swissmedic

Guidance document
Authorisation of allergen product

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1 Terms, definitions, abbreviations

1.1 Definitions

1.1.1 Allergen product

Allergen products are ready-to-use medicinal products containing unchanged or modified allergens and used for in vivo diagnosis (test allergen products) or for the treatment of allergies (therapeutic allergen products).
Skin tests or provocation tests are used to identify the specific allergens to which the body overreacts. An identified IgE-mediated allergy can be treated with SIT.
Allergen products for in vivo diagnosis are derived from a broad spectrum of allergenic source materials. Unchanged allergen extracts from biological source materials in solution are usually used for intracutaneous, prick and provocation tests. These tests are designed to detect type I allergies (IgE-mediated, immediate type). In most epicutaneous and patch tests, chemical substances in a semi-solid matrix (e.g. Vaseline) are applied to the skin with the aim of detecting type IV allergies (cell-mediated, delayed type).
The allergen products for SIT form a much smaller group of allergen products, since only a limited proportion of diagnosed type I allergies can be treated with SIT. Allergen products for SIT can contain unchanged allergen extracts from biological source materials or allergen extracts that have been modified either chemically and/or by adsorption onto different carriers (e.g. aluminium hydroxide, calcium phosphate or tyrosine). The biological source materials for the manufacture of the allergen extracts typically include pollen, mites, bee and wasp venom or animal hairs.
If allergen products contain differing biological source materials, these should be prepared by mixing individual extracts. Source materials from different species should not be mixed prior to extraction. The respective individual extracts (within a mixture) are considered to be active substances. Efficacy tests (*potency tests*) are carried out on the individual extracts before mixing, followed by activity tests (*total allergenic activity*) after mixing to produce the homogeneous mixture. Regardless of homology and cross-reactivity, the number of individual extracts in a mixture of allergen extracts should be kept to a minimum, and the number and relative proportions of the extracts justified. Moreover, allergens with proteolytic properties should be avoided, and seasonal allergens should not be mixed with perennial allergens. Insect venoms from different genera should also not be mixed.
If a ready-to-use allergen product is diluted by the treating doctor before administration to the patient, e.g. diluted with a basic buffer, this is considered to be a preparation step rather than a manufacturing step. In this case, the product information should clearly describe how the treating doctor should complete the preparation. The in-use stability must also be demonstrated with corresponding data.

1.1.2 Epicutaneous or patch test

Test for detecting a delayed allergic reaction with contact sensitisation (type IV allergy, cell-mediated). The allergens in epicutaneous or patch tests are almost exclusively low molecular weight chemical synthetic substances. These are applied to the skin using a carrier material. Symptoms generally appear two to three days after allergen contact.

1.1.3 Intracutaneous or prick test

In the intracutaneous test a defined quantity of the allergen product is injected into the skin. In the prick test, the allergen product is applied to the skin in drop form (usually on the inner aspect of the forearm). Using a fine lancet or needle, the skin is then punctured superficially to allow the respective substances to penetrate the epidermis. The risk of a severe allergic reaction is higher with the intracutaneous test than the prick test, which is the most commonly used intracutaneous allergy test. The prick test is an international standard procedure for detecting allergic IgE-mediated immediate type reactions (type I allergy). The results of both tests are read after approx. 20 minutes.

1.1.4 Provocation test

In the provocation test the allergen product is placed in direct contact, for example, with the nasal mucosa, the bronchi or the gastrointestinal tract. This test is also designed to detect immediate-type allergies (IgE-mediated, type I allergies).

1.1.5 Specific immunotherapy (SIT)

SIT is a therapeutic use of allergen products for reducing allergic symptoms by the repeated administration of allergens (e.g. subcutaneously or orally) in increasing concentrations. SIT is designed to influence the immune system so that it no longer overreacts when it comes into contact with the corresponding allergen. SIT is used to treat type I allergies.

1.1.6 Specificity, sensitivity

These two parameters characterise the ability of the diagnostic method to rule out false-positive or false-negative results.
A test with high specificity is very likely to produce a negative result in individuals who do not have an allergic reaction to the allergen in question.
A test with high sensitivity is very likely to produce a positive result in individuals who do have an allergic reaction to the allergen in question.

1.1.7 Allergic disease

In an allergic disease, the immune system reacts to exogenous substances which, though actually harmless, are identified as allergens, with an overreaction that manifests itself as typical symptoms triggered by inflammatory processes.
Immediate-type allergies (type I allergies[1]) are associated with IgE formation and an IgE-mediated release of mediators (including histamine and cytokines). The symptoms usually appear within 30 minutes. Clinical manifestations include:

- hay fever (rhinitis),
- conjunctivitis,
- nettle rash (urticaria),
- gastrointestinal symptoms (gastroenteritis),

[1] Immunological hypersensitivity reactions are subdivided into four different types by Coombs and Gell depending on the mechanism (Gell & Coombs, 1963).

- allergic asthma,
- laryngeal oedema,
- angioneurotic oedema (Quincke's oedema) and
- anaphylaxis, anaphylactic shock (the most dangerous, acutely life-threatening form).

With a few exceptions, the allergens that trigger type I reactions are proteins and usually originate from the natural environment (e.g. pollen from wind-pollinated plants, mites, animal hairs, moulds, foods and insect venoms).
In delayed-type allergies (type IV allergies), the immune system is sensitised via sensitised lymphocytes, which can then trigger an inflammatory reaction in the event of allergen contact even without antibody involvement (no IgE involvement). The first symptoms generally appear two to three days after allergen contact. Allergic contact dermatitis is the most common manifestation of a type IV allergy, and drug eruptions also play a role. Allergens of type IV reactions are proteins only in exceptional cases. They are frequently inorganic or organic, low molecular weight substances and metals.

1.1.8 Allergen

Allergies are triggered by allergens. Allergens are those antigens against which the immune response is directed. In a type I allergy, the allergens are usually proteins. In a type IV allergy, the allergens are usually low molecular weight chemical synthetic substances.
Thus, for example, a birch pollen grain carries various proteins on its surface. A part of these proteins is allergenic, i.e. when these proteins come into contact with the human body they are taken up by, and processed in, dendritic cells and presented via MHC II surface receptors to naïve CD4+ T-cells and naïve B cells, eventually forming antibodies which, if they are of the IgE type, can lead to allergic reactions and illnesses. A natural allergen that is chemically modified (e.g. by polymerisation with formaldehyde or glutaraldehyde) is known as an allergoid. Allergens can also be bound covalently to other molecules; the resulting conjugates then show different immunological properties.
An aqueous birch pollen extract might contain, for example, various allergens, i.e. a mixture of birch allergens is involved. An aqueous hazel pollen extract likewise contains various other allergens. This is known as a mixture of hazel allergens. Mixing these two extracts together produces what is known as a mixture of allergen extracts.
Whereas, from the taxonomic standpoint, allergens are distributed across numerous different species, at the molecular level they can be assigned to a very limited number of structurally related proteins.

Allergens that show a close structural relationship can be combined into homologous groups[2]. The following homologous groups are currently scientifically recognised:

a) Tree pollen of the beech (lat. *Fagales*) order, birch family (lat. *Betulaceae*)[3];
b) Tree pollen of the olive family (lat. *Oleaceae*);
c) Tree pollen of the cypress family (lat. *Cupressaceae*);
d) Grass pollen of the sweet grasses family (lat. *Poaceae*) and subfamily of *Pooideae;*
e) Weed pollen;
f) House dust mites of the genus *Dermatophagoides.*

[2] A.R. Lorenz, D. Lüttkopf, S. May, S. Scheurer, S. Vieths. The Principle of Homologous Groups in Regulatory Affairs of Allergen Products – A Proposal. Int Arch Allergy Immunol 2008 Aug 12;148(1):1-17 (http://www.ncbi.nlm.nih.gov/pubmed/18698143)
[3] According to Annex 1 of the EU *Guideline on Allergen Products: Production and Quality Issues*, this homologous group currently includes three trees and one shrub in the birch family (lat. *Betulaceae*) and 3 trees in the beech family (lat. *Fagaceae*). Both families belong to the beech order (lat. *Fagales*).

Annex 1 of the EU *Guideline on Allergen Products: Production and Quality Issues* contains a detailed list of the homologous groups formed to date (see EMEA/CHMP/BWP/304831/2007).

If the source materials with comparable physicochemical and biological properties for two different allergen products originate from a single homologous group mentioned above (e.g. pollen of the weeping birch and pollen of the hazel bush) and if the following three preconditions are satisfied:

a) the extracts for the two allergen products are produced by the same manufacturer,
b) the two ready-to-use allergen products are terminally manufactured by the same manufacturer and
c) the extraction method and the manufacturing processes are identical for the two allergen products,

then the two allergen products can be qualified as a reference medicinal product and related product. In this case, an applicant or marketing authorisation holder can claim and apply for this relationship with a corresponding justification. Naturally, two independent reference materials for the same authorisation holder can also exist within a homologous group, provided comprehensive documentation is available and subject to the above-mentioned preconditions.

1.2 Abbreviations

AllergO	Ordinance of the Swiss Agency for Therapeutic Products of 11 December 2009 on the Simplified Licensing of Allergen Preparations (Allergen Ordinance, SR 812.216.2)
CHMP	Committee for Medicinal Products for Human Use
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
DKG	*Deutsche Kontaktallergie Gruppe* [German contact allergy group]
DMF	Drug Master File
FeeO-Swissmedic	Ordinance on the Fees charged by the Swiss Agency for Therapeutic Products of 14 September 2018 (SR 812.214.5)
IgE	Antibodies in immunoglobulin class E
IVDK	*Informationsverbund Dermatologischer Kliniken* [Information network of departments of dermatology)
MHC II	Major histocompatibility complex, class II
NAS	New Active Substance
NTA	Notice to Applicants
Ph. Eur.	*European Pharmacopoeia*
SIT	Specific immunotherapy
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (Therapeutic Products Licensing Requirements Ordinance, SR 812.212.22)

2 Introduction

This Instruction specifies the requirements pertaining to the simplified authorisation of allergen products. Since this is a guidance document aimed at administrative bodies, it does not directly specify the rights and obligations of private individuals.

2.1 Legal framework

The simplified procedure for the authorisation of allergen products is based on the following:
Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA):

- Art. 10 Conditions for granting a marketing authorisation
- Art. 13 Medicinal products and procedures authorised in foreign countries
- Art. 14 Simplified authorisation procedure

Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (Therapeutic Products Licensing Requirements Ordinance, TPLRO):

- Art. 3 Documentation of analytical, chemical and pharmaceutical investigations,
- Art. 4 Documentation on pharmacological and toxicological tests,
- Art. 5 Documentation on clinical trials,
- Art. 13 Information for healthcare professionals;

Ordinance of the Swiss Agency for Therapeutic Products of 11 December 2009 on the Simplified Licensing of Allergen Preparations (Allergen Ordinance, AllergO)

3 Objective

Swissmedic uses this document first and foremost as a resource for applying the legal provisions on the authorisation of allergen products in a uniform and equitable manner. The intention of publishing this Instruction is to show private individuals what requirements have to be fulfilled, according to Swissmedic practice, to ensure that corresponding applications can be processed as quickly and efficiently as possible.
According to the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA, Art. 9 para. 1), both allergen products for in vivo diagnosis and allergen products for specific immunotherapy (SIT) are considered to be medicinal products subject to authorisation. The only allergen products exempt from authorisation are those used according to the exemption ruling of Art. 9 para. 2 TPA, e.g. as a magistral formula (e.g.: patient-specific mixtures of allergens).
Most of the preparations were assessed in the 1990s according to legal requirements that have now been updated. These medicinal products, as well as the newly developed allergen products, are qualitatively complex, extremely numerous and have a considerable risk potential (they can, for example, trigger anaphylactic shock and thus lead to life-threatening situations).
Since the Ordinance of the Swiss Agency for Therapeutic Products of 11 December 2009 on the Simplified Licensing of Allergen Preparations (Allergen Ordinance, AllergO) came into force on 1 March 2010, test and therapeutic allergens can be authorised in a simplified procedure. The authorisation procedure is simplified in that the documentation for the authorisation of an allergen product can be based on published specialist literature or on the documentation for another allergen product, known as the reference medicinal product.
The simplified authorisation procedure does not apply to allergen products containing biotechnological allergens or genetically-modified organisms. In these cases the standard authorisation procedure must be followed.

4 Scope

This Instruction applies to the authorisation of allergen products (see section 1.1.1) that do not contain biotechnological allergens or genetically-modified organisms.

5 Description

5.1 Simplified authorisation of allergen products

5.1.1 Principle

The simplified authorisation of allergen products involves two completely separate simplifications:

- Referencing the published specialist literature;
- Referencing the documentation of another allergen product (reference medicinal product).

In each case, the applicant must justify the transferability of the data from the published specialist literature or from a reference medicinal product. The justification must be plausible for Swissmedic. Existing authorisations of several allergen products under one authorisation number will be cancelled; each ready-to-use allergen product requires a separate authorisation.

5.1.2 Authorisation of allergen products according to Art. 13 TPA

If an authorisation for ready-to-use allergen products already exists in a country with comparable medicinal product control and a comparable authorisation procedure, the results can also be taken into account for the authorisation in Switzerland. Swissmedic must receive both the same scientific documentation, and all corresponding evaluation reports and decisions of the foreign authority (authorities). Provided the crucial requirements for allergen products are observed, the authorisation according to Art. 13 TPA can apply both to reference medicinal product and to related products.

5.1.3 Simplified authorisation based on published specialist literature

The applicant must submit a detailed bibliography demonstrating that the constituents of the allergen product:

- are generally used medically for the proposed indication and administration route and
- are acknowledged to be effective and associated with an acceptable degree of safety.

Reference may be made only to published scientific literature. This means that the studies or data are freely accessible and must originate from scientifically acknowledged sources. The applicant must provide a statement on its selection of the submitted publications and justify the transferability of the literature data to the medicinal product to be authorised. The statement should take account of, and evaluate, the current validity and significance of the documentation. All relevant documents and results, both favourable and unfavourable, must be submitted.

5.1.4 Simplified authorisation based on the documentation for a reference medicinal product

The terms “reference medicinal product ” and “related product” are introduced in order to designate the independence of two allergen products that are closely related to each other. The allergens in the related product show a sufficiently close structural relationship with the allergens in the reference medicinal product; the respective source materials show comparable physicochemical and biological properties (see also homologous groups under section 1.2.2).
The authorisation for a related product is issued only to a holder of the authorisation for the reference medicinal product. This ensures that whoever is responsible for the related product in respect of health also possesses all the specialist knowledge on the reference medicinal product. The applicant can apply for the authorisation of the reference medicinal product and related products at the same time. However, a related product can be authorised by Swissmedic only after the authorisation procedure for the reference medicinal product has been concluded with a legally valid approval. Specifically, this means that the authorisations for the reference medicinal product and the related product cannot be officially decided in the same letter. Simplifications for related products require the legally valid authorisation of a reference medicinal product.
If allergens are to be authorised as reference medicinal product and related products, from the group of allergens with a close structural relationship (see also homologous groups in Annex I of the *Guideline on Allergen Products: Production and Quality Issues*[4]*)* the applicant designates a *representative allergen product as a reference medicinal product and the rest of the allergen products as related products.*

In addition, the following conditions must be fulfilled:

d) The allergen extracts for the reference medicinal product and related product are produced by the same manufacturer.
e) The reference medicinal product and related product are produced by the same manufacturer.
f) Extraction and manufacturing processes are identical for the reference medicinal product and related products.

An example follows by way of illustration:

Reference medicinal product:	Birch
corresponding Related products:	1) Alder 2) Hazel 3) Mixture of early bloomers (birch, alder, hazel)[5]

Since comprehensive knowledge of the reference medicinal product in respect of clinical efficacy is required, the clinical significance of the relevant allergy is also taken into account in the classification of an allergen product as a reference medicinal product. For the documentation of the related products, the applicant can rely on relevant data for the reference medicinal product in order to demonstrate stability and in relation to clinical trials. A related product is always based on a single reference medicinal product. However, different related products can refer to the same reference medicinal product.

[4] EMEA/CHMP/BWP/304831/2007
[5] Since birch, alder and hazel all belong to the beech family (lat. *Betulaceae*), they are included in the homologous group of tree pollens of the beech order, birch family (Art. 6 para. 3a AllergO).

Referring to data concerning the reference medicinal product creates a dependence between the related allergen products in a group. If the reference medicinal product is deleted or discontinued for safety reasons, Swissmedic will probably initiate a review of all the related products in the corresponding group for safety reasons as a market surveillance measure. Even if the authorisation of the reference medicinal product is discontinued for other reasons, the marketing authorisation holder must ensure that Swissmedic has a fully documented reference medicinal product for the remaining related products whose authorisation is to be maintained. In many cases, the authorisation holder will probably have to select, and document accordingly, a new reference medicinal product from the group of its authorised related products.
The quality of an allergen product crucially depends on its manufacture. With the currently available analytical methods, allergen extracts / allergen products cannot be described and clearly characterised to the extent required for reliable statements to be made about the comparability of two allergen extracts / allergen products based on experimental testing alone. Comparable quality can be achieved only if the extraction method and manufacturing process do not differ significantly.
Therefore, both the reference medicinal product and the related products must be extracted and manufactured at the same location according to the same processes. This means that the extraction methods and manufacturing processes are identical in nature. Thus, for example, for the reference medicinal product and the related products, the allergens must be extracted from the biological materials in the same way (e.g. by aqueous extraction), and the allergen extracts must exist in the same form (e.g. as chemically unmodified glycerol-containing allergen extract, allergen extract chemically modified with glutaraldehyde or allergen extract bound by adsorption onto aluminium hydroxide). The reference medicinal product and the respective related products must also exist in the same pharmaceutical form (e.g. as solution, suspension or lyophilisate).

5.1.5 Product information

5.1.5.1 Allergen products for in vivo diagnosis

Allergen products for in vivo diagnosis are used exclusively by professionals. On the basis of Art. 14 para. 2 TPLRO, Swissmedic therefore allows the applicant, subject to Art. 10 para. 1 AllergO, the option of enclosing the Information for healthcare professionals as a package insert instead of the Patient information for these products (without the need to submit an application to Swissmedic in advance).
A common Information for healthcare professionals can be created for a reference medicinal product and the corresponding related products (Art. 10 para. 2 AllergO).
In justified cases, a common Information for healthcare professionals can be created for an applicant’s epicutaneous or patch tests (Art. 10 para. 3 AllergO).

5.1.5.2 Allergen products for SIT

Normally, an Information for healthcare professionals is sufficient for allergen products used for SIT. A Patient information must be created for any oral pharmaceutical forms that are taken by the patients themselves. Subject to compliance with the preconditions of Art. 14 para. 2 TPLRO, Swissmedic can, in individual cases and on request, approve the waiving of a Patient information.
In view of the relationship that exists between related products and the reference medicinal product, the applicant can create a common Information for healthcare professionals and a common Patient information (Art. 14 AllergO).

5.2 Requirements for the documents to be submitted

5.2.1 Administrative documents (Module 1)

The formal requirements regarding applications in general, and the formal requirements for Module 1 and the cover letter are laid down in the guidance document *Formal requirements HMV4* and in the associated directory, *Overview of documents to be submitted*.

5.2.2 Analytical, chemical and pharmaceutical documentation (Module 3)

5.2.2.1 General

The “Allergen products” monograph of the European pharmacopoeia, which is also valid in Switzerland, formulates binding requirements pertaining to the quality of the allergen products. These describe the quality of the allergen products both for in vivo diagnosis and for SIT. The scope of this monograph on “Allergen products” does not include chemical substances that are used exclusively for diagnosing contact dermatitis (e.g. epicutaneous tests), chemically synthesized products, biotechnologically produced (by rDNA technologies) allergens or preparations manufactured as individual formulations (magistral formula).
The competent committee of the European Medicines Agency (*Committee for Medicinal Products for Human Use, CHMP*) has described recommendations and principles concerning the requirements for the manufacture and quality of allergen products in the document *Guideline on Allergen Products: Production and Quality Issues*[6]. These basic requirements are internationally acknowledged as representing the scientific state of the art; they should accordingly be considered as such by the applicant. As a special feature, this document mentions the concept of homologous groups, which can be claimed to serve as a simplifying element in the event of a proven close relationship of allergen extracts in different allergen products. This concept is taken into account with the introduction of the terms “medicinal product” and “related product” for allergen products (Art. 4 ff. AllergO). Annex I of the aforementioned EU *Guideline* lists the individual homologous groups formed to date. These identify those source materials for which the relationship between a reference medicinal product and a related product can be assumed without a comprehensive justification (e.g. between the pollen of Betula verrucosa, white birth, and the pollen of Corylus avellana, common hazel), as well as those source materials for which this possible relationship must be justified in detail (e.g. for the tree pollen of Fagus sylvatica, copper beech, and the tree pollen of Robinia pseudoacacia, false acacia). If a corresponding justification and data are submitted, additional groups can be formed or new

[6] EMEA/CHMP/BWP/304831/2007

candidates added to existing groups. The European Medicines Agency plans to update Annex I of the *Guideline on Allergen Products: Production and Quality Issues* at regular intervals to keep it in line with the state of the scientific and technical art.
For allergen products, the quality of the active substances cannot be described in *Drug Master Files* (DMF).
Consistency must be demonstrated for at least three batches.
Within homologous groups, only the stability of the reference medicinal product needs to be demonstrated.

5.2.2.2 Allergen products for in vivo diagnosis

The scope of the documentation on quality is specified in Art. 11 TPA and Art. 3 TPLRO. All of these documents should be submitted for a reference medicinal product. As proof of the shelf life, a related product can rely on the stability data for the reference medicinal product, provided the applicant can prove the transferability of these results (Art. 7 AllergO).
For epicutaneous or patch tests, Swissmedic expects, as a minimum, information on the allergens used, the matrix used and the concentration in which the corresponding allergen is present in the mentioned matrix. Moreover, the homogeneous distribution of the allergens in the matrix and the stability of the ready-to-use allergen products must be demonstrated.
For other in vivo diagnostic agents, i.e. for intracutaneous, prick and provocation tests, the required scope of the qualitative and quantitative characterisation is based on the current state of knowledge concerning the respective allergens, the available sera / antibodies as reagents for the analyses and the frequency of the corresponding allergy.

5.2.2.3 Allergen products for SIT

The scope of the documentation on quality is specified in Art. 11 TPA in conjunction with Art. 3 TPLRO. All of these documents should be submitted for a reference medicinal product. As proof of the shelf life, a related product can rely on the stability data for the reference medicinal product, provided the applicant can prove the transferability of these results (Art. 11 AllergO).

5.2.3 Non-clinical and toxicological documentation (Module 4)

According to Art 4 TPLRO, the documentation on the pharmacological and toxicological tests can be submitted in bibliographic form if sufficient evidence is available in the published specialist literature (Art. 12 AllergO).
The nature and scope of the requirement documentation depend on the composition of the medicinal product. If the active substances and excipients are sufficiently known, with published studies and data on their pharmacological and toxicological properties, new investigations are not required, and bibliographic documentation can be submitted if it can be shown that the results in the cited sources in the published specialist literature can be transferred to the product.
Allergen products (with active substances that are usually prevalent) have a special status, since their active substances represent allergens with a risk to allergic individuals, but harmless antigens to non-allergic individuals. For many allergies, including asthma, rhinitis, hay fever, atopic dermatitis etc. no suitable animal models exist. With adequate justification in the expert report, the scope of the documentation can be restricted accordingly.

5.2.4 Clinical documentation (Module 5)

5.2.4.1 Allergen products for in vivo diagnosis

The documentation on clinical trials according to Art. 5 TPLRO must substantiate those aspects that are relevant for in vivo diagnostic agents. The efficacy of allergen products for in vivo diagnosis is characterised with the parameters of specificity, sensitivity and clinical relevance. Therefore, Art. 9 AllergO does not grant any further simplification, but specifies how the diagnostic efficacy should be demonstrated.
In the multicentre project IVDK (Information network of departments of dermatology), allergy departments from 40 skin clinics in Germany, Austria and Switzerland are collaborating on the recording, documentation, central evaluation and publication of data recorded in connection with the diagnosis of allergic contact dermatitis. In the selection of the epicutaneous tests to be used, all IVDK clinics follow the recommendations of the German contact allergy group (DKG[7]). The DKG has compiled epicutaneous test series that currently cover over 250 allergens. These specify both the concentrations of the individual allergens and the matrix to be used. The safety and efficacy of the epicutaneous tests described by the DKG are generally acknowledged. Swissmedic takes this into account accordingly. If the applicant follows the DKG recommendations in respect of allergen concentration and matrix, the safety and efficacy do not need to be demonstrated again in the authorisation documentation.
For intracutaneous tests, prick tests and provocation tests, and depending on the state of knowledge and the frequency of the allergy to be diagnosed, the specificity, sensitivity, clinical relevance and safety of the allergen product should be demonstrated with clinical trials or with a justified number of application documents. The documentation can be based on the data for a reference medicinal product if the applicant can prove that the results can be transferred to the related product (Art. 9 para. 3 AllergO).

5.2.4.2 Allergen products for SIT

SIT has been used for many decades in the treatment of allergic disorders. In SIT, allergens to which the patients are allergic are usually injected, or e.g. taken by mouth, in rising doses. The corresponding ICH guidelines for conducting the clinical trials designed to document the efficacy and safety of new allergen products in the scheduled dosage should be observed[8].
The competent committee of the European Medicines Agency (*Committee for Medicinal Products for Human Use, CHMP*) has described recommendations and principles in the document *Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases*[9]; these are acknowledged as representing the state of the art and should accordingly be considered as such by the applicant.
The studies must be conducted with the reference medicinal product intended for the authorisation and specifically focus on the intended indication dosage, administration route and duration of treatment. The inclusion and exclusion criteria for the study participants should be clearly defined in respect of the allergic disease using specific detection methods. A basic distinction should be made

[7] DKG
[8] ICH Guidelines
[9] CHMP/EWP/18504/2006

between seasonal and perennial[10] allergic disease. Any co-medication and all emergency treatments defined for use during the study must also be specified. In the case of seasonal pollen allergy, the pollen count in the environment must be recorded.
As regards the strategy and design of the clinical studies, the applicant can normally dispense with the standard pharmacokinetic and pharmacodynamic studies. However, the main studies must include a dose-finding part (Phase II) for the intended dosage regimen and a Phase III study, which must (usually) be placebo-controlled and large enough to clearly demonstrate the efficacy of the SIT. The Phase III must normally last for 2-3 years. Comparative studies against an authorised allergen product should be envisaged for e.g. insect venom allergies, since a placebo would not be acceptable for these patients. Studies with children must be planned and implemented specifically. The indication, dosage, administration route, duration of treatment and age of the patients proposed for authorisation must correspond with those in the Phase III studies.
The endpoints of the clinical trials should be adapted to the disease. The primary endpoint should include the severity of symptoms. Secondary endpoints can include provocation tests (e.g. rhinomanometry).
The safety of the SIT must be documented in sufficiently large studies. A proven positive benefit-risk ratio is crucial for authorisation.
The documentation for the clinical trials according to Art. 5 TPLRO can be based on the data for the reference medicinal product if the applicant can demonstrate that the results can be transferred to the related product.

[10] perennial = year-round

Change history

Version	Change	sig
1.2	New layout, no content adjustments to the previous version.	dei
1.1	Formal adjustments to the header and footer No content adjustments to the previous version.	dri
1.0	Implementation of TPO4	stb