagnosis of IgE mediated allergic diseases (type I allergies) that are of biological origin (allergen extracts derived from natural source materials),
- products intended for the *in vivo* diagnosis of type IV allergies.

The pathophysiology is similar for all type I allergies. The symptoms are mainly IgE-mediated, even if the clinical condition may manifest differently as rhinitis/rhinoconjunctivitis, bronchial asthma, urticaria, pruritus, eczema, gastrointestinal symptoms or severe anaphylactic reactions.
Severe anaphylactic reactions can be caused by any allergen regardless of prevalence, mono- or polysensitisation and thus in principle in any patients 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 at the site of contact with the allergenic substance.

While allergen specific immunotherapy is the only known disease modifying therapy for type I allergies, there is no such treatment available for type IV allergies. Thus, allergen extracts for diagnosis and therapy are needed to manage patients with type I allergies, while allergen products can be used only for diagnosis of type IV allergies and treatment of these type IV allergies involve allergen avoidance.

Allergic rhinitis/rhinoconjunctivitis can be caused by various different agents (e.g. pollen, mites, and moulds (from many different species each), various foods, and animal dander) and requires specific treatment based on the specific allergizing agent. When it is left untreated (including immunotherapy with products lacking efficacy), or is only treated by symptomatic medication it is prone to evolve into asthma which can progress to a chronic and life-threatening disease. A treatment that addresses the underlying disease pathogenesis by appropriately modulating the immune system has the potential to prevent further episodes of allergies, some of which may be serious, and may prevent progression to more serious conditions.

Although it is known that in principle specific immunotherapy is effective, efficacy of the individual product depends on allergen concentration, composition of the product, application route, intervals and number of applications etc. Thus each product must be evaluated individually for quality, efficacy and safety.

Existing guidelines (2, 3) aim at defining the current state of the art for the development and evaluation of therapeutic allergens and diagnostic agents in general. Thus they provide advice on requirements according to the current knowledge. However, for the evaluation of products according to these guidelines, sufficiently large numbers of patients are needed to be included in clinical trials. In case of allergies of low prevalence adequate patient cohorts may not be available and therefore other approaches need consideration. The proposed guideline intends to address the development of allergen products for the treatment of such allergies of low prevalence. While in principle the aspects of drug development in small populations could be taken into account (1) this approach is not likely to be efficient. The approach outlined in the existing guidance proposes that a specific development path has to be agreed upon on a case-by-case basis for each specific product As a consequence, there is a risk of considerable heterogeneity and uncertainty as each applicant may choose different approaches and strategies. Given the similarities of allergy and the rather large number of allergens that are being currently used this approach seems inefficient and could be streamlined based on criteria to be developed within a guideline.

In addition, for clinical trials measuring allergic symptoms and medication intake during in field allergen exposure, on the one hand only symptoms of one allergy need to be manifest during evaluation and on the other hand the observations should not be confounded by treatments for the co-existing allergies. Yet, the number of respective patients with only one allergy may be limited in some situations as patients commonly suffer from multiple allergies which may be symptomatic simultaneously (e.g. in overlapping pollen seasons). Efficacy and safety cannot be reliably determined in these patients using standard development. Limited availability of adequate patients may also result in restrictions to quality control methods as reagents required (e.g. patient sera) for specific methods (allergen profile, determination of total allergenic activity) may not be accessible. Therefore, other approaches will be discussed in the proposed guideline to aide development of allergen products in cases where either one or both of the conditions as described are evident. For this, it should be appropriately justified that a conventional development program is not feasible.

While there is considerable knowledge available on clinical endpoints, provocation tests or surrogate markers, there are ongoing discussions in the scientific community on acceptable endpoints in scenarios as described above, for example, applicability of allergen challenge tests in allergen exposition chambers, allowing allergen specific evaluation independent of potential co-sensitizations and other concepts. The appropriateness of these methodologies to support allergen product development requires further clarification. Accordingly, expectations on acceptable characteristics of the study population and suitable efficacy endpoints particularly in such settings need to be discussed.

This is also necessary for allergens used for in vivo diagnosis of allergies.

In summary, several challenges have been identified in the planning of product development and designing clinical studies intended to support the approval of medicinal products for the treatment and/or diagnosis of allergies in situations where a conventional development program is not feasible.

Such guidance should then be read in conjunction with existing guidelines (e.g. 1-4) and to provide additional considerations on allergen products as classified in the intended guideline. The guideline is not intended for diagnosis or therapy of common allergies where current guidelines can be adequately applied. Also, any medicinal allergen products manufactured using recombinant DNA technology (consisting of synthetic peptides, DNA or RNA constructs and/or cell preparations) will be not considered as principles and approaches discussed here are not applicable for such products as they differ substantially to the allergen products as discussed above.

4. Recommendation

The Rheumatology and Immunology Working Party recommends drafting a guideline for allergen products development in small populations to provide guidance on quality aspects and the clinical development taking into account the specific issues identified above.

Guidance should include general aspects on allergen product development (patient selection, assessment of efficacy, design of therapeutic studies, safety aspects and quality considerations) for allergen products where only a limited number of patients is available for development with a particular focus on the following matters:

- Specific manufacturing and quality control aspects, applying to all such allergen products and their intermediates manufactured by a method involving an industrial process as defined by Directive 2001/83/EC, as amended.

- Definition of classes of prevalence and/or feasibility of allergen sources to conduct clinical trials and recommendations for suitable medicinal product development strategies for these classes of allergen sources.

- Strategies for adequate dose selection considering aspects of feasibility and necessity.

5. Proposed timetable

Proposed date for release of draft guideline 07/2020.

6. Resource requirements for preparation

The resources needed for this guideline relate to RIWP members who will develop the draft guideline and proceed to develop a final version after the consultation period. It may be considered appropriate at a later stage (e.g. during or immediately following the consultation period) to convene a workshop to facilitate finalisation of the guideline.

7. Impact assessment (anticipated)

The most important impact is expected to be on:

- clinical development programmes and quality control to support applications for allergen products indicated for diagnosis or treatment of allergies;
- the content of CHMP scientific advice.

8. Interested parties

Patient organisations;

Healthcare professionals;

Academic networks and learned societies within the EU e.g. European Academy of Allergology and Clinical Immunology (EAACI) and national allergologic societies;

Pharmaceutical industry.

9. References to literature, guidelines, etc.

1. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical trials in small populations, 2006.
2. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical evaluation of diagnostic agents, 2009.
3. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases, 2008.
4. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) and Biologics Working Party (BWP). Guideline on Allergen Products: Production and Quality Issues, 2008.