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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON ALLERGEN PRODUCTS

Revised *

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7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 84 00 Fax: (+44-171) 418 85 51
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

ALLERGEN PRODUCTS

Note for Guidance

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1. INTRODUCTION

Directive 89/342/EEC extends the scope of Directive 65/65/EEC and 75/319/EEC to immunological medicinal products consisting of vaccines, toxins or serums and allergens. For this purpose, Article 1, paragraph 2 of Directive 89/342/EEC defines 'allergen product' as any product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergising agent. Thus, the adoption of Directive 89/342/EEC implies that any allergen's product is now subject to the requirements of EEC pharmaceutical legislation, namely as regards the quality, safety and efficacy testing and marketing authorisation. However, Directive 89/341/EEC also lays down exemptions from the general requirements of the EEC pharmaceutical legislation. Under Article 1, paragraph 4 of this directive, a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from Chapters II to V of Directive 65/65/EEC medicinal products supplied In response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health care professional and for use by his individual patients on his direct personal responsibility ('named patient exemption').

Therefore, for the purpose of this note for guidance, allergen products are divided into two categories:

a) industrially produced allergen products containing either a single allergen or defined mixtures placed on the market as medicinal products either for:

   · the purposes of in vivo diagnosis or for

   · treatment of allergic disease;

b) allergen product prepared on the basis of an individual prescription and intended to be used on a 'named patient' basis.

This Note for Guidance only refers to industrially produced allergen products placed on the market as medicinal products for the purpose of in vivo diagnosis or for treatment of allergic disease (point a) above).

2. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

2.1 Qualitative Particulars

The name (scientific name, e.g. genus and species as well as any common name), and type (e.g. pelt, dander, saliva) of the allergenic source material(s) should be stated. In the case of modified or adsorbed allergen products, this and the agents used in the modification procedures should be described. For all the excipients, the names, grades and quantities should be given. This also includes the composition of any separate packaged dilution or reconstitution fluid to be used with the product.

2.2 Quantitative Particulars

Whenever possible, the potency of the active ingredient should be expressed in units of biological activity, and the unit system used should be unambiguously indicated, in order to avoid confusion with similar unit systems currently in use on the market.

3. DESCRIPTION OF METHOD OF PREPARATION

The manufacturing process within the meaning of this section is the preparation of the finished product from the starting materials. The description should include details of any process employed, in particular sterilisation, filling, freeze-drying, addition of any preservative and of any stabiliser. Whenever materials of human or animal origin are present in the finished product as excipients, particular attention should be given to safety from transmission of infectious diseases. The use of materials and/or excipients known to give rise to sensitisation should be avoided or justified.

4. CONTROL OF STARTING MATERIAL

4.1 General Requirements

The allergenic source material should be described in as much detail as possible. Details concerning collection, pre-treatment and storage should be supplied for each separate alIergen. The name and the address of the supplier shall be stated. Specifications and control methods for the source material(s), applied by the supplier, should be included. The specifications should ensure that the qualitative and quantitative composition of the material is as uniform as possible from one delivery to another. They should encompass requirements and control methods relating to identity and purity. Quality control of source materials should be documented. The source materials should be stored under controlled conditions.

4.2 Additional Requirements for Specific Source Materials

4.2.1 Pollens

Nature of the fields, seeds used, field characteristics and treatment, visual control, manner of collection and random sampling should be described. The manner of collection of pollens should be stated. Tests for content of foreign pollens, spores, extraneous plant material from the same species and non-related contamination should be included. The content of representative pesticides and lead should be measured on a limited number of pollen batches, in order to demonstrate that their level is kept at a minimum.

The pollen content from other species should be limited to 1% of mixed pollens and 0.5% of a single pollen as determined by a microscopic particle count. Detectable spores should not exceed 1%. Contamination by particles of plant origin, other than pollen, should not exceed a total of 10% in terms of microscopic count. Justification should be given if these standards cannot be compiled with.

4.2.2 Moulds

The strain or strains of moulds should be specified. The cultivation method should be described. Details of the composition of the cultivation medium should be submitted.

Strains which produce mycotoxins such as aflatoxins or ochratoxins should not be used unless justified. In this case, the source material should be tested for mycotoxins; the source materials should be tested for mutagenicity before processing unless the removal of mycotoxins has been validated.

Synthetic and consequently allergen-free media shall preferably be used. Morphological characteristics (mycelium and spores/spores only/ mycelium only) as well as the cultivation method in the isolated raw material should be specified. Conditions of culture must be validated to provide evidence that mycotoxins are not produced.

4.2.3 Mites

The cultivation method and the composition of the cultivation medium should be described. When substrates of human origin are used in the culture medium, the absence of risk of transmission of infectious diseases should be demonstrated. To this end, the manner of collection of these substrates should be described in detail. Any allergenicity of the medium should be as low as possible in order not to produce any unspecific reactions of the finished product. Therefore, the use of animal dander or any animal protein in the culture medium should be avoided. It should be indicated whether for further processing, mites only or the whole mite culture is used.

4.2.4 Animal allergens

The species of the animal should be stated. An account should be given of the health examination of the animals from which the raw materials are collected. Materials should be collected from animals that do not exhibit overt infections at the time of collection. The collector should certify that the animals used are overtly healthy and have not recently been treated with antiparasitics or other drugs.

When killed animals are used, the epidermals should be collected within a few hours. The animal must be stored in conditions ensuring that post-mortem decomposition processes do not affect the epithelium; these storage conditions should be described. Collection of hair and dander must take place using methods which provide a good epithelial harvest without injuring the skin of the animal. Methods employing the grinding of whole skin/pelts must not be used. The composition of the final source material (e.g. hair, dander, pelt, saliva, urinary fluid) should be indicated.

4.2.5 Hymenoptera venom

The method of collection of venom from the venom sacs of hymenoptera species should be described and should be such as to ensure that the raw material is of a proper quality.

4.3 Description of the Production Process

The production process should be described, step by step with a diagram (flow-chart) indicating the principles of the process, accompanied by an explanatory text. The different stages of the production process, such as grinding, extraction, filtration, clarification, dialysis, concentration, fractionation, sterilisation, lyophilization etc. should be clearly defined. The description should state the stage at which aseptic precautions are introduced. Intermediate or bulk products in the process should be identified and the in-process controls performed at these or other stages of production reported. The principle of the purification and

fractionation methods should be defined, and it should be clearly apparent at which step in the process special biochemical techniques are used.

The manufacturer should demonstrate his capability of obtaining batch to batch consistency.

4.4 Batch to batch consistency

Since allergen products are generally represented by a complex mixture of allergenic and non-allergenic components, they cannot be easily standardised and each component cannot be defined, with a few exceptions, in a quantitative way. Although some international reference preparations or standards are available, It is commonly accepted that allergenic extracts cannot all be standardised in the same manner as the other biological products.

An extract will be different from one company to another and possibly, within a single company, from one batch to another. These characteristics represent a real problem as regards any future harmonisation of the extracts between companies. It must be stressed that at least a good batch to batch consistency has to be reached by a company within its production runs by introducing in House Reference preparations (IHR) which should be used as internal reference preparation and using a number of biological and analytical methods. The IHR is derived from a production run following the manufacturing process defined in the dossier; it establishes a reference point against which extracts from all future production runs will be compared. Thus the qualitative composition of regular production batches should match the IHR.

4.4.1 Characterisation of the in house reference preparations (IHR)

The IHR shall be characterised using available relevant methods and its specific allergenic activity shall be established, and data should be provided on protein and, whenever possible, carbohydrate composition. Some of the following methods should be applied: Crossed-immunoElectrophoresis (CIE), isolectric focusing, electrophoresis in polyacrylamide gel, determination of the distribution of molecular weight by SDS-PAGE analysis, HPLC, gel electrophoresis and quantitative determination of total protein. Information regarding the allergenic specificity of the proteins in the IHR may be obtained from experiments involving combinations of electrophoretic methods and immunoblotting techniques or Crossed-Radio-immuno-Electrophoresis (CRIE). Sensitivity spectra (allergograms) derived from such basic documentation, thus identifying the major, intermediate and minor allergens. The presence of all relevant allergens in the IHR shall have been demonstrated in comparative studies involving several batches of extract. As far as possible, the individual allergens should be identified using internationally accepted nomenclature or the correspondence with allergens described in the scientific literature should be given, including literature references. The potency of this IHR should be judged by immuno-assays (e.g. IgE-inhibition, ELISA-techniques, immunofluorescence techniques) or/and Skin Prick Test and expressed in terms of Units of Biological Activity. When a product consists of one or a few well characterised allergenic components, potency can be assayed by means of alternative relevant techniques, such as single radial immunodiffusion, quantitative immunoelectrophoresis or other quantitative techniques. All these methods and the immunological reagents mentioned above should be in accordance with the scientific knowledge at the time of application.

The stability of the IHR and storage conditions should be documented.

4.4.2 Use of the IHR

The characterised and standardised IHR for a given allergen product should be used to prove batch to batch consistency, by using relevant methods already employed in the characterisation and standardisation of the IHR. The choice of the methods used must be justified and limits for variations of the method should be defined and documented.

5. CONTROL TESTS CARRIED OUT AT AN INTERMEDIATE STAGE OF THE MANUFACTURING PROCESS OF THE FINISHED PRODUCT

Control tests carried out at intermediate stages of manufacture should be defined. When certain control tests cannot be applied to the finished product, for instance in the case of chemically modified, precipitated or adsorbed allergen preparations, quality specifications should be defined for the product just prior to the modification, dilution, etc.

6. CONTROL TESTS CARRIED OUT ON THE FINISHED PRODUCT

Measurements of the total allergenic activity of individual batches of an allergen extract should be undertaken preferably by IgE Inhibition or by direct IgE-binding or other immuno-assays, all methods having to be suitably validated.

The estimated potency derived from the assay of total allergenic activity should be not less than 50% and not more than 200% of the stated potency.

The characteristics of the finished product should ideally be documented for all strengths (dilutions). Where appropriate testing is not possible due to methodological limitations, this should be justified.

For adsorbed/modified products, where measurement of allergenic activity is not possible on the finished product, documentation of adsorption/modification should be provided.

7. STABILITY

The note for guidance "Stability tests on active ingredients and finished products" should be followed. However, In some circumstances, It is impossible or difficult to fully evaluate the allergenic potency and other characteristics of the finished product. In these cases, such as adsorbed-modified or adsorbed-unmodified allergens, it would be acceptable to carry out stability tests just before applying the modifying treatment.

In addition, the stability of adsorption should be monitored over the proposed shelf-life, since free allergens can cause immediate (anaphylactic) reaction.

For stability data, the concept of taxonomic family may be applied and data obtained on one member of such a family may be extrapolated within that same family. This extrapolation should be discussed and justified. In the case of mixtures of members of different taxonomic families, extrapolation is not acceptable.

No less than 30% of the stated allergenic activity should be maintained at the end of shelf-life.

8. SAFETY TESTING

Details of the safety testing undertaken should be provided. Safety testing may have to be adapted to individual products and, if so, any omissions with regard to the requirements laid down in Part 3 of the Annex to Directive 91/507/EEC should be justified.

For safety testing, the concept of taxonomic family may be applied and data obtained on one member of the family may be extrapolated to another member of that family providing the manufacturing procedures applied are the same. In the case of mixtures of members of different taxonomic families, extrapolation is not acceptable.

9. EFFICACY TESTING

Details of clinical trials performed should be provided.

For the performance of clinical trials, the concept of taxonomic family may be applied and data obtained on one member of the family may be extrapolated to another member of that family providing the manufacturing procedures applied are the same. In the case of mixtures of members of different taxonomic families, extrapolation is not acceptable.