Guidance Document

for

Regulation and Control of Indigenous Allergen products

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Chronology of Events

S. No.	Activity	Process Time
1.	Draft of guidance document prepared and forwarded to members of National Expert Committee for review and comments	27.06.2016
2.	Ist Draft Guidance Document placed on NIB Website for inviting comments from Industry Stakeholders *No comments received during this period*	01.07.2016 to 31.07.2016
3.	Discussion for Finalization of Guidance Document for indigenous Industry in the 5th Meeting of National Expert Committee on modalities for batch release of Allergen Extracts	12.07.2016
4.	Approval of draft guidance document in 6th National Expert Committee meeting on Allergen products.	29.09.2016
5.	Guidance document to be placed on NIB website	November 2016
6.	Discussion on Guidance Document with manufacturers in 9th National Expert Committee meeting on Allergen Products. Approved amendments incorporated.	25.04.2017
7.	Updated Guidance Document to be placed on NIB website.	June, 2017

Table of Contents

Guidance document published by National Institute of Biologicals (NIB) is intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for indigenous manufacturers of Allergen Products.

1.0 INTRODUCTION

Allergy is a disease that is a consequence of Type I hypersensitivity reactions which are vigorous responses of the immune system triggered by the interaction of allergens with specific immunoglobulin E (IgE) antibodies leading to the release of inflammatory mediators including histamine, cytokines and lipid mediators. Allergies are one of the most prevalent diseases globally.

Allergen products that are used to diagnose or treat allergic diseases are defined as “Pharmaceutical preparations derived from extracts of naturally occurring source materials containing allergens ...”

While test allergens are an important part of clinical allergy diagnosis, SIT with allergen products containing the same antigens is an immuno-modulatory treatment option which is intended to generate persistent relief from allergy symptoms.

Allergen extracts have been used for diagnosis and treatment of allergy for around 100 years. During the second half of 20th century, the notion increasingly gained foothold that accurate standardization of such extracts is of great importance for improvement of their quality. As a consequence, manufacturers have implemented extensive protocols for standardization and quality control.

The success of immunotherapy (IT) depends on proper selection of patients, allergens, doses, quality of allergens, and compliance to the treatment. The treatment of allergic diseases is based on allergen avoidance, pharmacotherapy, allergen immunotherapy and patient education. Standardized allergen extracts of known potency and defined shelf life should be used both for allergy diagnosis and immunotherapy. However, efforts are required to upgrade the standardization of antigen defined with Allergy Unit, etc. Quality control is crucial for safe and effective diagnosis and treatment.

The Manufacturers should maintain a high quality of antigens, especially the potency, purity, and specificity.

Guidance is available in western/ developed countries, but India specific Guidance is required considering the following factors:

(1) variations in the soil characteristics and the environment of India from western world,

(2) difference in the type of allergens, as in India outdoor allergens are more common than indoor allergens, which are more common in western countries,

(3) keeping pets is not very common in India but cattle are commonly inhabitated in the residential campus in villages,

(4) having various types of food items, and thus exposure to many possible allergens,

(5) most of Indian population is agrobased, and

(6) the financial capability may be limited with respect to costly investigations, like specific IgE.

This guidance document has been prepared consulting the literature and inputs from members of NIB National Expert Committee constituted by CDSCO and approved by Hon'ble HFM on modalities for batch release of Allergen Extracts in India in August 2014.

2.0 BACKGROUND

Batch to batch inconsistency and non-standardized commercial allergenic extracts used in India and abroad for diagnosis and immunotherapy compromise accuracy of in-vivo diagnosis by skin prick tests and effective allergen immunotherapy. There is a need to upgrade the quality control of allergen extracts and develop allergen certification center in India similar to Food and Drug Administration (FDA) and Centre for Biologics Evaluation and Research, (CBER) USA. So far, the only Monograph on Allergens is available in European Pharmacopoeia. In view of above, guidance document is required to guide the indigenous manufacturer to prepare standardized allergen extracts of high quality

3.0 PURPOSE

This note is intended to provide guidance on the type of data / information which should be attached with the application for manufacturing / marketing authorization of allergen products in India.

4.0 SCOPE

This document refers to commercially produced allergen products (such as animals, pollen, moulds, mites, venoms etc.) containing either a single allergen or defined mixtures manufactured in batches and placed as medicinal products either for:

– The purposes of in vivo diagnosis i.e. diagnostic.

– Treatment of allergic disease i.e. immunotherapy, custom made for therapeutic use.

5.0. GUIDANCE FOR IMPLEMENTATION

5.1. Definition:

Allergen products are used for:

1. *in vivo* diagnosis
2. Immunotherapy

5.2. **Groups and Families of Allergens**

Allergen products are derived from several groups of allergen source materials such as pollen, mites, animals, food substances, chemicals etc. Such groups are not necessarily homogeneous.

The allergen products may be classified in following groups:

5.2.1 Pollen: Grass, weeds and trees

5.2.2. Fungi (moulds): such as *Alternaria, Cladosporium, Aspergillus*

5.2.3. House dust mite: such as *D farinae, D pteronyssinus*

5.2.4. Insect: such as Cockroach, Moth, Mosquito

5.2.5. Animal allergens (for each animal species): Such as epithelial, dander, feathers.

5.2.6. Stinging insects: such as Honey bee

5.2.7. Dusts: such as House dust, cotton dust, silk

6.0 GENERAL REQUIREMENTS FOR ALLERGEN PRODUCTS:

a) Name of the allergenic source material(s):
(Scientific name, e.g. genus and species, any common name / synonym)

b) Type of the allergenic source material(s):
(e.g. pollen, fungus etc.)

c) Name of excipients with details of grades and quantity:

d) Composition of diluent or re-constitution fluid:

e) Concentration (expressed in weight / volume and / or protein content)

6.1 Starting Material:

6.1.1 Source material(s): Description of following to be provided in detail by the manufacturer

a) Name and address of the manufacturer
b) Details of collection
c) Place of collection
d) Processing
e) Storage conditions for each allergen.
f) Purity of raw material
g) All substances of animal origin shall be either sterilized or subject to an inactivation procedure by a suitable validated method or tested to be free from extraneous agents.

6.1.2 Additional requirements

a) For biological activity each allergen product shall be tested separately
b) Prevention of cross contamination

1 **Pollen:**

a) The manner of collection of pollen should be stated. Tests for

content of foreign pollen, spores, extraneous plant material from the same species and non-related contamination should be included. Thresholds for these contaminants should be established.

b) The pollen content from other species should be limited to 1% of mixed pollens and 0.5% of 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 complied with.

2 **Moulds:**

a) The strain of mould should be specified.

b) The cultivation method and its duration should be described.

c) Details of the composition and preparation of the culture medium should be submitted.

d) Strains which produce mycotoxins such as aflatoxins should not be used.

e) 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 for preparation of the allergen products shall be specified.

3 **Mites:**

a) The cultivation method and the composition and preparation of the cultivation medium shall be described.

b) Purity to be specified

4 **Animal allergens: epithelial (dander), feathers**

a) The species / breed of the animal shall be stated.

b) Materials should be collected from healthy animals that do not exhibit overt infections at the time of collection.

c) The composition of the final source material (e.g. dander, feather) should be indicated.

5 **Stinging / non-stinging insects:**

The genus, species and the source of procurement of insects / venom should be described.

6.2 Control of Raw Material

Raw materials not described in Indian Pharmacopoeia

The recommendations given in section “raw materials” shall apply for raw materials for method of preparation and testing of raw materials. The following details should be provided.

For products of biological origin testing should cover the identification characteristics, and the bio-potency (SPT on patients).

Data should be maintained for protein profile of each allergen product by SDS-PAGE.

6.3 Description of the Production Process

The production process should be described using flow-chart diagrams indicating the principles of the process, accompanied by an explanatory text. The different stages of the production process, such as grinding, defatting, extraction, clarification / filtration, dialysis / ultrafiltration, sterilization, 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 should be reported.

The manufacturer shall ensure batch to batch consistency.

7.0 FINISHED PRODUCT- ASSAY RESULTS REQUIRED IN THE APPLICATION FOR MARKETING AUTHORIZATION

As applicable for raw material.

7.1 Safety Testing

i) Safety data must be generated using the maximum concentration and dose of product (single allergens) which is to be recommended for administration at one time.

ii) Efficacy data are required to support the claims being made using the product administered in accordance with the proposed recommendations for use.

iii) Scientific literature can play an essential part in the documentation of efficacy provided it is relevant to the product to be marketed. Where such publications do exist, they may be used as supporting evidence of efficacy.

iv) For any new allergen product not approved anywhere in the world has to submit the pre - clinical and clinical data.

v) Since only a very small number of a given species may be allergic to certain Diagnostic and Therapeutic products case reports may be accepted, as supporting evidence of efficacy.

vi) Post marketing surveillance data shall be provided by the manufacturer.

7.2 Stability

A shelf life longer than 12 months is only acceptable with stability studies obtained by immunological methods.

7.3 Batch to Batch Consistency

The manufacturer shall ensure batch to batch consistency based on protein profile of each extract by SDS-PAGE.

8.0 FINISHED PRODUCT – BATCH TESTING

8.1 Control Tests carried out on the Finished Product

i) Measurements of the allergenic activity of individual batches of an allergen extract should be undertaken preferably by Skin Prick Tests (SPT) on patients.

ii) A sterility test and any other test should be performed in accordance with the IP.

9.0 INFORMATION TO BE PROVIDED BY THE MANUFACTURER WITH THE APPLICATION

A detailed information / documents will be submitted by the manufacturer at CDSCO for issue of license / marketing etc. in the checklist approved by the National Expert Committee (Annex-I)

10.0 CHRONOLOGY OF COMPILATION

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11.0 REFERENCES

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2. Allergen Products. European Pharmacopoeia 8.2, pp 3945-3947.
3. Specific Requirement for the production and control of allergen products. September 1994. Directive 81/852/EEC as amended.
4. Guidelines on Allergen Products: Production and Quality. Issue: May 2009.
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Annexure-I

CHECKLIST FOR VERIFICATION OF INFORMATION TO BE PROVIDED BY APPLICANT AT CDSCO

General Information for allergen products:

Additional information to be furnished for in-vitro & in-vivo Allergen products (see overleaf)

1	Name of Manufacturer/ Importer		
2	Product Name • Name • Brand name • Batch No. / Lot No. • Date of Expiry		
3	Intended Use	*In vitro*	*In-vivo*
		1. Diagnostic 2. R & D	1. Diagnostic (SPT/ ID) 2. Therapeutic 3. R & D
4	Manufacturing	Indigenous/ imported	Indigenous/ imported
5	License No: Manufacturing / Import Valid up to Attach authenticated copy of manufacturing license/ Free Sale Certificate issued by NRA		
6	Bulk Material:	Imported/ Indigenous	Imported/ Indigenous
7	Details of manufacturing procedures/ steps concerning Tests i) Microbiological testing (Sterility testing) ii) Protein Content by Modified Lowry Method# iii) Protein Profile: SDS PAGE pattern iv) Biological testing (Skin Prick Test) Comparison of old vs new batch to be done by the manufacturer	Provided/ Not provided	Provided/ Not provided
8	Dispensing / Packing done	Locally/ Source Country	Locally/ Source Country
9	Relevance of Allergen for Indian patients Bibliography references if available for India. *Allergens for which literature about their Allergenicity on Indian patients is not available but if international/ global data is available, may be permitted only for research to generate Indian data.*	Provided/ Not provided	Provided/ Not provided
10	Storage and Transport conditions	Provided/ Not provided	Provided/ Not provided
11	List of end users in India (Clinicians/Allergy Centers)	Provided/ Not provided	Provided/ Not provided

Annexure-I contd.

CHECKLIST FOR VERIFICATION OF INFORMATION TO BE PROVIDED BY APPLICANT AT CDSCO

Additional Information required for in-vivo Products

S. No	Documents Required (in English)	Documents submitted Yes/No	Comments	Compliance status
1	**Details of Allergens**			
	Common Name			
	Scientific Name (up to species name)			
	a) Single Allergen (Purified / Crude Extract) b) Mixed Allergens (Purified / Crude Extract)			
2	**Literature or Instructions for use.**			
3	**Any other information**			

Additional Information required for in-vitro Products

S. No	Documents Required (in English)	Documents submitted Yes/No	Comments	Compliance status
1	**Details of Coated Allergens**			
	Common Name			
	Scientific Name (up to species name)			
	Allergen(s) :Single / Multiple / Mixed			
	In case of Multiple or Mixed Allergens a) Represent Single kit b) Represent Multiple kit			
	Nature of Coated Allergen : a) Crude Extract b) Purified Extract c) Recombinant Product d) Purified Protein			
2	**Product to be used for :** a) Quantification of Total IgE b) Quantification of Allergen specific IgE c) Component of kit (Reagents etc.) **d)** Equipment/ System			
3	**Operation manual or Instructions for use.**			
4	**Laboratory test results verifying the product's specifications.**			
5	**Intended Use:** • **Diagnostic**: SPT/Patch/Intradermal • **Therapeutic**: SCIT/SLIT • **R&D**			
6	**Any other information**			

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Signature of the authorized personnel of manufacturer