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REVIEW

Quality requirements for allergen extracts and allergoids for allergen immunotherapy

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Abstract All allergen products for allergen immunotherapy currently marketed in the European Union are pharmaceutical preparations derived from allergen-containing source materials like pollens, mites and moulds. Especially this natural origin results in particular demands for the regulatory requirements governing allergen products. Furthermore, the development of regulatory requirements is complicated by the so far missing universal link between certain quality parameters, in particular biological potency, on the one hand and clinical efficacy on the other hand. As a consequence, each allergen product for specific immunotherapy has to be assessed individually for its quality, safety and efficacy. At the same time, biological potency of allergen products is most commonly determined using IgE inhibition assays based on human sera relative to product-specific in house references, ruling out full comparability of products from different manufacturers. This review article aims to summarize the current quality requirements for allergen products including the special requirements implemented for control of chemically modified allergen extracts (allergoids).

Introduction

Like all industrially produced medicinal products, products for allergen-specific immunotherapy (AIT) require a marketing authorization for distribution in the European Union (EU). However, several characteristics distinguish AIT products from other medicinal products, necessitating special regulatory requirements.[1] Examples for these special characteristics are the wide variety of allergenic substances, the widespread use of chemically modified and/or adsorbed allergen extracts and the bio-variability of the natural source materials. Furthermore, each AIT product has to be regarded as unique, even if products originate from the same source material. For example, there are currently 13 AIT products available on the German market for treatment of birch pollen allergy. Although the active substances in all of these products originate from aqueous extracts prepared from pollen of the tree species *Betula verrucosa*, each of these products has to be assessed individually for its quality, safety and efficacy. Among other reasons, this is necessary because differences in the manufacturing processes from the natural source materials to the drug products may lead to considerable differences in protein composition (Fig. 1).

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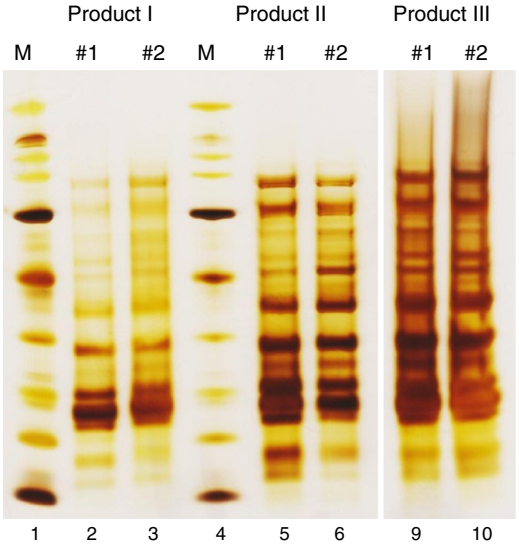

Figure 1 Protein profiles of birch pollen allergen extracts. SDS-PAGE under reducing conditions was performed with native intermediates of three birch pollen allergen products from different manufacturers. Of each product, two batches (#1, #2) are presented. The molecular weight marker (M) ranges from 6.5 kDa to 200 kDa. Two empty lanes of the gel (7 and 8) have been cut from the picture to allow for better side-by-side comparison.

In addition, the natural origin of the allergen source materials entails the problem of bio-variability in both allergenic as well as non-allergenic components. For example, Codina et al. recently summarized the knowledge on factors reported to influence the composition of pollen, including the geographical location of the plant, weather and soil conditions, the year of the harvest as well as genetic varieties of plant species.[2] In another study it was shown that the Amb a 1 content of short ragweed (*Ambrosia artemisiifolia*) pollen deviates up to 10-fold when comparing pollen harvested at the same location but in different years.[3] Consequently, the extent of batch-to-batch variability allowed in allergen products is significantly greater than, e.g. for chemically derived medicinal products. Furthermore, quality control is complicated for many AIT products marketed in the EU because they are not native extracts but chemically or physically modified. In these cases, many analytical methods cannot be performed at the level of the final product, but are limited to intermediates. Therefore, special regulatory requirements for such products were implemented in recent years. Last but not least, the vast number of allergenic materials had to be taken into account when defining the regulatory framework for allergen product quality control. This includes some special regulations for rare allergens as well as for allergens from closely related species. This review article summarizes the current quality requirements arising from European legislation or European regulatory documents and how the indicated characteristics of AIT products have been accounted for.

Regulatory background

Allergen products have been subjected to European pharmaceutical legislation in 1989, when Directive 89/342/EEC extended the Directives 65/55/EEC and 75/319/EEC, including additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens. The directive defined that an ''allergen product shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent''. This definition remained unchanged in the subsequent Directive 2001/83/EC. Importantly, Directive 2001/83/EC states that all medicinal products, either prepared industrially or manufactured by a method involving an industrial process, are required to receive marketing authorization before distribution in a Member State. Despite this requirement, there exist many national exceptions, leading to a highly heterogeneous regulatory situation for allergen products in the EU.[4,5] Especially the distribution of so-called ''named patient products'' (NPP; medicinal products manufactured for an individual patient) according to an exemption as stated in the Directive 2001/83/EC is still very common in many member states, although this exemption from marketing authorization was originally included in the Directive to enable the treatment of rare allergies using customized products. To counteract the distribution of AIT products containing highly prevalent allergens under the guise of NPPs, the Therapy Allergy Ordinance (TAV) was implemented in Germany in 2008.[1,6–8] The transition phase is still ongoing. In parallel, various other Member States have established different national strategies to facilitate market access of allergen products.[4] In order to counteract this regulatory heterogeneity, a draft reflection paper on harmonization of regulatory procedures for allergen products in the EU was presented to the Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) in November 2015.[9] Subsequently, a drafting group was established with the objective to propose harmonized regulatory approaches for allergen products in the EU. This process is ongoing and no results of the work of this drafting group have been published so far.

The central requirements for quality control of allergen products are obligatorily laid down in the European Pharmacopoeia (Ph. Eur.) in the Monograph on Allergen Products.[10] After some extensive revisions in the past, the most recent changes to the monograph account for the establishment of two recombinant major allergen reference standards[11,12] as well as the publication of several separate source material monographs like the Monograph on Pollens for Allergen Products.[13] The requirements of the Ph. Eur. are mirrored in the *Guideline on Allergen Products: Production and Quality Issues* (EMEA/CHMP/BWP/304831/2007), complemented with more detailed information in accordance with the current state of knowledge.[14] For example, this Guideline introduced the concept of homologous groups to allergen product regulation.[15] This concept created a new basis for data extrapolation between allergen groups justified by sound scientific criteria. Meeting the needs of a field with such a wide variety of active substances, data on safety and efficacy can be extrapolated to a certain extent within a homologous group if products fulfil specific criteria.[16] However, extrapolation of quality data is limited to stability data as well as process validation.[14]