Quality of Allergen Products for Specific Immunotherapy – A Guidance for Industry for Compilation of Module 3 for the EU CTD (Quality) Considering the German Therapy Allergen Ordinance, the revised European Pharmacopoeia Monograph on Allergen Products (2010:1063) and the new "Guideline on Allergen Products – Production and Quality Issues" (EMEA/CHMP/BWP/304821/2007)

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Regulatory Affairs is a very dynamic field. This thesis reflects the regulatory situation for allergen products for SCIT derived from natural source materials as of May 2010.

List of Abbreviations

AMG	German Medicinal Products Act
CREATE	Development of Certified Reference Materials
	for Allergen Products and Validation of Meth-
	ods for <i>The</i> ir Quantification
CHMP	Committee for Human Medicinal Products
CofA	Certificate of Analysis
CTD, EU-CTD	Common Technical Document, European ICH
	Region-CTD
DP	Drug Product
DS	Drug Substance
EP, Ph. Eur.	European Pharmacopoeia
ELISA	Enzyme-Linked Immunosorbent Assay
EMA, EMEA	European Medicines (Evaluation) Agency
GMP	Good Manufacturing Practice
IHRP	In-House Reference Preparation
IgE, IgG	Immunoglobulin E, Immunoglobulin G
MAA	Marketing Authorization Application
NCE(s)	New Chemical Entity(ies)
NPP(s)	Named Patient Product(s)
MHC Class II	Major Histocompatibility Complex Class II
NCA	National Competent Authority
PEI	Paul-Ehrlich-Institut
RA	Regulatory Affairs
S(C)IT	Specific (Subcutaneous) Immunotherapy
TAV	Therapy Allergen Ordinance
TH-1 Cells, TH-2 Cells	T-Helper Cells types I and 2
US, USA	United States of America

For convenience, the German abbreviation for legal documents such as "German Medicinal Products Act (AMG) was retained although the titles translated to English are different.

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1. Objectives

The regulatory environment for allergen products in Germany has undergone significant changes in recent years. Novel regulatory requirements were introduced with the Therapy Allergen Ordinance, issued in 2008, that put especially named patient products under a more stringent control by the Paul-Ehrlich-Institut (PEI). Furthermore, the quality standards and requirements for allergen products were raised with the revised Guideline for Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007) and a revised monograph on allergen products (2010:1063 Producta Allergenica) of the European Pharmacopoeia. In response to these changes, manufacturers have to meet the challenge of establishing marketing authorization application dossiers for allergen products that were marketed as Named Patient products without marketing authorization. What is more, available guidance on the compilation of dossiers for these products is very limited.

This thesis aims to offer such guidance focusing on allergen products derived from natural sources for subcutaneous use in specific immunotherapy.

Therefore, the novel regulatory requirements as stipulated in the Guideline for Allergen Products and the revised monograph on allergen products 2010:1063 shall be summarized and the changes in comparison to the Note for Guidance on allergen products and the former version of the monograph on allergen products highlighted.

The "Concept of Homologous Groups" as scientific basis for many new quality requirements concerning allergen products shall be presented.

Considering these novel regulatory requirements, a quick reference manual for the compilation of Module 3 of the EU CTD for allergen products intended for subcutaneous specific immunotherapy shall be developed on the basis of the current ICH M4Q (R1) guideline.

2. Introduction

This chapter presents a brief introduction to allergy and asthma, specific immunotherapy, the concept of named patient products and the recent regulatory changes for allergen products.

2.1 Allergen Products for Specific Immunotherapy

2.1.1 Allergy and Asthma

The prevalence of allergic diseases and asthma is steadily increasing all over the world. The worldwide prevalence of asthma is estimated to 300 million individuals with annual death rates of over 250,000 individuals.¹ In Germany, the incidence of allergic rhinitis and asthma has risen about 5 % per year since the 1950s. 12 % of the German population suffer from allergic rhinitis, 10 % from asthma and about 9 % from contact allergies². In Europe, it is estimated that asthma costs an annual sum of 22 billion \notin ³ with Asthma-related costs exceeding the financial burden of HIV/AIDS on healthcare systems worldwide⁴. Meanwhile, it is recognized that allergic rhinitis is a pre-stage of asthma. If allergic rhinitis is left untreated, the continuous stress on the upper respiratory pathways can lead to inflammation of the lower airways, resulting in asthma⁵. Therefore, it is imperative to treat allergic rhinitis and other allergic diseases as early as possible on a symptomatic and a causative level⁶.

Symptoms of allergic diseases can be treated with antihistamines and corticoids; the only causative treatment, however, is de-sensitization employing specific immunotherapy (SIT, see 2.1.2).

2.1.2 Specific Immunotherapy

Allergen avoidance is not always feasible; therefore, SIT as causative treatment can provide relief for patients suffering from Immunoglobulin E (IgE)-antibody mediated Type I allergic diseases⁷. The products for SIT that are currently marketed comprise nasal sprays, sublingual forms (tablets, solutions) and solutions for injection⁸. Within the scope of this thesis, the focus shall be on solutions for subcutaneous administration (SCIT) derived from natural source materials, which have been established as effective treatment in the following indications: IgE-mediated allergic rhinitis⁹, allergic bronchial asthma¹⁰ and hypersensitivity reactions to hymenoptera venoms¹¹.

In his groundbreaking publication from 1911, the English physician L. Noon described a prophylactic inoculation of a patient with grass pollen extracts to treat and prevent hay fever¹². Nowadays, SCIT is based on subcutaneous injections of solutions containing 5-20 μ g of each single allergen¹³ over a course of time, mostly 3-5 years, beginning with a lower dose, continuing with increasing doses and maintaining a high dose level during the remaining therapy course¹⁴. Applied like this, SCIT has been shown to modulate the reactions of the immune system to respond differently to the respective allergen: Instead of severe IgE-antibody mediated allergic reactions, SIT shifts the immune response towards a milder Immunoglobulin G (IgG)-mediated response. The underlying mechanisms have not yet

been fully elucidated, but a redirection of the T helper cell response followed by a different cytokine release profile is believed to shift the immune response towards the IgG-mediated pathway¹⁴.

2.1.3 <u>Products for SCIT</u>

Different forms of allergen extracts are used for SCIT. As most allergens are proteins, they can be extracted from their natural source material and yield aqueous extracts of the native allergens. If native extracts are used for SCIT, they have to be injected several times daily to several times weekly⁷. They are easy to prepare but do have drawbacks: Some administered native allergens are easily degraded in the patient's body, so that SIT with unmodified allergens may require frequent injections⁷. To address the degradation issue, semi-depot allergen extracts have been developed. They consist of allergens adsorbed to a carrier material such as aluminum hydroxide or tyrosine and can be injected weekly or in intervals of several weeks. Another drawback of native allergen extracts is directly relevant for the safety of the product: The potential to elicit allergic reactions is highest with unmodified allergens as they are similar to the natural allergens and easily recognized by a patient's IgE antibodies. This safety issue was addressed by developing methods to alter the spatial structure of the allergen proteins and thus hindering IgE recognition by polymerization with aldehydes (formaldehyde, glutaraldehyde), yielding "allergoids"¹⁵. These products have a more favourable safety profile and type I allergic reactions in response to SCIT are less likely to occur⁷ Allergoids are a suitable treatment alternative to native extracts that exhibit reduced allergenicity while maintaining immunogenicity.

2.1.4 <u>Standardization of allergen extracts</u>

As allergen extracts are prepared from natural source material, they are complex mixtures of antigenic compounds and exhibit a considerable biological variability. This makes it difficult to standardize the extraction process and hence the final product. Standardization, however, is a key issue for the quality and safety of allergen products¹⁶. In Europe, certified reference materials for the standardization of allergen products are not widely available. Therefore, manufacturers employ the In-House Reference Preparation (IHRP) principle for the standardization of their products: Each batch of the product is compared to a respective internal reference standard. The general monograph on allergen products of the European Pharmacopoeia¹⁷ and the Guideline on allergen products have to comply with. An allergen product should be characterized with respect to three major criteria, and these criteria should be standardized as much as possible¹⁹:

- The total allergen composition should be determined in order to ensure that all major allergens are present in the product
- Allergens that are defined as relevant by the manufacturer should be measured to ensure that they are present in constant ratios

• The total allergenic activity should be quantitated to determine the overall potency of the product.

Currently, the potency of allergen extracts can either be biologically standardized (skin testing, see below) or by using *in vitro* techniques (IgE binding assays). For the biological standardization of allergen products, two different standardization systems are in place: the US-American approach²⁰ which uses intradermal testing in 15 highly sensitized individuals, and a Scandinavian approach based on the Danish Allergen standardization Program from 1976²¹, which employs skin-prick tests on 20 moderate and highly sensitized individuals. Both methods are used throughout Europe for the standardization of allergen extracts and rely on the quantification of the skin reaction from which biological units are derived. Usually, manufacturers characterize their IHRPs with respect to the abovementioned criteria, set individually differing biological units and compare each batch of allergen product that is manufactured to the respective IHRP. This does allow for consistency of batches of one manufacturer but does not provide for comparability of batches of different manufacturers²². IgE-inhibition tests are frequently used as *in vitro* standardization methods and are required in the EP monograph on allergen products as control for batch-to-batch consistency. These tests however lack informative value on the therapeutic effects of an allergen product or about the content of single allergens¹⁹.

One means to advance standardization of allergen extracts could be the establishment of recombinant major allergens as certified reference materials and the respective ELISAs for the measurement of these major allergens in allergen products, employing the recombinant allergens as standards. The CREATE project (Development of Certified Reference Materials for Allergen Products and Validation of Methods for Their Quantification), a program funded by the European Union (EU) under the fifth framework program in the field of allergen standardization²³.aimed at developing certified reference materials for allergen products based on purified recombinant allergens. These allergens should serve as standards for the calibration of *in vitro* allergen quantification assays. These assays could then be applied to allergen products and would permit an uniform quantification of the major allergens contained in the products in mass units. This way of standardization would allow for comparability of allergen products from different manufacturers. Two recombinant major allergens, rBet v 1 and rPhl p 5a were found to be suitable as reference materials in a follow-up project to CREATE. The respective ELISAs were also validated, therefore, these two allergens should be established as biological reference preparations and the respective ELISAs as EP standard methods²⁴. Currently, further efforts are being made to advance standardization of allergen products. New physico-chemical methods are being developed for example to detect allergens and their isoforms in allergen preparation by tandem mass spectrometry, which can also be applied to allergoids²⁵. Furthermore, array technologies are being developed for the detection and measurement of indoor allergens²⁶ Until these methods and more certified official reference standards are widely available, the IHRP concept will most likely be further advanced and probably gain even more recognition in official regulatory texts.

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2.2 Therapy Allergen Products with Marketing Authorization

Therapy allergen products that have been authorized in the European Community have undergone extensive testing in terms of quality, safety and efficacy, and a full documentation has been submitted to the National Competent Authority (NCA) in order to obtain a Marketing Authorization (MA). The regulatory environment for allergen products is briefly stated in <u>chapter 3</u>.

Authorized medicinal products are optimized with regard to efficacy, safety and quality including stability. The risks and benefits of the product have been assessed and a MA has been granted on this basis, ensuring a positive risk-benefit profile of the product. Furthermore, in Germany, all batches of licensed therapy allergen products are also subject to official batch release including experimental testing by the Paul-Ehrlich-Institut (PEI), the NCA that is responsible for vaccines, blood and bio-pharmaceutical products. The procedure equals that of vaccines: The manufacturer submits samples of the respective batch to the PEI where analyses are performed to check whether the batch meets the specifications as laid down in the MA. The batch of the product is only released if it meets the specifications. This applies to every batch that is produced. In Germany, more than 240 therapy allergen products are authorized, covering more than 80% of the allergies that are eligible for SIT²⁷.

However, as allergies are highly individual diseases, many therapy allergen products are made on demand for certain patients and are produced in very small numbers as Named Patient Products (NPPs), which do not have a valid MA. It is estimated that currently, 50 % of the therapy allergens in Germany are NPPs.²⁸

2.3 Named Patient Products for SIT

A NPP in the context of SIT is an allergen product which is prepared according to the prescription made for an individual patient by his or her physician. The definition of NPPs applies to the follow-ing²⁹:

- 1. allergen extracts that are made from allergenic material from a patient's environment
- 2. allergen extracts that are manufactured beforehand employing an industrial production process from commercially available material i.e. pollens or pet hair, that are made for a single or very few patients on the basis of an individual prescription
- 3. diverse allergen mixtures that are mixed from allergen extracts manufactured beforehand for an individual patient on the basis of an individual prescription

Definitions 1 and 3 represent real individual products, while definition 2 somewhat undermines the concept of NPPs as an industrial production process is involved.

The philosophy of NPPs in the field of allergology is based on the thorough assessment of a patient's allergic reactions and on a customized medication for de-sensitization to the causative allergen(s). As patients are often allergic to several allergens and show reactions of different severity, therapy allergen products for SIT are frequently mixed from individual allergen preparations in proportions reflecting the reaction severity to each allergen. This allows for a very finely tuned therapy course; hence, SIT

could be seen as an early approach to personalized medicine. SIT products in Germany are therefore either personalized products (single allergens or allergen mixtures) which are marketed as NPPs and did not require a MA until the Therapy Allergen Ordinance (TAV) came into force; or they are authorized medicinal products with a regular MA, as described above (chapter 2.2.)³⁰.

Distinctive precautions have to be taken with NPPs: In order to target type I hypersensitivity reactions to different allergens, several individual allergen extracts can be mixed and then employed in SCIT so that one injection contains several allergens which are clinically relevant for a patient. The optimal maintenance dosage of a single allergen source (e.g. one pollen extract) is between 5-20 µg per injection¹³, for safety reasons, the overall allergen content can not be increased ad infinitum³¹. The more different allergen extracts a mixture contains, the lower the concentration of the individual extract in the mixture. This curbs therapy efficacy for all allergens contained³² in the product and can result in therapy failure. Furthermore, not all allergens can be mixed. Allergens from moulds, mites and other insects frequently contain proteins with enzymatic properties which modify and/or degrade other proteins, compromising the stability of such mixtures and posing a significant risk as the patient could receive a potentially dangerous treatment. If a physician is not experienced, the possibility of mixing extracts of all allergens which tested positive in a patient is appealing, possibly resulting in treatment of the respective patient with a suboptimal dose for each allergen, or worse, an unsafe mixture. This was one of the reasons that the TAV was issued in Germany in 2008. This Ordinance and the reasons for its issuance will be further discussed in <u>chapter 3.1.2</u>, and 6.

3. Compilation of a Marketing Authorization Application Submission Dossier for Allergen Products – Scientific and Regulatory Basis

This chapter outlines the scientific and regulatory basis for submitting a MAA for therapy allergen products. The Concept of Homologous Groups as scientific basis for regulatory issues concerning allergen products is presented. Emphasis is put on the TAV for NPPs.

The main <u>regulatory documents</u> in Germany covering authorized therapy allergen products, among other directives, regulations and guidance, are:

- the German Medicinal Products Act (AMG), currently in its 15th version³³
- German Ordinance on the Manufacturing of Medicinal Products and Active Ingredients (AMWHV)³⁴
- the current Monograph for Allergen Products of the EP (2010:1063)¹⁷
- "Arzneimittelprüfrichtlinien" (national adoption of Directive 2003/63/EC, amending Dir. 2001/83/EC)³⁵
- Directive 2001/83/EC³⁶
- Guideline on Allergen Products: Production and Quality Issues. EMEA/CHMP/BWP/ 304831/2007¹⁸

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- Note for Guidance on Preclinical, Pharmacological and Toxicological Testing of Vaccines³⁷
- Guideline on the Clinical development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases³⁸

The content of the following legal and guidance documents is summarized in this chapter as relevant for allergen products: Directive 2001/83/EC, AMG, TAV, Ph. Eur. Monograph on Allergen Products (1063), the Guideline on Allergen Products: Production and Quality issues (EMEA/CHMP/ BWP/304831/2007).

3.1 The Concept of Homologous Groups

In 1992, a first national guidance on the requirements of an MA dossier for allergen products³⁹ was published in Germany. In 1996, the European Note for Guidance⁴⁰ on allergen products was published, followed by the first EP monograph on allergen products in 1997⁴¹. As product lines for SCIT are generally very similar regarding their production process, often only differing in the type of allergen employed, the "representative allergen" principle was introduced: This principle implied that quality, safety and efficacy data which were obtained from tests with a representative allergen could be extrapolated to other members of the family. Extrapolation was only possible to members of the same family, and had to be justified. For the other members of this family, a detailed description of the source material as well as tests and documentation regarding batch consistency were required in addition to the data extrapolated from the lead allergen. This grouping of allergen products of high homology and data extrapolation within this concept allowed for a reduction of laboratory and animal experiments as well as clinical trials.

In Germany, the concept of taxonomic families was introduced with the "Technischer Leitfaden für die Aktualisierung der Zulassungsunterlagen der bereits auf dem Markt befindlichen Allergenextrakte", issued by the PEI in April 1992³⁹. A tentative classification for allergen extracts according to the concept of taxonomic families was also given in this guidance document. This classification was rather unspecific: It distinguished between gymnosperms and angiosperms, with the angiosperms being further differentiated into monocotyledonous (i.e. grasses) and dicotyledonous (i.e. trees) plants⁴². With more and more molecular genetic methods available, especially DNA and protein sequencing, it was obvious that the taxonomic family concept did not guarantee similar characteristics of extracts of taxonomically related plants. Therefore, efforts were made to establish a new concept of relation for allergen extracts that was based on genetic, biochemical and immunological similarity of the extracts, called "the principle of homologous groups"⁴³. Lorenz et al. conducted an extensive literature search on the cross-reactivity and homology of allergen sources such as pollens, mites, insect venoms and vertebrates and established homologous groups on the basis of the following two criteria:

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- the allergen sources are derived from comparable tissues and thus have comparable biological and physicochemical properties (matrix composition, i.e. protein, carbohydrate, lipid, enzyme composition and water content)
- the allergen sources (either single allergens or whole extracts) show cross-reactivity on the basis of studies with patient's sera (IgE recognition), allergen specific animal sera or, in some cases, monoclonal antibodies

Following these criteria, six homologous groups were established with one or more representative allergen sources. These representative allergens were chosen on the basis of available scientific data and on the cross-reactivity with allergens from the other species of the proposed group. The proposed homologous groups and the respective representative allergens are listed in the annex to this work.

The concept proposed by Lorenz et al. has been implemented in two new Guidelines: The Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/ 304831/2007) and the Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006)³⁸.

Six homologous groups proposed by Lorenz et al. were adopted in the Guideline on allergen products, adding the species that could, with justification, expand the respective homologous groups. The criteria for homologous group formation however have been expanded to four in the Guideline: in addition to comparable source tissues and cross-reactivity, the formulation of the allergen products in question need to be identical; furthermore, the production processes for the allergen extract and the finished product of the allergen products in question have to be the same in order for any data takeover according to the concept of homologous groups.

This way of presenting the homologous groups in the Guideline makes it clear that the concept is a rather variable tool that will undergo evolution as it is applied. Furthermore, it leaves room for the applicant to apply this concept flexibly as long as the four criteria stated in the guideline are fulfilled and the choices are based on a scientifically sound rationale.

In the Guideline on the Clinical Development of SIT products, the concept of homologous groups was referenced as "concept of cross-reacting allergens", emphasizing the immunological similarity of the members of the respective homologous groups. As the Guideline for allergen products is referenced, the criteria for application of the concept as stipulated in this Guideline have to be complied with. A full set of data evaluating the efficacy has to be provided for the representative allergen of a homologous group and can be extrapolated to other allergens of this group. A justification has to be provided if extrapolation of data shall be done for allergens that do not belong to a homologous group; furthermore, extrapolation of efficacy data between allergens not belonging to the same homologous group is not possible. This is similar to the requirements stipulated in the Guideline on allergen products and also allows for a flexible application of this concept.

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3.2 Directive 2001/83/EC, the German Medicinal Products Act and the Therapy Allergen Ordinance

3.2.1 Directive 2001/83/EC and the German Medicinal Products Act

Directive 2001/83/EC as amended (last amendment: Directive 2009/120/EC) is the central document governing medicinal products in Europe. A Directive provides compulsory requirements which have to be transposed into the legislation of the member states. In Germany, the AMG represents this transformation of Directive 2001/83/EC into German national law.

The first document to govern allergens within the framework of European legislation was Directive 89/342/EEC which extended the scope of Directives 65/65/EEC and 75/319/EEC and laid down additional provisions for immunological medicinal products (vaccines, toxins, sera and allergens)⁴⁴. This directive defines allergen products as "[...] any product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent". Therefore, both allergen products for diagnostic as well as for therapeutic use fell under the scope of this Directive and were clearly defined as medicinal products.

This definition has been retained in Directive 2001/83/EC³⁶, which applies to "all medicinal products [...] either prepared industrially or manufactured by a method involving an industrial process"⁴⁵. All allergen products which are manufactured industrially fall under the scope of this Directive. The central requirement of Directive 2001/83/EC is stated in Article 6: "No medicinal product may be placed on the market of a Member State unless a Marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive [...]". Therefore, any allergen product which is manufactured employing an industrial process has to be granted a MA before it can be placed on the market in the EC. Directive 2001/83/EC was amended by EU Directive 2004/27/EC which introduced the definition of "medicinal products manufactured by an industrial process". As virtually all therapy allergens are produced by industrial processes, this provision would have required all therapy allergens to have a valid MA. The AMG, however, provides a national exception: Section 21(2) No. 1g states that therapy allergens which are manufactured for a patient on the basis of an individual prescription do not require a MA⁴⁶. This exception was introduced with the 14th version of the AMG in order to accommodate the special nature of allergen products intended for the diagnosis or treatment of rare allergies. For these allergen products, clinical studies providing data on the efficacy of the product cannot be conducted due to a lack of patients needed to obtain statistically significant data. The exception for therapy allergens in the AMG was therefore made to enable the manufacture and marketing of these products in accordance with the German legislation. This way, patients suffering from rare allergies or are sensitized to combinations of allergens⁴⁷ can be effectively treated with customized products. However, many allergen products that are intended for the treatment of allergies with a higher or even a high prevalence are sold on a named patient basis in Germany, although they are manufactured involving an industrial process. Control of this market, was another reason for issuing the TAV in Germany.

3.2.2 <u>The Therapy Allergen Ordinance in Germany</u>

In Germany and many other European states, NPPs may be manufactured and sold on the basis of a valid manufacturing authorization and current Good Manufacturing Practice (GMP) certification of the manufacturer. This means that they are not tested for quality, safety and efficacy by the NCA, which could pose a problem especially in the area of SIT. It is possible that these products are of a lower quality than licensed products and could elicit more side effects. Many allergen product manufacturers market NPPs that are made from bulk extracts which then are diluted or mixed in the individual ratio determined and prescribed by an allergologist for an individual patient. There is no reason why these bulk products should not be treated as medicinal products as defined by Directive 2001/83/EC and thus be evaluated for quality, safety and efficacy. For this reason, the TAV was issued by the Federal Ministry of Health, and came into effect on November 15th, 2008⁴⁸. This ordinance applies to certain allergens prevalently used in SIT which are named in the appendix of the ordinance document.

The TAV has three key aspects:

- § 1: Extension of the requirements for MAA to therapy allergens that are manufactured for individual persons from pre-manufactured bulk extracts which contain one or more of the allergens listed below.
- § 2: Official batch testing: The bulk extract of therapy allergens for which § 1 applies has to be batch tested and released according to § 32 AMG before the NPP is made from these bulk extracts and supplied to the physician.
- § 3: The PEI had to be notified until 14th of May, 2009, of therapy allergens for which § 1 applies and for which manufacturers want to submit a MAA. This notification had to contain the SmPC of the product as well as the description of the manufacturing process, relevant in-process controls, specifications and analytical methods. The MAA has to be submitted to the PEI until December 1st, 2010. Until a MA has been issued, these products may be marketed.

The PEI also had to be informed of therapy allergens for which no MAA will be submitted ("denotification") by May 14th, 2009. This denotification, like the notification, had to be accompanied by the documents mentioned above. Allergen Product manufacturers may market these products for another three years after the TAV has come into effect (14th Nov. 2011). Batch testing and release applies to all notified and denotified therapy allergens from October 1st, 2009.

In contrast to § 25 paragraph 4 (2) AMG, applicants shall have one year to remedy deficiencies instead of 6 months. This time span may be extended to up to seven years to address clinical deficiencies resulting from the special features of therapy allergens. If deficiencies are not remedied within the given time frame, the MA shall not be issued.

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The TAV applies to frequently prescribed allergens and mixtures of these allergens with other allergens:

- Poaceae (Sweet Grasses) except Poa Mays (corn)
- Betula sp. (Birch)
- Alnus sp. (Alder)
- Corylus sp. (Hazel)
- *Dermatophagoides sp.* (house dust mites)
- Bee and Wasp venoms

Therapy allergens that are prescribed for desensitization to rare allergens, for example extracts from mugwort or ragweed pollen, do not fall under the scope of the TAV and thus can still be marketed without a MA. Also, these allergen porducts are not subject to official batch testing and release. However, if these rare allergens are mixed with allergens which do fall under the scope of the TAV, the TAV also applies to the rare allergens.

Therapy allergens that are authorized in other European countries do not fall under the scope of this ordinance. In addition, therapy allergens for which a regular MAA has been submitted and is currently under assessment in another European country are not covered by the TAV.

Hence, allergen manufacturers face a number of serious changes within the next years and are well advised to focus their business strategies on the completion of these tasks.

3.3 The Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007)

The Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/

304831/2007, hereafter referred to as "Guideline") is one of the key documents to provide guidance concerning the quality of allergen products which are manufactured either from natural extracts or biotechnologically. This chapter shall provide a concise summary of the Guideline, emphasizing the requirements that were not present in the "Note for Guidance on Allergen Products" (CPMP/BWP/243/96, hereafter referred to as "NfG")⁴⁰, which was the first guidance for allergen products, published in 1996.

Taking into account the scientific and technical advancement, the content of the NfG was completely revised in 2006-2008 to include guidance on biotechnologically manufactured allergen products, standardization efforts, new requirements for IHRPs and stability studies, and to introduce the new "Concept on Homologous Groups"⁴³, which replaces the concept of taxonomic families.

The NfG was not structured according to active substance and finished product. In 7 chapters, guidance on starting materials, production process, Batch-to-batch consistency, control tests on intermediates and the finished product and stability of the finished product was given. The NfG was preceded by a short introductory paragraph giving information about the background, the legal basis of allergen

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products and the scope of the NfG: It only applied to industrially produced allergen products. Products manufactured on a named patient basis were explicitly excluded.

The new Guideline exhibits a different structure: An Executive Summary states the purpose: "Quality recommendations for allergen products of biological origin, whether derived from natural or recombinant sources, used for SIT or in vivo diagnosis of IgE-mediated allergic diseases".

The introductory paragraph (1. Introduction) of the new Guideline gives information about the scientific and medical background of allergic diseases and products for their diagnosis and therapy. The next paragraph (2. Scope) outlines the scope of the Guideline: This Guideline applies to ALL allergen products and their intermediates. Therefore industrially produced allergen products as well as products manufactured on a named patient basis, derived from natural or biotechnologically produced source materials, modified or unmodified, are covered by the Guideline.

The last paragraph preceding the main guideline text states the legal basis which is the Directive 2001/83/EC (Introduction, General Principles and Part 2 of Annex I).

The main guideline text (4. Main Guideline Text) is divided into 4 chapters: "General Concepts" (chapter 4.1.), introducing the concept of homologous groups (see chapter 3.4., below), providing guidance on how to prepare allergen mixtures as well as on the comparability of allergen products through all stages of development, "Active Substance" (4.2.), "Standards and Reference Material" (4.3.) and "Finished Product" (4.4.). Although the guideline structure does not completely follow the structure of the EU CTD, information for virtually all EU CTD sections can be found in the guideline text. A detailed correlation of the information stated in the Guideline to the respective sections of the EU CTD Module 3 is given in the third part of this work.

Main Guideline Text (4.)

The main guideline text starts with the "General Concepts" paragraph which provides an introduction to the concept of homologous groups as the scientific background for many quality requirements stated in the Guideline. This concept is based on biochemical and molecular biological evidence and replaces the traditionally applied concept of taxonomic families. The NfG referenced this concept without really introducing it, a brief description of the concept of taxonomic families could be found in the Technical guidance provided by the PEI in 1992³⁹ For the new Guideline, a short, tabular comparison of these two concepts with the major changes highlighted would have been of great help for allergen product manufacturers. This has been done for this work and is presented at the end of this chapter (table 1).

In addition to introducing the concept of homologous groups, the "General Concepts" paragraph provides guidance on the preparation of allergen extract mixtures. The main statement is that the source materials should be extracted individually, i.e. extractions of mixed source materials should not be done. Each extract is considered as an active substance, and should be potency tested prior to mixing for the manufacture of the finished product. This is a requirement that goes hand in hand with the knowledge that the number of allergens in an extract should be limited. It is important for the efficacy of an allergen product to achieve a defined therapeutic concentration for single allergens in a mixture. The more allergens a product contains, the lower their concentration has to be and the less efficacious the treatment¹³ The inclusion of this knowledge in the Guideline forces the manufacturers to make an informed choice on which allergens to include in their products and to provide a scientifically sound justification. Detailed guidance is given on which allergens shall not be mixed.

The last point addressed in the "General Concepts" paragraph is the comparability of allergen products. Many allergen products have been on the market for a long time, and as the MA holder is obliged to keep the products up to date scientifically and in terms of safety, development work has to be performed which might include changes in or of the manufacturing process. The ICH guideline Q5E gives details on comparability for non-biotech medicinal products. It is referenced in the context of this Guideline, hence, it has to be complied with.

Active Substance (4.2)

The Active Substance section of the Guideline starts with general information on the active substance (*General Information, 4.2.1.*), listing the different active substances employed in allergen products. Furthermore, it defines the active substance as "a stable preparation at the latest step before mixing or formulation". Also, the importance of standardization concerning the active substance is highlighted in this paragraph.

The next paragraph deals with the manufacture of the active substance (*Manufacture*, 4.2.2.) and provides guidance on the presentation of the manufacturing process including modification and adsorption methods for modified and/or adsorbed products and in-process controls. Emphasis is put on the fact that all manufacturing steps have to be validated which is in line with the respective ICH guide-lines⁴⁹. The NfG did not contain a specific section on the manufacture of the active substance; instead, relevant information was distributed within the whole NfG text. The clear and logical way the information is presented in the Guideline makes it easier for the manufacture to follow the requirements.

The following paragraph "<u>Control of Materials</u> (4.2.3.)" deals with the control of source materials for extracts and other raw materials and provides detailed requirements for the different biological source materials. Requirements have become more stringent due to scientific advancements in the field: The new Guideline demands a detailed definition of the source materials instead of just a description as stipulated in the NfG. Also, requirements are stated for the control of the materials: Specifications have to be set and justified for impurities, storage conditions have to be established on the basis of stability studies and all source materials have to be qualified. The requirements for the different source materials as stated in the Guideline are directly relevant for the CTD section <u>3.2.S.2.3</u>. Control of Materials and are discussed there in detail.

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The next chapter, "*Characterization and Control of the Active substance*" (4.2.4.) is structured according to the different active substances:

- allergen extracts
- modified allergen preparations
- recombinant allergen preparations,

the latter of which shall not be discussed in the context of this thesis.

The paragraphs present detailed guidance on the stage at which characterization and quality control of the active substance has to be performed. The central requirement of the Guideline is that tests for the control and characterization of allergen extracts are performed on the active substance stage, unless a characterization is not possible due to technical reasons (as for example for modified allergens such as allergoids). The manufacturer has to define specifications and acceptance criteria for in-process controls at the respective intermediate stage. These should be justified and be part of the release specifications. Details are given which in-process tests should be considered.

This part of the main Guideline text is therefore highly relevant for the Drug Substance sections of the CTD. The requirements are detailed in <u>chapter 4.1</u>. of this work (3.2.S.4. Control of Drug Substance).

In comparison to the NfG, the Guideline offers more information but also imposes more responsibility on manufacturers: They have to define and quantitate the allergens they consider relevant for their preparations. Validated assays with certified reference standards shall be used for this means and the manufacturing process has to be designed in a way that these allergens are maintained during manufacture.

The only similar text passage in the NfG was section 4.4., "Batch to Batch Consistency". However, this section rather served as an introduction to the IHRP concept and less for the characterization and control of an active substance. Therefore, the chapter "Characterization and Control of the Active Substance" in the Guideline is of great value for manufacturers. For adsorbed and modified products, it is the responsibility of the manufacturer to develop suitable methods for characterization and control of the adsorbed/modified active substance. The NfG stated that if a test cannot be performed on a product due to chemical modification or adsorption, quality specifications should be defined just prior to the modification or dilution step. Compared to the NfG, the requirements laid out in the Guideline have become more stringent here as well. Manufacturers are obliged to characterize the modified active substance and the modification itself. This is probably due to safety concerns, as unstable or unexpected modifications can increase the risk of side effects of an allergen product. This issue is also addressed in the stability section for the active substance (chapter 4.2.5. of the guideline), see below.

"*Potency Assays*" (4.2.4.4.) provides guidance on how to assess the potency of an allergen product. The NfG states that "whenever possible, the potency of the active ingredient should be expressed in units of biological activity, and the system should be unambiguously indicated, in order to avoid confusion with similar unit systems currently in use on the market". This paragraph of the NfG left many details open to interpretation, this gap is closed by the new Guideline. It gives detailed requirements on how to assess the potency of allergen extracts or purified allergens without structural modifications. This information is relevant for sections 3.2.S.3 (characterization) and 3.2.S.4. (Control of Drug Substance) and is presented there in detail.

Stability (4.2.)

The principle of homologous groups can be applied to stability studies: A full set of data is required for the representative allergen of a homologous group, and relevant data may be extrapolated to nonrepresentative allergens. The applicant should provide a justification on which data are to be extrapolated and should also include a discussion on this issue. A detailed list of which data can be extrapolated would have been helpful for the manufacturers at this point but is not given in the guideline.

If sufficient stability data are not available for non-representative allergens, these data can be collected in stability studies that are conducted on an ongoing basis in the context of the overall shelf life of the active substance. The manufacturers should commit to performing these studies and provide a detailed study protocol with the MAA dossier (section 3.2.P.8.2.).

Standards and Reference Materials (4.3.)

A whole section is dedicated to the topic "Standards and Reference Materials"; its importance as a single section within the Guideline is unmistakable. The text of this section is relevant to both the Drug Substance and the Drug Product sections of EU CTD Module 3 (3.2.S.5. and 3.2.P.6.),

One motivation for revising the Note for Guidance on Allergen Products was the advancement in standardization efforts concerning allergen products, and the incorporation of results gained in this context. Thus, the chapter on Reference Standards and Materials has been extensively revised, and new guidance on the standardization of products of one manufacturer as well as a few concepts on how products of different manufacturers can be standardized are given.

The section text is preceded by the statement that "reference standard materials should be established and characterized for all types of allergen products". This puts one of the next paragraphs into a different perspective: In the NfG it was stated that allergen products are nearly impossible to standardize between different manufacturers and even within different batches of a single manufacturer. This statement left some room for personal or corporate interpretation.

In the new Guideline, it is very clearly stated that every effort for standardization of the products should be made and IHRPs are only to be used as long as there are no official standards available. Detailed guidance on how to standardize and characterize IHRPs is given: Manufacturers should use methods based on skin reactivity tests of patients and follow the methods as described either by Turkeltaub (US system²⁰) or the Nordic Council of Medicines system (widely used in Europe²¹). Should not enough patients be available, *in vitro* methods can be used if justified. However, no guidance is given whether specific *in vitro* methods are to be used and how the data should be evaluated. This would probably have been helpful for manufacturers. In this case, discussion with the NCA

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would be of great value. Details for the IHRP are discussed in chapter 4.1., sections 3.2.S.5. and 3.2.P.6. (Reference Standards or Materials).

In general, the revised IHRP section provides detailed guidance for manufacturers on how to best standardize their products. The revision clearly aims at achieving more uniformity between the products of different manufacturers by strengthening the IHRP concept. The fact that elaborate guidance on the IHRP is provided in the "Active Substance" part of the Guideline underlines the importance of the active substance for the allergen product. However, finding a general standard for allergen products still does not seem to be feasible as long as no nationally or internationally certified reference standards and only very few standardized and certified assays are available.

Finished Product (4.4.)

The finished product section is divided into 5 subsections covering details of the description and composition, the manufacture, control, the container closure system and stability of the finished product. The paragraph on the <u>description</u> of the finished product is rather short. It just states a few details such as that all active substances should be listed if the product consists of more than one active substance, and that adsorption and adding of excipients are considered to be formulation steps which therefore should be described in the manufacturing process for the finished product. In the NfG, active substance and finished product were not dealt with separately, the same guidance was given for both stages and could be found in chapter 4.3. of the NfG. The separation of active substance and finished product as presented in the Guideline is in line with the CTD structure (Drug Substance and Drug Product) and makes it easier for the manufacturer to comply with the relevant parts of the Guideline for each stage of the product.

The paragraph on <u>manufacture</u> gives detailed guidance on how the manufacturing process should be described and how process validation should be conducted. The requirements for descriptions of the manufacturing process are in line with the relevant guidelines (ICH CTD⁵⁰, TSE⁵¹) and the Annex 2 of the Directive 2001/83/EC. For process validation, the principle of homologous groups can be employed, which allows for a reduced validation program for non-representative allergens. If a full set of data is available for the representative allergen of the respective homologous group and the production process is identical, process validation data can be extrapolated for the non-representative allergen of the same homologous group.

The chapter on "Control of the finished product" (4.4.3.) is partitioned into five paragraphs: control of

- non-modified allergen preparations
- allergen mixtures
- adsorbed products
- non-standardized allergen extracts



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The control of recombinant products is also addressed in a short paragraph which shall not be discussed in the context of this work.

For each type of allergen product, detailed guidance is provided on how to control the respective product while leaving room for the manufacturer to choose the appropriate tests and testing stages based on a sound scientific rationale.

In general, the characteristics for any allergen product should be documented for all strengths (dilutions).

The adsorption of allergens to depot materials such as tyrosine or aluminum is a modification intended to increases the product's safety. Therefore, it is essential that success and stability of the adsorption are measured. The NfG did not accommodate this point and just stated that if it is not possible to determine the allergenic activity for modified/adsorbed finished products, documentation of the adsorption/modification should be provided. This did leave room for interpretation, and the new Guideline now gives specific requirements on how adsorbed and/or modified products are to be characterized (see chapter 4.1., section 3.2.P.5.).

The last paragraph of the chapter is dedicated to non-standardized allergen extracts. A biological standardization of these products is not possible as not enough patients are available in order to establish appropriate sera pools. Therefore, manufacturers have to resort to *in vitro* tests to characterize and control these products. A list of tests that may be applied containing the determination of an antigen and protein profile, total protein content, determination and measurement of individual allergens is given, and if one of these parameters is not tested, this must be justified.

In general, this section provides detailed guidance on how to control the different allergen products. Together with general guidance given in the ICH CTD guidelines, this should enable the applicant to successfully compose the respective CTD sections for the MAA.

The guidance given on "*Container Closure*" (4.4.4.) is very similar to the respective CTD guideline⁵⁰ and is detailed in chapter 4 (3.2.S.6. and 3.2.P.7.).

The chapter "*Stability*" (4.4.5.) for the finished product has been completely revised for the new Guideline. As in the Active Substance section, the relevant ICH guidelines are referenced for the finished product, so compliance with these guidelines is mandatory where applicable⁵². The principle of homologous groups can be applied to stability studies and replaces the concept of taxonomic families, which was referenced in the NfG. Stability data obtained from one member of a taxonomic family could be extrapolated to other members of the same family based on discussion and justification. Applying the principle of homologous groups, a full set of stability data has to be gathered from the representative allergen of one homologous group. With limitations, these data can be extrapolated to the non-representative allergens of the same homologous group, provided the manufacturing process is identical. The applicant can choose and justify a limited number of parameters to be assessed in stability studies for the non-representative allergens and should discuss the results. It has to be taken into

account that the nature of some allergens does not allow for extrapolation of data even within the same homologous group, for example if the representative allergen has different enzymatic properties from the non-representative allergen and vice versa. Therefore, a certain amount of scientific insight is required in order to properly apply the concept of homologous groups.

The last two sections in the NfG, Safety Testing and Efficacy Testing, have not been included in the Guideline. Instead, a separate "Guideline on the Clinical Development for Products for Specific Immunotherapy for the Treatment of Allergic Diseases"³⁸ deals with these issues and revisits the principle of homologous groups: This concept can also be applied to safety and efficacy issues.

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	Taxonomic Families (PEI Technical Guidance)	Concept of Homologous Groups
Scientific Basis	 Close <i>taxonomic</i> relationship between the active components of respective allergen products Allergen source materials are divided into several groups according to their taxonomic relationships 	 Similar <i>biochemical composition, and homology/cross-reactivity of the respective allergens</i> of the source materials of respective allergen products Allergen source materials are divided into several homologous groups according to their biochemical/molecular biological relationships
Criteria for group formation	Taxonomic relation	 the allergen sources are derived from the same tissues -> comparable biological and physico-chemical properties (matrix composition, i.e. protein, carbohydrate, lipid, enzyme composition and water content) the allergen sources show cross-reactivity on the basis of studies with patient's sera (IgE recognition), allergen specific animal sera or, in some cases, monoclonal antibodies
Groups	Pollens: Differentiation into • Gymnosperms • Monocotyledonous angiosperms • Dicotyledonous angiosperms • Dicotyledonous angiosperms • Fungi (moulds): • Aspergillus family • Ustilago family • Yeasts Mites and housedust: mites, housedust Animal allergens: • Epithelials (dander) • Hair • Pelt	 <u>Tree pollens:</u> the "Birch group", comprising birch, alder, hazel, oak and hornbeam the "Oleaceae" group: olive, ash, privet and lilac, the "Cupressaceae" group: cedar and cypress, <u>Grass and cereal pollens: Poaceae family</u> sweet vernal grass, oat, orchard grass/cocksfoot, meadow fescue, velvet grass/Yorkshire fog, barley, perennial rye grass, Kentucky bluegrass, cultivated rye, cultivated wheat. <u>Weed pollens</u> ragweed, mugwort, pellitory Mites:

Table 1: Comparison of the "Concept of Taxonomic Families" to the "Concept of Homologous Groups"

	Food allergens: several families	European and American house dust mites
		Either one as representative allergen
	Pharmaceutical and industrial chemicals: a family	Hymenoptera venoms: No homologous group due
	can only be established for antibiotics such as peni-	to lack of protein similarity
	cillins, tetracyclins etc.	<u>Vertebrates</u> : selected cat and dog proteins could
	Bacterial and Parasital allergens: no families	form a homologous group if scientifically justified
Representative Allergens	No real representative allergens are given, manu-	• birch
	facturer should justify choice	• olive or ash
		• cedar and cypress
		• timothy grass, orchard grass or kentucky blue-
		grass
		• ragweed or mugwort
		• European and American house dust mites
Extrapolation	Extrapolation possible on the basis of:	Extrapolation is limited to defined parameters and
	• close relationship between the active components	criteria:
	in question, especially regarding the properties	• Extrapolation may only be performed from the
	tested.	representative allergen of one group to non-
	• justification of the selection of the representative	representative allergens of the same group.
	allergen, the suitability of the selected model and	• The production process must be identical for
	the validity of the extrapolation.	active substance and finished product
	• Data gathered from individual allergens may not	• The formulation of the active substance and
	be valid for mixtures	finished product must be identical
	Extrapolation is possible for:	• Extrapolation is not possible for mixtures of
	• Stability studies	allergens from different homologous groups
	Pharmacological and toxicological Documen-	• The manufacturer must consider different enzy-
	tation	matic properties of proteins
	 Clinical Documentation 	Extrapolation is possible for:
		Process Validation (DS and DP)
		• Stability (DS and DP)
		• Clinical Program (as covered in the Guideline
		on the Clinical Development of Products for
		Specific Immunotherapy for the Treatment of
		Allergic Diseases, CHMP/EWP/18504/2006)



3.4 The European Pharmacopoeia Monograph on Allergen Products (1063)

The EP provides authoritative quality standards for medicinal substances, ensuring the supply of highquality medicines for all European Citizens. The EP is applicable in all member states of the EU and other signatory states. The general and specific monographs of the EP are official standards which manufacturers are legally bound to comply with, as laid down in Directive 2001/83/EC; 2001/81/EC. Furthermore, texts that are referenced in monographs receive a mandatory status.

Although allergen products are a highly diverse class of products, the EP monograph on allergen products is a general monograph, and in its newest version (2010:1063) encompassing most allergen products currently on the market, excluding chemicals/chemically synthesized products and products manufactured by using recombinant DNA technology. The first monograph on allergen products was published in the third EP Edition in 1997⁴¹. For the first time, details regarding source materials (pollens, mites and moulds, animal epithelia) and tests applicable to the finished products were published. A few updates were made to the monograph for allergen products in 2007 (edition 5.8. of the EP) and published with edition 6.0. of the EP in 2008 without changes. Similar to the development of the new Guideline for Allergen Products, the monograph on allergen products was completely revised in the last 2 years to accommodate the scientific advancement of allergen product manufacture and control. The EP monograph for allergen products is divided into 5 sections:

- 1. Definition
- 2. Production (with subsections Source Materials, Manufacturing Process, In-House Reference Preparation)
- 3. Identification
- 4. Tests
- 5. Storage
- 6. Labelling

In the following, each section shall be briefly summarized. Changes from the monograph published in 2008 (ed. 6.0) to the monograph published in 2010 (ed. 6.6.) are highlighted.

1. Definition

The section "Definition" defines allergen products, provides details on the function of these products and offers a description of the different forms of allergen products that are available. Also, the different indications (diagnostic use and immunotherapy) are introduced with their special forms of preparations and routes of administration. In the 6.0.edition, the last paragraph of this section provided the scope of the monograph by listing allergen products it did <u>not</u> apply to: Among chemically synthesized and recombinant allergen products, this monograph did <u>not</u> apply to finished products that are prepared and used on a named-patient basis. Furthermore, the monograph of 1997, this section did not

undergo any changes when the monograph was updated in 2007 and 2008 (ed. 5.8. and 6.0, respectively). In contrast, edition 6.6. presents several changes and amendments to this section.

First of all, the scope of the monograph precedes the first section and is extended to "finished products used on a named patient basis". Therefore, with the 6.6. edition of the EP, NPPs are subjected to the same quality requirements as finished allergen products (and finished medicinal products in general). Furthermore, scientific definitions are used, and the wording of the monograph text has been made more precise and specific (for example "*prick*" tests was changed into *skin* tests, thus covering the range of currently applied skin tests with the monograph). The list of different preparation types ("finished products, bulk preparations, solutions or suspensions [...]") has been deleted from the 6.6. monograph and new definitions have been introduced, possibly due to the reorganization and update of the manufacturing process section. It can and possibly should be interpreted from these changes to this first section that European Regulatory Authorities are working towards documents that enforce stricter regulations and limit exemptions for all allergen products by improving the specificity of the pharmacopoeial text.

2. Production

The section "Production" is the most elaborate of the monograph. It provides a short overview on the nature of allergen products, their wide range of source materials, manufacturing processes and the IHRP. The section is divided into the subsections "Source Materials", "Manufacturing Process", and "In House Reference Preparation".

With the update in 2007, a paragraph on virus safety was added to the "Production" section, which states that if materials of human or animal origin are used for the production of an allergen product, compliance with the EP chapter on viral safety (5.1.7.) must be maintained.

The subsection "Source Materials" details requirements for the raw materials used in allergen product manufacture. This section was divided into subsections according to the nature of the different source materials: Pollens, Mites and Moulds, Animal Epithelia.

For the 6.6. monograph, the Source Material subsection has undergone major remodelling. Several requirements have been added; also, the paragraphs have been made more specific to be consistent with enhanced quality standards for allergen products. This is in line with the development of the Guideline for Allergen Products from 2009, which also emphasizes the quality of raw materials (see chapter 3.3.).

The introductory first paragraph of the section states that source materials for allergen products are of animal or vegetable origin, and lists the most common sources (pollens, moulds, mites, animals, insects and certain foods). The reference to viral safety is kept in the 6.6. monograph and placed right below the introductory paragraph, stressing its importance for all source materials discussed. The next paragraph states the requirements regarding identity and purity for source materials: "The source materials are *defined* by their origin [...]" instead of *described*, as worded in the 6.0 monograph, control

methods and acceptance criteria in terms of identity and purity" have to be established, undermining the efforts to ascertain a high and consistent quality of the raw materials to yield safe and effective allergen products. Also, the storage conditions are addressed in the 6.6. monograph: "The source materials are stored under controlled conditions justified by stability data". This has been a requirement for chemical active substances for a long time⁵³ and has now also been adopted for the source materials for allergen products.

The specifications that the source materials have to meet are detailed, according to the specific nature of the source materials, in the following text passages of the monograph. A table providing a survey of the respective source material specifications is provided in chapter 4 (section 3.2.S.2.3. Control of Materials).

<u>Pollens</u>: Potential chemical contaminants such as pesticides or heavy metals must be "minimized", but no limits are given. Furthermore, limits for foreign pollen content and mold spores are detailed. These limits have remained the same up to the 6.0. monograph and are still valid in the 6.6. monograph. In addition, a limit of 0.5 % has been adopted for the contamination with any individual pollens in the 6.6. edition of 2010. Until the 6.6. monograph came into force, it was sufficient to determine foreign pollens by microscopic examination. The new requirements state that a microscopic particle count must be performed in order to determine the amount of foreign pollen. Also, a requirement that the contamination of pollens with other plant particles must be kept to a minimum has been added. The manufacturers are responsible for setting and justifying reasonable limits. This does leave room for interpretation; it allows the manufacturers to be flexible as long as the justifications for the limits set can be backed up by solid data.

<u>Mites and Molds</u>: From 1997 to 2008, mites and molds were combined in one paragraph. Requirements for biologically active contaminants such as mycotoxins in molds were stated as well as requirements for culture media. In the 6.6. monograph, separate subsections were dedicated to mites and moulds. For molds, it has been added that the manufacturer needs to take measures to avoid contamination of the strain to be used for production with other mold strains. Another interesting addition concerns the production of mycotoxins: For allergen products derived from molds as source materials intended for parenteral use, manufacturers have to validate the production process that these products would comply with the test for abnormal toxicity for immunosera and vaccines for human use (EP chapter 2.6.9.). Data gathered from the test itself do not have to be presented for every batch, but this requirement should be considered as part of the process validation.

For mites, one addition has been made in the 6.6. version, similar to the one made to molds: the manufacturer needs to take measures to avoid contamination of the strain to be used for production with other mite strains.

In the 6.0. monograph, the last paragraph of the subsection on source material is a short statement on animal epithelia. It is emphasized that the source materials may only be obtained from healthy animals

in order to minimize the risk of transmissible disease agents. This subsection has been expanded for version 6.6. by adding a paragraph on hymenoptera venoms and one on food. Both paragraphs list the requirements that species serving as source materials need to be identified and specified (hymenoptera venoms) or indicated and if applicable, the plant part used for production of the allergen product stated (food), respectively. Also, quality requirements are given for foods – the food source material for allergen products needs to be of a quality suitable for human consumption, furthermore, the origin of the foodstuffs as well as their processing stage need to be stated by the manufacturer.

Manufacturing Process

In the 6.0. monograph, the subsection "Manufacturing Process" provided a detailed overview of the different stages of manufacture and discriminated between native allergen extracts, intermediate allergen products and bulk allergen products.

- Native allergen extracts were defined as obtained by extracting the allergen source material employing a suitable extraction medium and then separating the extract from the source material.
- Intermediate allergen products were defined as derived from the native allergen extract by chemical or physical processing, such as chemical conjugation or physical adsorption to carrier materials. Further modification methods are briefly described; also, it is stated that intermediate allergen products may be freeze-dried.
- Bulk allergen preparations were defined as products in solution or suspension which will not be further modified but filled into final containers or diluted for application.

In the 6.6. monograph, the stages of the manufacturing process have been updated and aligned with those known for chemical entities:

- source material (which is specific for products of biologic origin)
- active substance (Drug Substance)
- finished product (Drug Product)

All other stages of the manufacturing process are regarded as intermediates.

Another interesting update in version 6.6. is that the allergenic properties of the components need to be preserved upon extraction; this has to be determined by appropriate *in vivo* or *in vitro* tests. If these tests cannot be performed, the extraction ratio of allergenic source materials and solvents need to be given as a minimum requirement. This conforms to the requirement stated in the Guideline that the manufacturing process should be designed to maintain the relevant allergens. This requirement aims at improving the control of extraction processes as a means for increased standardization of allergen products. Furthermore, aseptic production conditions are addressed for allergen products that are presented as eye, inhalation or skin testing preparations. The focus on microbial quality has been enhanced, also with regard to packaging, storage and distribution. Furthermore, the problem of degradation is addressed as such that manufacture of allergen products has to take place under conditions that

minimize exogenous and endogenous enzymatic degradation. Adding suitable preservatives to an allergen product is allowed; however, the nature and the concentration of the preservative need to be justified.

In-House Reference Preparation

The next sub-section, termed "In-House Reference Preparation" details requirements for the IHRP and makes suggestions for methods of characterization. In the 6.0. monograph, the parameters for characterization were:

- Protein content and profile,
- allergenic components (detection and characterization),
- content of individual allergens and
- biological potency,

as assessed employing suitable methods. If biological potency of the IHRP could not be established using *in vivo* techniques, suitable alternatives for *in vitro* testing were given.

For the 6.6. edition, the IHRP section has received multiple updates. This development parallels the revision of the Guidance on Allergen products. Here, emphasis has also been put on the detailed characterization of IHRPs as they are the only possible means of standardization for the products of one manufacturer. In accordance with the "Definitions" section, the IHRP is used as a reference in the batch control of *active substances and intermediates*, and if possible, in the batch control of *finished products*. As the 6.6. monograph also applies to NPPs, the IHRP is also employed for these products.

Taking into account the scientific development in the past years, an array of state-of-the-art methods has been added as suggestions for *characterization* of the IHRP for the manufacturers to choose from. Furthermore, as also stated in the Guideline, it is now required to determine the content of relevant allergens in the IHRP wherever possible.

According to the 6.6. monograph, the biological potency of the IHRP has to be determined by *in vivo* techniques. It was acceptable according to the 6.0 monograph to test the IHRP for its biological potency employing *in vitro* methods if *in vivo* testing was not possible. Similar to the NfG, It was however not specified in which cases *in vivo* testing on the IHRP was regarded as "not possible". In monograph 6.6., it is stated that *in vitro* determination of the IHRP's *biological potency* can only be accepted if there are not enough patients available for skin testing. This is likely only true for allergies occurring with a low frequency. In this case, the manufacturer has to employ a suitable immunoassay to determine the biological potency of the first IHRP; and all following IHRPs need to be compared to the first one. This approach clearly furthers standardization of allergen extracts; however, "biological units" which are to be used for expression of biological potency are still a non-standardized way of measuring this feature and differ greatly between manufacturers.

In general, the IHRP subsection has been updated and manufacturers are given more detailed guidance on how to characterize the IHRPs for their products. This corresponds to the trend for more standardization that has recently been seen on the market for allergen products and which is most likely to continue in the future.

3. Identification

In accordance with the previous sections, the "Identification" section has also been updated and its content adapted to the scientific advancement. While it was acceptable according to the 6.0. monograph to confirm the identity of an allergen product at the intermediate or an other applicable stage, the 6.6. monograph states that "tests have to be performed as late as possible in the manufacturing process", which conforms to requirements outlined in the Guideline. As it is not possible to confirm the identity of NPPs on the finished product, the tests for identity confirmation are performed "on the active substance and/or the intermediate stage between active substance and finished product". This paragraph is actually repeated in the "Tests" section, thus stressing the importance for identity confirmation at the latest possible stage of a product. If no IHRP is available, the manufacturer can employ a representative batch for identity confirmation. This needs to be justified.

4. Tests

The description of tests and limits is preceded by two general paragraphs of which the first states that "not all tests are applicable to all allergen products and that the products have been classified into different categories with increasing test requirements according to quality and intended use" (EP 6.0.).

This section has undergone extensive remodelling and updating for the 6.6. monograph. Emphasis is put on the fact that the tests should be performed as late as possible (see above). The 6.6. monograph still recognizes that some tests may not be applicable to all products but requires a justification, especially if allergenic activity and/or protein profile of the product cannot be measured. This shows again that the requirements have been increased, now also including NPPs. The tests themselves are an array of biological, immunological and chemical tests. Furthermore, the products have to comply with the general text on sterility and abnormal toxicity.

A comparison and description of the tests to be applied and their limits is given in table 2.

5. Storage

The section "Storage" recommends that absorbed allergen products should not be frozen. In the 6.6. monograph, it has been added "unless otherwise justified and authorized". This means that a manufacturer can deviate from the monograph if supported by solid data and authorized by the NCA.

6. Labelling

This section states the requirements for the labelling of allergen products. Both sections have not changed from 1997 to 2010. It can be assumed that for the German market, the labelling information stated in the monograph has to be given in addition to the details required by the AMG §§ 10 and 11, given the special nature of allergen products.

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Table 2: Comparison of the Tests sections in the EP Monographs on Allergen Products (1063) from 1997, 2008 and 2010.

Test	Ph. Eur. Edition 5.8. (1997)	Ph. Eur. Edition 6.0. (2008)	Ph. Eur. Edition 6.6. (2010)
Water (2.5.12)	Not more than 5% for freeze- dried products	Not more than 5% for freeze- dried products	(2.5.12. or 2.5.32) Maximum 5% for freeze-dried products In the case of oral lyophilisates, the water content may be higher than 5 % where justified and author- ized
Sterility (2.6.1.)	Allergen products intended for parenteral, bronchial and conjunc- tival administration comply with the test for sterility	Allergen products intended for parenteral, bronchial and conjunc- tival administration comply with the test for sterility	Allergen products presented as parenteral and eye preparations, preparations for inhalation or skin testing comply with the test for sterility
Microbial Contamination			For non-sterile allergen products, recommendations are provided in 5.1.4. Microbial quality of non- sterile pharmaceutical preparations and substances for pharmaceutical use
Protein Content	80 - 120 % of the stated content of a given batch. If the biological potency can be determined then the test for protein content may be omitted	80 - 120 % of the stated content of a given batch. If the biological potency can be determined then the test for protein content may be omitted	(2.5.33) $80 - 120$ % of the stated content, unless otherwise justified and authorized. If the biological potency can be determined then the test for protein content is performed as a batch-to-batch consistency test and the protein content is within 50 - 150 % of the stated content
Protein Profile	The protein composition deter- mined by suitable methods corre- sponds to that of the IHRP	The protein composition deter- mined by suitable methods corre- sponds to that of the IHRP	The protein profile determined by suitable methods corresponds to that of the IHRP. The presence of rele- vant allergen component is verified where possible. The choice of relevant allergen components to be tested must be justified.
Abnormal toxicity (2.6.9.)	Allergen products obtained from molds and intended for parenteral administration (except skin prick tests) comply with the test for	Allergen products obtained from molds and intended for parenteral administration (except skin prick tests) comply with the test for	The production method is validated to demonstrate that allergen products obtained from molds and in- tended for parenteral administration, if tested, would comply with the test for abnormal toxicity for im-

	abnormal toxicity for immunosera	abnormal toxicity for immunosera	munosera and vaccines for human use. (moved into the
	and vaccines for human use	and vaccines for human use	section "Source Material": Molds)
	Not less than 80 % and not more	Not less than 80 % and not more	80 - 120 % of the stated amount but in any case not
	than 120 % of the stated amount	than 120 % of the stated amount	more than 1.25 mg per human dose unless otherwise
	but in any case not more than	but in any case not more than	justified and authorized, when aluminum hydroxide or
$\Delta \operatorname{luminum}(2513)$	1.25 mg per human dose unless	1.25 mg per human dose unless	aluminum phosphate is used as adsorbent
Aluminum (2.5.15)	otherwise justified and author-	otherwise justified and author-	
	ized, when aluminum hydroxide	ized, when aluminum hydroxide	
	or aluminum phosphate is used as	or aluminum phosphate is used as	
	adsorbent	adsorbent	
	Not less than 80 % and not more	Not less than 80 % and not more	80 - 120 % of the stated amount when calcium phos-
G_{1}	than 120 % of the stated amount	than 120 % of the stated amount	phate is used as adsorbent
Calcium (2.5.14)	when calcium phosphate is used	when calcium phosphate is used	
	as adsorbent	as adsorbent	
	The antigens are identified by	The antigens are identified by	
Antinan Dur Cla	means of suitable techniques us-	means of suitable techniques us-	
Antigen Profile	ing antigen-specific animal anti-	ing antigen-specific animal anti-	
	bodies	bodies	
	Relevant allergenic components	Relevant allergenic components	Relevant allergenic components are identified by
	are identified by means of suit-	are identified by means of suit-	means of suitable techniques using allergen-specific
Allergen Profile	able techniques using allergen-	able techniques using allergen-	human antibodies
	specific human antibodies	specific human antibodies	
	The activity is $50 - 200$ % of the	The activity is $50 - 200$ % of the	The activity is $50 - 150$ % of the stated amount as as-
	stated amount as assayed by inhi-	stated amount as assayed by inhi-	sayed by inhibition of the binding capacity of specific
	bition of the binding capacity of	bition of the binding capacity of	immunoglobulin E antibodies or a suitable equivalent
Total Allergenic Activity	specific immunoglobulin E anti-	specific immunoglobulin E anti-	<i>in vitro</i> method
	bodies or a suitable equivalent <i>in</i>	bodies or a suitable equivalent <i>in</i>	
	vitro method	<i>vitro</i> method	
X 1 ¹ · 1 · 1 A 11	50 - 200 % of the stated amount,	50 - 200 % of the stated amount.	50 – 200 % of the stated amount of each relevant al-
Individual Allergens	determined by a suitable method	determined by a suitable method	lergen component, determined by a suitable method

Text in **bold: changed/added** from 2008 to 20010 Text crossed out: omitted from 2008 to 2010

4. Module 3 (Quality) of the EU CTD

This chapter focuses on the compilation of an EU CTD Module 3 for allergen products that were previously only available as named patient products without a MA. Guidance on which information to include in a MAA dossier for allergen products is very limited and manufacturers have to adapt the guidance given for NCEs in ICH M4Q (R1)⁵⁰ for their products. Using ICH M4Q as basis, the new regulatory requirements laid down in the allergen product Guideline and the revised EP monograph 1063:2010 were integrated into the respective CTD sections. Thus, this chapter provides guidance on which aspects to include in the EU CTD Module 3 for allergen products intended for SCIT and derived from natural source materials.

4.1 Drug Substance Sections (3.2.S.)

3.2.S.1. General Information (3.2.S.1.1. Nomenclature, 3.2.S.1.2. Structure, 3.2.S.1.3. General Properties)

In the "General Information" section, the name of the active substance has to be stated and information on the structure and general properties of the active substance is provided. As stated in the Guideline, the full name of the active substance should be given (scientific name, genus, species and common name) in order to unequivocally identify the source material and active substance for an allergen product.

Information on the structure of the active substance for allergen products is not easy to provide as it is often a mixture of proteins and other macromolecular entities extracted from natural source material. The manufacturer should characterize the extracted proteins in as much detail as possible to give basic information on the structure. Literature references could also be employed to provide data, especially for well-known allergens. For many major allergens, the general properties have been determined and published⁴³, therefore this information can be provided. Information on plant tissue of origin, molecular size, biological activity, enzymatic properties or solubility of the proteins should be stated. Physicochemical characteristics such as an estimate on expression of the respective allergen in its tissue of origin, glycosylation, aggregation or the amino acid sequence could be provided.

3.2.S.2. Manufacture

3.2.S.2.1. Manufacturers

Here, all pertinent organizational information on every manufacturer/contractor and their respective responsibilities shall be provided

3.2.S.2.2 Manufacturing Process and Process Controls

The description of the manufacturing process can be presented like for a chemical entity, containing a flow diagram and a narrative description of the process. The respective guidelines offer steps to follow

for preparation of this section (ICH M4Q Rev 1, ICH Q6B⁵⁴). The flow chart should be a comprehensive visual rendition of the manufacturing process and contain a complete list of in-process controls and tests that are performed at each step. If the DS is held, the conditions (temperature, time) should be given. The flow chart should be accompanied by an elaborate narrative of the manufacturing process. Detailed information should be given on the extraction of allergens from their source material, the steps where materials enter the process and of the in-process tests which serve to control these steps. Critical steps of the process should be identified. For products intended for parenteral administration, aseptic procedures should be indicated in the flow chart and described in the narrative of the production process. Also, for modified allergen extracts, a detailed description of the modification steps should be provided as these steps are regarded as part of the formulation.

3.2.S.2.3. <u>Control of Materials</u>

This section is extensively covered in the Guideline for Allergen products and in the revised Monograph on Allergen Products of the EP. It is of special relevance for allergen products as the source materials are mostly of biological origin and the quality of the source material directly influences the performance of the allergen product. Detailed requirements for source materials are given in the EP and the Guideline, the relevant specifications are stated in the EP. These requirements are stated below; the specifications are listed in <u>table 3</u>.

Plants/Plant Parts

It is important to provide data on the cultivation and collection of plants/plant parts, the storage and transport conditions, tests for the control of identity and purity should be described and the acceptance criteria justified. Any pre-treatment of source material should be detailed and justified. Manufacturers have to be aware that pre-treatment of source material, i.e. treatment of pollens with solvents for defatting will have an impact on the impurity profile of the drug substance.

Pollens:

The Guideline of Good Agriculture and Collection Practice⁵⁵ is referenced in the Guideline. Therefore, it has to be complied with, and a certificate from the pollen supplier should be presented in this section. Should genetically engineered plants be used as source materials, this has to be justified. Furthermore, the geographic location of the fields has to be described, and test methods and acceptance criteria for impurities should be included in the description of the source material. Relevant pesticides, heavy metals and solvents have to be kept to a minimum. However, the sentence from the NfG "the measurement of their content on a limited number of pollen batches in order to demonstrate that their level is kept to a minimum" is not included in the new Guideline. Therefore, it would make sense for an applicant to qualify all pollen material, set and justify specifications, state them in the dossier and on the Certificate of Analysis (CofA) for the respective material and control each batch. Another possibility is to include these specifications in the technical agreement with the suppliers and present rep-

resentative supplier CofAs on demand. The same applies to the contamination with other plant particles, which have to be kept at a minimum, as opposed to 10 % as stated in the NfG.

Molds:

For molds, requirements for the characterization of strains have been updated to include biochemical and genetic methods as opposed to just morphological methods; furthermore, emphasis is put on the use of allergen-free medium to enhance product safety. The composition of the culture medium should be stated in this section. Appropriate measures have to be taken to avoid contamination with other strains. These requirements also apply to *mites* as source material.

<u>Animal Materials</u>: For animal materials, the Guideline text was extended to stating that contamination with mites and moulds should be avoided and storage conditions for the material should be described. This is especially important for the use of killed animals, as decomposition occurs quickly and therefore safety-relevant impurities can build up in the corpse. Therefore, storage conditions and methods for collection of the animal materials should be described here.

The paragraph on hymenoptera venoms has been expanded. Details on the collection method of the venom should be given in this section, furthermore, the animals used for collection of the venoms need to be characterized taking into account morphological details and other parameters. Relevant pesticides have to be kept to a minimum, best proven by supplying a certificate that no pesticides were used in hymenoptera culture.

Mixing of source materials

Mixing of <u>the same</u> source materials from different suppliers in order to obtain batches of uniform source materials is acceptable. However, a detailed description and justification of the underlying concept for mixing the source materials should be included in this section. Furthermore, uniformity of the source material should be justified and tested. The Guideline clearly states that <u>different</u> source materials should not be mixed prior to extraction.

For other raw materials, specifications, information on the source and a justification for its use should be provided with emphasis on allergenic components, i.e. in culture media.

Source Material	Specification	Comment
Pollens	 Pesticides -> content minimized Heavy Metals -> content minimized Solvents -> content minimized foreign pollen -> 1% of total mixed pollens any individual pollen -> 0.5 % maximum perticides of plant origin other than pollen >> minimum 	 see EP general chapter 2.8.13 minimized. Justify! see EP general chapter 2.4.24 determine by microscopic particle count determine by microscopic particle count instify maximum ellowed contemination
Molds	 particles of plant origin order than poren => minimum minimize biologically active contaminants avoid contamination by other mold strains minimize allergenic media constituents media constituents of human or animal origin must be justified validate production method to ensure that products comply with test for abnormal toxicity (EP chapter 2.6.9.) 	 Justify maximum anowed containmation any presence must be justified if required, substances must be suitably treated to ensure inactivation or elimination of transmissible agents of disease
Mites	 avoid contamination with foreign mite strains minimize allergenic media constituents media constituents of human or animal origin must be justified 	• if required, substances must be suitably treated to ensure inactivation or elimination of transmissible agents of disease
Animal epithelia/ out- growth/ dander	obtain from healthy animals to avoid possible transmissible agents of disease	provide certificates
Hymenoptera Venoms	 identify and specify species used for venom collection specify method of insect collection and venom extraction 	collection/extraction methods must ensure that source material must be of proper quality
Food	state scientific name of animal or vegetable species, indicate which part is used	food must be suitable for human consumption

Table 3: Specifications from EP Monograph on Allergen Products 01/2010:1063

3.2.S.2.4. Control of Critical Steps and Intermediates

Critical steps should be identified and listed in Section 3.2.S.2.2.

In this section, tests that are performed at these critical steps in the process should be listed and acceptance criteria with the respective data provided. The results gathered from tests performed should demonstrate that the process is controlled in order to provide a DS of consistent quality.

3.2.S.2.5. Process Validation and/or Evaluation

Validation and evaluation studies should be performed by the manufacturer to ensure that the process is suitable for its intended use. A summary of all validation studies and the results should be presented here. Taking into account the principle of homologous groups, manufacturers can perform process validation and evaluation studies for products containing the representative allergen of a homologous group and may extrapolate the data to products made with the non-representative allergens of the same homologous group if the criteria as laid down in the Guideline are fulfilled. Manufacturers should identify critical steps and key parameters for the manufacturing process of non-representative allergens and integrate these tests into the reduced validation program.

Should allergenic or toxic substances be employed for the manufacture of the active substance, the manufacturing process should be designed and validated to ensure that these compounds are removed. The manufacturer should submit data to demonstrate this. Furthermore, the process should be designed in a way that the relevant allergens are maintained throughout the process, which should be demonstrated by data gathered from suitable in-process tests. For allergen products derived from molds as source materials, manufacturers have to validate the production process to ensure that these products would comply with the test for abnormal toxicity for immunosera and vaccines for human use (EP chapter 2.6.9.)

For sterile products, validation of all aseptic and/or sterile process steps should be included.

3.2.S.2.6. *Manufacturing Process Development*

The development of the manufacturing process for the DS should be described in detail and critical changes made to the process during development highlighted, the reasons stated and discussed. This could for example be the use of different critical equipment, other extraction techniques, chemicals or changes in manufacturing site. The evolution of the manufacturing process from development to preclinical, pilot, clinical and commercial batches should be discussed and the batch data presented in Section 3.2.S.4.4. referenced here. A rationale for critical changes should be provided and their impact on the quality of the DS assessed and discussed. Significant changes in the manufacturing process should be backed up by data gathered from comparability studies performed with relevant batches of the DS. The manufacturer should submit a detailed discussion of the results along with a justification for the choice of tests. ICH Q5E and Q6B⁵⁶ can provide additional guidance.

3.2.S.3. Characterization

Characterization of allergen extracts is a challenging task because these extracts often contain numerous macromolecules and for several extracts, the clinical relevance of all single constituents have not yet been determined. Furthermore, guidance given for NCEs cannot be used for allergen extracts. The Guideline states that manufacturers shall define the relevant allergens for their products. These allergens should be characterized and the test results presented in this section. In the last years, many physico-chemical methods have become available to characterize the relevant protein allergens extracted from natural source materials⁵⁷.

3.2.S.3.1. Elucidation of Structure and other Characteristics

Structure, molecular size, electrophoretic pattern, isoelectric point and solubility of the relevant allergens should be presented in this section.

The easiest way to tackle this issue is to list the allergens that have been deemed relevant and to briefly justify the choice. A tabular listing should do. If available, literature data on the structure could be used in combination with the identification of the respective protein by electrophoretic and immunological methods and a description of the extraction process in order to ensure comparability of the literature data with the extracted allergen.

The molecular size of an allergen can be determined by size exclusion chromatography. The electrophoretic pattern can be assessed by SDS-PAGE with a suitable size marker; the isoelectric point can be determined using isoelectric focusing. The solubility of a protein, if relevant, can be tested by simple solubility assays in different solvents.

Characteristics such as isomerism, polymorphism or stereochemistry which are given for NCEs are rarely applicable due to the nature of allergens.

3.2.S.3.2. Impurities

Impurities are always present in biological materials, be it environmental pollution, residual solvents from pre-treatment procedures or contamination with plant or other naturally occurring particles. The impurity profile of the DS should be discussed here and reference to supportive analytical data made. Detailed guidance is provided in the following guidelines: Q3A, Q6B⁵⁸. Each possible impurity should be assessed and the results of a "worst case" calculation presented and discussed. Impurities that could be carried over from the DS to DP should be listed and either assessed in this section or in the corresponding DP section, 3.2.P.5.5.

3.2.S.4. Control of Drug Substance

In this section, the specifications set for the DS and their justification as well as analytical procedures and their validation are presented. Also, analyses of representative and consecutive batches of the DS are summarized and presented. One important feature of allergen products is its potency. This should be tested at the active substance stage. Different tests are employed for the different active substances:

<u>Allergen extracts, allergens without structural modifications</u>: Total allergenic activity has to be measured by competitive IgE binding test and the correlation to the content of relevant allergens needs to be made, if these have been defined. For relevant individual allergens, immunological methods have to be applied for identification/quantification.

For <u>allergoids</u>, the discrimination between native and modified compounds is of special importance. Discriminatory tests or a combination of immunological tests have to be applied in order to obtain these data.

For <u>conjugates</u>, the immunomodulatory properties should be considered when testing for potency. For allergoids and conjugates, the manufacturers should assure that relevant individual allergens are identified and quantitated wherever possible by comparing the product to a certified reference standard or IHRP. Also, minor allergens relevant for safety shall be identified and quantitated.

The other control methods are very similar to what is required for NCEs, therefore, allergen product manufacturers can rely on the same guidance as is given for NCEs. Table 4 lists the information to be provided in Section 3.2.S.4.

Deler			
Section	Information to be provided	Guidelines ⁵⁹	
3.2.S.4.1. Specifications	 Specifications should be listed to allow for a total quality control of the product. Emphasis should be put on immunological assays, purity/impurities/contaminants and quantity/potency. Specifications for source materials and excipients should also be included. 	ICH Q6B	
3.2.S.4.2. Analytical Procedures	A list of all analytical procedures should be provided which are used to characterize and control the Drug Substance.	ICH Q2(R1), ICH Q6B	
3.2.S.4.3. Validation of Analytical Proce- dures	Validation data should be provided to prove that the analytical methods are suitable for the characterization of the DS	ICH Q2(R1), ICH Q6B	
3.2.S.4.4. Batch Analyses	 Analyses of 10 representative batches should be presented. Consistency of manufacture should be demonstrated. Manufacturers should provide the results of tests on the consistency of production and the success of modification and/or adsorption steps. 	ICH Q3A, ICH Q3C, ICH Q6B	
3.2.S.4.5. Justification of Specifications	 A justification for the specifications should be provided on the basis of how the specifications contribute to the total quality control of the product. A rationale for including or excluding tests that demon- strate the quality of the product should be provided. 	ICH Q3A, ICH Q3C, ICH Q6B	

Table 4: Information to be provided in Section 3.2.S.4.

3.2.S.5 <u>Reference Standard and Materials</u>

In this section, manufacturers should provide information on the reference standard or material that is used to test the active substance. The requirements for the IHRP are laid out in detail in the new Guideline. A key requirement is that the IHRP should be derived from a production run as described in the dossier (this was adopted from the NfG). Should the manufacturer add any stabilizing agents or modify the IHRP in order to increase stability, these measures have to be justified.

Manufacturers should exhaustively characterize their IHRP(s). Several methods are provided that should be used to structurally and biochemically characterize their IHRPs:

- Isoelectric focusing
- Molecular weight distribution by SDS-PAGE
- Capillary electrophoresis
- Chromatographic techniques
- Mass spectrometry
- Identification of individual allergens by antibody techniques

These methods should be stated in this section and the results should be presented in appropriate form and discussed. Methods and protocols should be annexed to the section.

The quantification of specific allergenic activity and determination of the concentration of relevant individual allergens have already been addressed as key requirements in the NfG. The new Guideline takes this up; results of these tests should be presented in this section.

The composition of the IHRP should be described in detail. Its protein and carbohydrate content shall be determined and the relevance of glycoproteins for IgE binding considered which is especially important with bee and wasp venoms. Also, the manufacturer should demonstrate the presence of all relevant allergens as defined. Individual allergens should be identified by immunological methods. The allergenic property of the IHRP should be determined using immunoblotting techniques with pooled patient sera, and the serum of individual patients can be used to obtain an allergogram. The composition of sera pools should also be provided in this section and the underlying rationale should be discussed and justified.

If a manufacturer has to establish a new IHRP, the Guideline provides guidance on how to compare the new to the previous IHRP: Parallel testing of new and previous standard should be performed. For this purpose, manufacturers should use predefined *in vitro* methods. *In vivo* methods for standardization can also be employed. The respective methods should be listed here, the choice of method should be justified and the rationale discussed in this section, detailed test protocols should also be annexed. The results obtained from parallel testing should be in agreement between new and old IHRP and should be presented in appropriate form in this section. Manufacturers should establish correction factors in case deviating results are obtained and trending analyses should prevent a shift in characterization parameters. The analyses and results should be described and discussed here.

3.2.S.6. Container Closure

If the DS is held and not immediately onward processed, the manufacturer needs to demonstrate the suitability of the container chosen for DS storage. This section can be presented exactly as for NCEs, guidance is given in ICH M4Q(R1)

3.2.S.7. Stability

The chapter "*Stability*" (4.2.5.) of the Active Substance part of the Guideline provides detailed guidance about the requirements that apply to the active substance if it is stored.

All relevant ICH stability guidelines are referenced in the Guideline and therefore apply (ICH Q1A, Q1B, Q5C). The concept of homologous groups can be applied to the stability studies: A full set of stability data has to be provided for the representative allergen of a homologous group. For non-representative allergens, some data may be extrapolated from those obtained with the representative allergen, based on a detailed and scientifically sound justification. Stability studies with batches of DS prepared from source material at the end of its shelf life should be performed, the protocols and results provided and discussed.

3.2.S.7.1. Stability Summary and Conclusion

In this section, manufacturers should provide a detailed description on all stability studies performed on the DS, such as regular stability studies, forced degradation studies or studies for other ICH regions if applicable. The protocols and results should be summarized. A conclusion and discussion of the data should be provided.

3.2.S.7.1. Stability Data

Stability data should be summarized and presented as appropriate. Furthermore, manufacturers should provide information on analytical methods and their validations used in stability studies.

4.2 Drug Product

In this section, the requirements for the subsections of EU CTD Module 3.2.P. are outlined. The sections "Pharmaceutical Development" (3.2.P.2.), "Manufacture" (3.2.P.3) and "Stability" (3.2.P.8.) are of special interest in this context as allergen products often represent legacy products which have to be adapted to current scientific and regulatory requirements.

3.2.P.1. Description and Composition of the Drug Product

Manufacturers should provide a detailed description of the finished product, including a complete list of all active substances. A description of the dosage form, the per-unit amount, component functions,

relevant container closure system and packaging components such as syringes or vials with reconstitution fluids should be provided in this section.

3.2.P.2. Drug Product

This section and its subsections provide a first survey of the DP.

3.2.P.2.1. Components of the Drug Product

This section consists of 2 subsections, Drug Substance (3.2.P.2.1.1.) and Excipients. For DPs that contain a mix of active substances, each active substance and the mix should be discussed in terms of compatibility with excipients, such as adjuvants or preservatives. Key physicochemical characteristics of the active substance which are relevant for the DP should be listed and discussed. This is especially important for allergoids, because the modification is an essential step in formulation and highly dependent on the properties of the DS.

The excipients should be described detailing properties and function (3.2.P.2.1.2.). If adjuvants are used for the DP, they should be characterized and their function discussed according to the Guideline on Adjuvants in Vaccines for Human Use⁶⁰. Each adjuvant should be discussed separately. The following characteristics of the adjuvant(s) should be stated:

- origin and nature of the adjuvant(s): natural, synthetic, endogenous
- chemical composition if applicable
- characterization of the source material
- characterization of the adjuvant (physical, biochemical, adsorptive, purity)
- tests which are part of the routine batch testing of the adjuvant(s)
- stability of the adjuvant

The adjuvant/antigen combination should be briefly discussed here and reference to the stability of the combination should be made.

3.2.P.2.2. Drug Product

This section should provide a brief overview about the nature, the development, the properties and the formulation of the DP.

3.2.P.2.2.1. Formulation Development

The manufacturer should provide a short summary on the development of the DP formulation and highlight changes that were made during development. If applicable, results from comparability studies should be presented and discussed. As SCIT products are always injectables, the route of administration is not necessarily a subject of discussion. However, especially with adsorbed products, if usage is discussed, a brief description of the formulation development with respect to the application device (i.e. syringe) and the product's compatibility with the device should be included.

3.2.P.2.2.2. *Overages*

Should overages be included in the formulation, this should be stated and justified. This is especially important with adsorbed products as non-adsorbed active substance(s) might cause safety risks.

3.2.P.2.2.3 *Physicochemical and Biological Properties*

Several important parameters should be discussed for SCIT products:

- pH and ionic strength of the final formulation
- reconstitution
- particle size distribution
- aggregation
- potency

Manufacturers should also consider other tests which could be relevant for their specific product.

3.2.P.2.3. Manufacturing Process Development

Especially with NPPs that have been on the market for a long time, a detailed description of the manufacturing process development should be provided. Often, the manufacturing process has changed greatly over time and changes that are regarded as significant should be discussed in detail. Changes made from the production of pivotal clinical batches to commercial batches manufactured according to the process described in 3.2.P.3.3. should be highlighted, especially with regard to product performance. Data gathered from comparability studies should be discussed and presented in an annex to the section. As SCIT products are designed for parenteral administration, the method of sterilization should be detailed.

3.2.P.2.4. Container Closure System

Details for the container closure system as described in 3.2.P.7. should be described. For SCIT products, this usually consists of glass vials sealed with rubber stoppers and an aluminum ring. The nature of the materials should be described; the rationale for their choice with emphasis on the protection of the DP from environmental conditions and the compatibility of the materials should also be briefly stated. This is not different from NCEs, therefore the respective guidance should be taken into account.

3.2.P.2.5. *Microbiological Attributes*

SCIT products are sterile products intended for parenteral use. Therefore, manufacturers should discuss the effectiveness of the preservative, if applicable, and the capability of the container closure system to prevent microbial contamination of the product. Tests that are performed to ensure sterility of the product could be described and supportive data provided in an annex to the section.

3.2.P.2.6. *Compatibility*

The compatibility of the DP with all parts of the packaging, devices or vessels with which it comes in contact to should be discussed in detail.

3.2.P.3. Manufacture

In this section, details about the manufacture of the DP are given.

3.2.P.3.1. Manufacturers

The complete data of any manufacturer/contractor involved in DP production should be provided along with the responsibility of each manufacturer/contractor

3.2.P.3.2. Batch Formula

The batch formula used for DP manufacture should be provided. Any overages and the quantity of all components should be listed on a per batch basis, including a reference to their quality standards. Any quality certificates should be provided in the appropriate sections (i.e. Control of Excipients, 3.2.P.4.)

3.2.P.3.3. Description of Manufacturing Process and Process Controls

The description of the manufacturing process can be presented in the same way like for the DS: Manufacturers should provide a flow diagram and a narrative description of the process. Guidance provided in the respective guidelines (ICH M4Q (R1), ICH Q6B) can be followed.

The flow diagram should show where materials enter the process, identify critical steps and intermediate tests. Final product controls should be highlighted. As SCIT products are intended for parenteral administration, aseptic procedures should be indicated in the flow chart and described in the narrative of the production process. Also, for modified allergen extracts, a detailed description of the modification steps should be provided. Should allergenic or toxic substances be employed for the manufacture of the active substance, the manufacturing process should be designed and validated in a way that these compounds are removed. The quantitation of these compounds should represent an in-process control. The manufacturer should submit data to demonstrate this. All critical steps of the process should be identified; suitable control tests set up and listed in this section. Acceptance criteria should be defined for these control tests. For SCIT products, sterile process steps should always be regarded as critical steps and be carefully controlled. Parenteral products need to comply with the test for sterility as outlined in general chapter 2.6.1. of the EP. This test should be added as one of the process controls. If adsorption of the allergens to an adsorbent is part of the manufacturing process, this should also be regarded as a critical step and be carefully controlled. Should any intermediates be generated in the process, this should be regarded as a critical step and the intermediates should be characterized thoroughly. If adjuvants are used in the DP, tests for routine verification of the adjuvant-allergen combination should be identified and acceptance criteria defined and justified.

3.2.P.3.4. Controls of Critical Steps and Intermediates

A tabular overview of all critical steps as defined in 3.2.P.3.3. and the respective acceptance criteria should be provided here. For the acceptance criteria, a justification should be given and supporting experimental data presented. Data on the characterization of any intermediates should be presented and discussed. Emphasis should also be put on the quantitation of any toxic or allergenic substances if used in the process. Furthermore, aseptic process steps and sterility tests should be thoroughly controlled and the data presented and discussed here. Further guidance is provided in ICH Q6B.

3.2.P.3.5. Process Validation and/or Evaluation

The manufacturing process needs to be validated. Results from validation studies should be presented and discussed. If the process has changed, comparability studies should be conducted and the results presented. Results obtained with validation batches after process changes should be compared with those from earlier batches before the change. This should be discussed in detail and the data presented. For allergen products, a few special requirements have to be taken into account, especially for those products derived from moulds: the manufacturing process needs to be validated to ensure that the products comply with the test for abnormal toxicity for immunosera and vaccines as stated in the EP (2.6.9.). Furthermore, if compounds of allergenic potential are used in manufacture, these compounds have to be removed during the process (see above, section 3.2.P.3.4.). This has to be validated as well. If substances are employed where viral safety is a concern, a detailed evaluation should be provided in the annex to Module 3 (3.2.A.2.). If adjuvants are present in the DP, tests to control the adjuvant/allergen combination should be validated. As with the DS, the concept of homologous groups can be applied to process validation studies: A full set of validation data needs to be available for the product of the representative allergen of a homologous group, these data can be extrapolated to the products of non-representative allergens of the same homologous group, provided that the manufacturing process and formulation is identical.

A comprehensive process validation scheme for the DP should be included in annex 3.2.R. (Regional Information, relevant for EU). Should the validation not yet be completed upon submission of the MAA, a summary of the intended validation studies should be provided in this annex.

3.2.P.4. Control of Excipients

The section on Control of Excipients can basically be written as for a NCE, except if adjuvants are present in the SCIT product. Adjuvants need to be characterized according to the Guideline on Adjuvants in Vaccines for Human Use⁶³. If more than one adjuvant is present in the DP, each should be described separately as an excipient.

The sections 3.2.P.4.1. (Specifications), 3.2.P.4.2. (Analytical Procedures), 3.2.P.4.3. (Validation of Analytical Procedures), 3.2.P.4.4. (Justification of Specifications), can be presented as for NCEs.

3.2.P.4.5. (Excipients of Human or Animal Origin) should list any excipients of human or animal origin. These excipients should comply with the TSE requirements⁵¹. Furthermore, any allergenic potential of excipients especially from animal origin should be identified and evaluated. Any novel excipients should be characterized in detail in section 3.2.P.4.6. (Novel Excipients), especially with respect to their function in the DP.

3.2.P.5. <u>Control of Drug Product</u>

The control of allergen products is different from that of NCEs or other biologics. Detailed guidance is given in the Guideline; specifications are stipulated in the new EP monograph on allergen products. Several control tests should be performed on the DP, depending on its nature:

Non-modified allergen preparations:

Total allergenic activity of the product should be determined (competitive IgE-binding test). Potency units should be defined and the products labelled accordingly. the Guideline emphasizes that if standardized and validated test systems are available, these should be applied for the quantification of individual allergens. The w/v content of the individual allergens should then be stated in the product SmPC (EU CTD Module 1) in addition to potency.

Allergen mixtures:

Determining the potency of individual allergens is regarded as important. Should that not be possible, for example due to cross-reactivity of individual allergens within the mixture, a competitive IgEbinding test should be employed to determine the total potency of the product.

Adsorbed products:

The manufacturer has to determine the efficacy and stability of the adsorption. This should be done by quantitating the total amount of soluble protein and/or the presence of IgE binding components in the supernatant at least at release of the product and at the end of shelf life. This is a parameter which should be regularly checked during stability studies performed on adsorbed products (see section 3.2.P.8.).

Non-standardized allergen extracts:

The antigen and protein profile as well as the content of total protein and individual allergens should be determined employing suitable *in vitro* methods. Should any of these parameters not be tested, a justification must be provided.

Manufacturers should state the nature of their product in this section and list and justify the control tests applied. The respective specifications should be set and justified in section 3.2.P.5.6.

3.2.P.5.1. Specifications

For each finished product, appropriate specifications should be set. Should it not be possible to perform any of the control tests on the finished product, as it is the case with many modified products, the tests should be conducted at the latest possible intermediate stage prior to modification, and specifications should be defined for this stage. This is in line with the current EP monograph as well as the Guideline. If it is not possible to conduct certain tests as appropriate methods are not available, this should be indicated by the applicant and justified. Table 5 lists the relevant specifications for allergen products:

Characteristics	Specification
Sterility/microbial contamination	according to EP 2.6.1. /5.1.4.
Protein content	80 - 120 % of the stated amount,
	as batch-to-batch-consistency test: 50 -150 %
Protein profile	presence of relevant allergens, conforms to IHRP
	suitable tests to be chosen and justified by manufacturer
Potency	quantization of IgE and IgG binding components, potency needs to
	be tested for each individual allergen active substance in a mixture.
	The total potency of the mixture can be determined if cross-
	reactivity between the individual allergens makes a discrimination
	impossible
Allergen profile	identification of all relevant allergenic components using suitable
	antibody-based tests (choice and justification by manufacturer)
Total allergenic activity	50 - 150 % of the stated amount. Assay has to be based on the bind-
	ing capacity of specific IgE antibodies or a suitable equivalent in
	<i>vitro</i> method.
Individual allergens	50 – 200 % of the stated amount of each relevant allergen compo-
	nent. Suitable method to be chosen and justified by manufacturer
success/stability of adsorption	determination of total amount of soluble protein and/or the presence
	of IgE binding components in the supernatant

Table 5: Relevant specifications for allergen products

The sections 3.2.P.5.2. (Analytical Procedures), 3.2.P.5.3. (Validation of Analytical Procedures) and 3.2.5.6. (Justification of Specifications) can be presented as for other Biologics or NCEs.

3.2.P.5.4. Batch Analyses

The data of batch analyses performed on 10 batches should be provided. If different batches are used (pilot scale batches, clinical batches, commercial batches), the concept of choosing the respective batches should be described. A tabular overview of all relevant batch data should be given and any deviations should be discussed and justified. Representative CofAs of the finished product should be provided. In general, the manufacturer should show the batch-to-batch consistency of the product.

3.2.P.5.5. Characterization of Impurities

The manufacturer should provide a detailed characterization of the impurities that can be present in the product. Alternatively, this can be done in section 3.2.S.3.2. "Impurities, as many impurities in biological products arise from the source material. Emphasis should be put on impurities potentially present from starting/source materials which cannot be eliminated during the manufacturing process. It is imperative to set and justify acceptable limits for these impurities. Also, impurities that can derive from excipients such as natural adjuvants should be taken into account. Degradation products and products from the reaction of the DS with excipients or the DP with parts of the container closure sys-

tem should also be identified and the acceptance criteria stated and discussed. Guidance is also provided in ICH Q6B.

3.2.P.6. Reference Standards or Materials

Information on the reference standard used for characterization of the DP should be provided in this section. If an IHRP is used for the DP, it should allow for the characterization of all relevant features of the product, such as protein profile, carbohydrate content, identification of all relevant allergens and potency. As for the active substance IHRP, the DP IHRP should be biologically standardized using appropriate methods based on skin reactivity (Turkeltaub²⁰ or Nordic Council of Medicines²¹). In the Guideline on allergen products, detailed guidance on the IHRP is provided in the "active substance" chapter (4.3. Standards and Reference Materials). If a different IHRP is used for the DP, this guidance should also be followed (see DS section 3.2.S.5.).

3.2.P.7. Container Closure

This section can be presented exactly as for NCEs. Guidance is given in ICH M4Q (R1).

3.2.P.8. Stability

The concept of homologous groups can be employed to assess the stability of the DP. Manufacturers need to provide a full set of stability data for the representative allergen. Stability studies for the non-representative allergens can be performed on an ongoing basis as real-time stability studies after granting of the MA. In case of cross-reacting allergens from the same homologous group, the applicant may not be able to assess the stability of the individual active substances and should assess the overall potency by competitive IgE binding assays. A rationale for the test strategy employed should be given. Sterility, the efficacy of antimicrobial preservatives and, for non-sterile products, the microbial quality should be tested where applicable. This is in line with the requirements detailed in the current EP monograph. If adjuvants are used, the stability of the adjuvant/allergen combination has to be evaluated. The extent of dissociation of allergen from the adjuvant and its integrity should be tested. If the DP is also an adsorbed product, the stability of the adsorption of allergen/adjuvant should be assessed as well.

<u>Stability of allergen mixtures</u>: Should the product contain a mixture of allergens that belong to different homologous groups, the applicant has to perform stability studies assessing each individual allergen. In this case, extrapolation of data from a representative allergen is not possible.

<u>Stability of modified/adsorbed products</u>: The stability of the adsorption and/or modification has to be assessed at the end of shelf life by quantitation of the total soluble protein amount and/or the IgE binding components in the supernatant. Should a product contain native and modified allergens, its potency can be assayed employing mediator release tests which allows for a direct assessment of the product's stability. <u>Potency assays</u> within the scope of stability studies should be conducted employing appropriate and validated *in vivo* or *in vitro* methods. For adsorbed and/or modified products, this may not always be possible. In this case, manufacturers should establish suitable *in vitro* tests to determine the potency of their product. These tests should be performed at the beginning and end of the proposed shelf life, beginning during development of the product. This way, the stability of the finished product is documented at the time the MAA is submitted.

3.2.P.8.1. Stability Summary and Conclusion

The stability summary and conclusion should contain a description of the types of studies that were conducted and the respective protocols. The results of all relevant stability studies should be presented and discussed. A conclusion and implications for the labelling of the product should also be presented (storage conditions, shelf life, in-use storage and shelf life).

If adjuvants are present in the DP, a summary of the long-time stability data of the adjuvant/allergen combination with special emphasis on relevant physical and biochemical properties should be presented.

3.2.P.8.2. Post-Approval Stability Protocol and Stability Commitment

If stablility data are not available for non-representative allergens at the time of MA submission, the applicant include a commitment in this section to conduct these studies and provide a detailed protocol on real-time stability studies.

3.2.P.8.3. Stability Data

Stability data gathered from stability studies should be presented in a suitable form. Manufacturers should also provide information on the analytical methods used for generating these data. Only validated methods shall be employed, information on the validation should also be provided. Cross-reference to section 3.2.P.5.3. should be made if applicable.

3.2.A. Appendices

In the appendices to Module 3, diverse information on for example the facilities and equipment (3.2.A.1.), the adventitious agents safety evaluation (3.2.A.2.), and a comprehensive set of regional informations (3.2.R.) can be found.

5. Impact of the Therapy Allergen Ordinance on Allergen Product Manufacturers and the Authority

Many allergen product manufacturers are small or medium sized enterprises and do not have a large regulatory affairs department. According to Directive 2001/83/EC, allergens are regarded as medicinal products which need a MA in order to be rightfully marketed, but for many years, a significant amount of allergen products were marketed as NPPs with manufacturers liberally applying the exemption made for NPPs in § 21 (2) 1g. As companies did not apply for MAs, the need for a well-staffed regulatory affairs department was not seen. One reason for issuing the TAV was to control this NPP market and since it came into force in November 2008, many allergen product manufacturers have to take on an increased regulatory workload: MAA dossiers need to be prepared for their NPPs that were previously not authorized; furthermore, batch release is also an issue that the regulatory affairs departments have to take care of. Therefore, most German allergen product manufacturers are currently hiring regulatory affairs professionals to meet the deadline for dossier submission (1st of December, 2010) and in anticipation of deficiency letters and maintenance issues for their dossiers submitted under the TAV⁶¹. The increased costs for submission and maintenance will most likely prompt allergen product manufacturers to adjust their portfolios in a way that allergen products which are sold on a less frequent basis will be taken off the market⁶². The "Kassenärztliche Vereinigung Bayerns" has conducted a survey by asking all allergen product manufacturers listed in Germany (Lauer-Taxe 2009) which products they have notified for MAA submission. One company did not answer the questionnaire, but 8 companies will submit a total of 73 MAAs for SCIT products to the PEI by 1st of December, 2010⁶³. The PEI will also need to expand its budget to be spent on the assessment of MAAs. It was originally estimated that the currently 9 known manufacturers in Germany will submit a maximum of 500 MAAs (SCIT and SLIT) of which only about 20 % were estimated to be full dossiers (dossiers for representative allergens) and 80 % to be reduced dossiers based on the data submitted for representative allergens. In sum, the PEI estimates that roughly 8 million € will be needed for the assessment of the MAAs that will be submitted. For the maintenance of the MAs to be granted, around 180,000 € are estimated, another ca. 25,000 € will be needed yearly for the processing of batch testing and release applications⁶⁴. These costs will have to be covered by the manufacturers.

Allergen product manufacturers will have to calculate whether the sales of therapy allergens intended for the treatment of rare allergies in mixtures with allergens that are covered by the TAV will cover for the batch testing and release costs and for the costs of submitting a MAA. Some manufacturers might consider a portfolio adjustment and refrain from the sale of mixtures but move to the sale of single allergen products, so that allergens not covered by the TAV can be marketed without the extra costs of MAA and batch testing and release.

Another issue concerns marketing considerations: Many allergen product manufacturers have licensed products and NPPs. They might want to raise the prices for the NPPs submitted for MAA in order to

get a return on their investment. Therefore, manufacturers need a strong rationale to convince physicians that a product for which an MA has been granted is of a better quality than it was before, hence the pricing had to be adjusted. This will most likely result in an increasingly tough competition between manufacturers which is an advantage for reimbursement costs on the one side, on the other side it may cause smaller manufacturers to go out of business and decrease the variety of therapy allergens offered for treatment.

Advertising is another point to consider: Currently, all manufacturers advertise their NPPs to physicians. However, § 3a of the German Medicinal Products Advertising Act (HWG)⁶⁵ states that advertising a medicinal product which needs to be authorized in order to be rightfully marketed but does not have a valid MA is prohibited. Here, a compromise should be found until the MA for a product has been granted.

Last, but not least, many manufacturers will have to alleviate deficiencies in the clinical parts of their dossiers. They might have to conduct studies in order to deliver data on safety and efficacy of their product. All manufacturers had to submit Pediatric Investigation Plans with detailed outlines of clinical studies planned in the pediatric population and will have to conduct pediatric studies. First, these studies will need a certain budget, but also the recruiting of patients will not be that easy – the 9 allergen manufacturers in Germany will be competing for patients. A stringent study protocol as well as convincing recruitment of patients will be key to including the number of patients necessary to achieve the power the studies need in order to deliver conclusive data.

6. Conclusion and Outlook

Directive 2001/83/EC states that medicinal products need to be authorized before they may be placed on the market. The German AMG provides an exception for NP allergen products; these can be placed on the market without a valid MA. Hence, these products are not tested for quality, safety and efficacy by the NCA. This provision in the AMG aimed at retaining a variety of allergen products for the treatment of rare allergies which cannot be filed for MA for different reasons. However, many manufacturers market NPPs that are intended for the treatment of frequently occurring allergies and thus could be filed for MA with the PEI. The TAV was issued to put an end to this practice and bring these products under the control of the authority, thus preventing risks to public health that could emanate from NPPs that are not officially evaluated. This German initiative to better control the allergen product market has become a trend in Europe recently: The Spanish authority is currently drafting a similar ordinance⁶⁶, the Italian authority has recently requested that manufacturers submit the Drug Substance part of EU CTD Module 3 of the products they currently market in Italy for evaluation (deadline 15th of May). A therapy allergen ordinance is drafted there as well⁶⁷. Switzerland has issued a new ordinance on the submission of abbreviated dossiers for allergen products that have an authorized reference product or their safety and efficacy can be proven by literature references⁶⁸. This ordinance excludes NPPs which can still be marketed in Switzerland without a MA, but Swissmedic is currently evaluating the NPP market and might draft an ordinance that includes certain NPPs similar to Germany⁶⁹. The novel regulatory environment in Europe together with the TAV should provide safe and efficacious NPPs of high quality which is important for the treatment of such individual diseases as allergies. For the future, it might be worth thinking about extending the requirement for batch release to allergen products that contain allergens not regulated by the TAV to check their quality as well.

Allergen product manufacturers face the challenge to compile MAA dossiers for their products that were previously marketed as NPPs without a valid MA. Guidance covering the information that has to be provided in the "Quality" part of the MAA dossiers for allergen products is scarce. Therefore, existing guidance that is focused on NCEs has to be adapted for therapy allergens and the dossiers have to be written using ICH M4Q (R1) and a few other guidelines for biologics as reference.

This thesis aimed at summarizing the new regulatory requirements and their scientific basis and to provide a quick reference guide for the compilation of Module 3 of the MAA dossier for allergen products derived from natural sources and intended for SCIT.

This was done by integrating the guidance and provisions given by the new Guideline for allergen products and the EP monograph 2010:1063 into the existing guidance for NCEs using ICH M4Q (R1) as basis. Thus, allergen product manufacturers may use this thesis as guidance for successfully compiling Module 3 of MAA dossiers. Hence, this thesis can contribute to the timely and straight-forward preparation of MAA dossiers for allergen products and help manufacturers to meet the deadline of December 1st, 2010, for the submission of these MAAs to the PEI.

7. Summary

The regulatory environment for allergen products in Germany has undergone significant changes in recent years. Novel regulatory requirements were introduced with the Therapy Allergen Ordinance, issued in 2008, that put especially named patient products under a more stringent control by the Paul-Ehrlich-Institut (PEI). Furthermore, the quality standards and requirements for allergen products were raised with the revised Guideline for Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007) and a revised monograph on allergen products (2010:1063, Producta Allergenica) of the European Pharmacopoeia. In response to these changes, manufacturers have to meet the challenge of establishing marketing authorization application dossiers for allergen products that were marketed as Named Patient products without marketing authorization. What is more, available guidance on the compilation of dossiers for these products is very limited.

In its first part, this thesis provides a brief introduction to allergy and asthma, products for specific immunotherapy for subcutaneous use and introduces the concept of Named Patient Products in contrast to allergen products with a regular Marketing Authorization (Chapters 1 and 2). The third part provides a summary of the current regulatory environment and its scientific basis for allergen products derived from natural source materials and intended for subcutaneous specific immunotherapy (chapter 3). Furthermore, a quick reference guide for the compilation of Module 3 of the EU CTD is provided in chapter 4. Using ICH M4Q (R1) as basis, the novel regulatory requirements for allergen products are integrated into the CTD structure. The last part of this thesis provides a brief evaluation of the impact the German Therapy Allergen Ordinance has on the German market for allergen products and ventures an outlook on similar regulations being drafted in Europe (Chapters 5 and 6).

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Annex

Homologous Groups as proposed by Lorenz et al.⁴³

Tree pollens:

- the "Birch group", comprising birch, alder, hazel, oak and hornbeam, representative allergen source: birch
- the "Oleaceae" group: olive, ash, privet and lilac, representative allergen sources: olive or ash
- the "Cupressaceae" group: cedar and cypress, with either one being the representative allergen source

Grass and cereal pollens: Poaceae family

- sweet vernal grass, oat, orchard grass/cocksfoot, meadow fescue, velvet grass/Yorkshire fog, barley, perennial rye grass, Kentucky bluegrass, cultivated rye, cultivated wheat. Representative allergens: timothy grass, orchard grass or Kentucky bluegrass.
- This group can be extended to couch grass/crested wheatgrass, bent grass, meadow foxtail, false oat and brome grass if Kentucky bluegrass or timothy grass are chosen as representative allergens, as cross-reactivity between these species has been shown.

Weed pollens

The weed pollen group consists of ragweed, mugwort and pellitory with ragweed or mugwort being the representative allergen source.

Mites

The European house dust mite and the American house dust mite were assigned to one group with either one being the representative allergen source.

Insect venoms

The two clinically relevant insect venoms, bee and wasp venoms, were not assigned a homologous group due to missing protein homology. The high rates of cross-reactivity of patient sera to the different insect venoms were identified to be due to cross-reactive carbohydrate determinants.

Vertebrates as clinically relevant allergen sources:

Due to the expression of the allergens in different parts of the animal body, the formation of homologous groups is difficult and requires a scientific justification. This could be for example an identical source material used for preparation of the extracts; or allergens in the extract have been proven to be cross-reactive by inhibition studies, which in this case should be backed up by scientific literature. Homologous group formation of cat and dog could be possible, if justified accordingly and supported by scientific data provided by the applicant.