

Regulatory aspects of specific immunotherapy in Europe

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Purpose of review

The recent developments in the regulation of allergen products and their impact on specific immunotherapy (SIT) in Europe are summarized, and unmet needs are discussed.

Recent findings

New guidance on the quality, the clinical development, and marketing authorization status of allergen products for SIT has been released. The most important documents are Guidelines from the European Medicines Agency, a revision of the European Pharmacopoeia Monograph on Allergens, regulations, and position papers of scientific societies.

Summary

The increased demands on quality, safety, and efficacy will lead to allergen products being better characterized and with enhanced proof of efficacy and safety. In addition, national activities to regulate the existing broad spectrum of named patient allergen products have been started. At the same time these developments represent a challenge to manufacturers to meet all new requirements. Some problems, for example regarding patient-tailored products containing recombinant allergens remain and may require novel regulatory approaches.

Keywords

efficacy of allergen products, Named Patient Products, quality of allergen products, regulation of allergen products, specific immunotherapy

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Introduction

Specific immunotherapy (SIT) of type I allergies was introduced approximately 100 years ago [1,2]. For decades SIT has been used in a ‘traditional’ fashion, with recommendations and guidelines for clinical practice mainly based on expert opinions rather than on scientific evidence. The use of nonstandardized Named Patient Products (NPPs) was very common [3]. Sizes of clinical studies were small and studies often uncontrolled. The number of placebo-controlled studies increased in the 1990s; however a wide variety of study designs was used making it impossible to compare different trials. The demand for Good Clinical Practice (GCP) introduced by the Directive 2001/20/EC [4] represented a major step towards the introduction of evidence-based medicine and strongly influenced the field of allergology. Moreover, the release of the EMA Guideline CHMP/EWP/18504/2006 [5••] now provides the basic design of studies for products for SIT.

In the field of allergen quality, efforts were made in the 1980s to develop international standard extracts and define international potency units, but for various reasons these standards have never been broadly used (reviewed in [6]). Regulatory guidance documents on allergen

extract quality were largely unchanged since the mid 1990s until 2008 [7•]. Various developments in molecular and clinical allergology changed this situation, for example the availability of purified recombinant allergens and their use in allergen standardization [8•] and clinical trials [9••], and the use of modern proteomics and physicochemical techniques in the characterization of allergen products [10••,11]. In Europe, the recognition of these developments by regulators led to the revision of existing regulatory documents and to the development of new documents, which will in turn impact the practice and availability of SIT. Significant differences exist in the regulation of products for SIT and the SIT treatment practice between the United States and Europe [12•]. Reviewing the current status in both regions comprehensively would result in an excessive size of this article. Therefore, this article focuses on recent developments in the regulatory field and the impact on specific immunotherapy in Europe.

Impact of different documents on the practice of specific immunotherapy and the availability of allergen products

In this review, different types of documents are cited which have different impact on the practice of SIT and

the market for allergen products. First of all, laws, regulations, and ordinances published in the Official Journals of the European Community or of the Member States have to be followed by the Authorities and as a consequence are demanding for pharmaceutical companies. In contrast, the Guidelines published by the European Medicines Agency (EMA) give recommendations and suggestions but are not legally binding. However, in general such Guidelines are applied by Authorities, especially if they are not only released by the EMA but are also adopted in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH activities are aimed at achieving harmonization of such requirements between the European Community, USA and Japan. Manufacturers have to provide justification if diverging from the suggestions of such guidelines. However, there is a possibility that Guidelines are applied in a slightly different way by different National Authorities of EU Member States. In summary, demands by regulatory documents, for example on increasing quality or a higher level of clinical characterization will significantly affect the availability of allergen products, for example allergen mixtures, and therefore also on the clinical practice of SIT.

Position papers of scientific societies and other publications are rated as expert opinions by the Authorities and contribute to the current state of the art. Such documents have a direct impact on the practice of SIT, and may have an impact on the assessment of products. However, such documents are not necessarily considered in decisions made by regulatory Authorities.

Quality of allergen products

Efforts to reach a unique and standardized quality level of allergen products are still hampered by the lack of international standard extracts. Official reference preparations of allergen extracts developed in the 1980s are almost not in use and their quality status is yet unclear. But, quantum leaps towards the development of international biological reference preparations and the specification of corresponding ELISA systems have been made. Lately, groundbreaking developments in the field of using individual allergen components as biological references could be achieved within the European Union CREATE project and the follow-up project BSP090 [8[•],10^{••}]. Two of the recombinant allergens studied, rPhl p 5 and rBet v 1, were already further investigated in clinical trials. The CREATE project was followed by the joint activity called BSP090 coordinated by the European Directorate for the Quality of Medicines (EDQM) [13[•]]. The overall goal of this project is the establishment of rBet v 1 and rPhl p 5 in conjunction with corresponding validated ELISA systems as Ph. Eur. reference prepa-

arations. In a small ring trial it was found that three of the four different ELISA systems studied are suitable for quantification of Phl p 5a and Bet v 1 in extracts by using the recombinant counterparts as reference. A collaborative study involving several Official Medicines Control Laboratories (OMCLs), CREATE partners, and manufacturers is planned [14[•]].

In May 2009, the 'Guideline on Allergen Products: Production and Quality Issues' (EMA/CHMP/BWP/304831/2007) [15^{••}] came into effect and thus replaced the 'Note for Guidance on Allergen Products' (CPMP/BWP/243/96) [16] first released in 1992 and revised in 1996. Besides implementing the concept of homologous groups [17^{••}], the new guideline can be considered a landmark development in the regulatory field of setting quality standards for allergen products since it reflects crucial developments concerning the standardization as well as the characterization and control of allergen preparations (see Table 1) [5^{••},7[•],15^{••},16]. It opens the door for the introduction of new methods like mass spectroscopy for quantification of individual allergens and even potency testing.

Moreover, in 2010, a revised version of the Monograph on Allergen Products (01/2010:1063 Producta Allergenica) [18^{••}] was published in the European Pharmacopoeia (6th edition, 6th supplement). The fact that this document is legally binding for all European manufacturers makes it an important regulatory document with a tremendous influence on the quality level of currently manufactured allergen products. The revised version of this monograph clearly increases quality requirements for allergen products (see Table 2) [18^{••},19] and – for the first time – applies also to NPPs.

At the same time, further advances were made concerning the molecular characterization of allergoids. Recently, the conservation of major allergens during the modification process and the induction of a specific immune response against these individual allergens of the allergoid product have been demonstrated for the first time for allergoids of birch and house dust mite extracts [20^{••},21]. The results suggest a high degree of preservation of major and minor allergens which were found in the native extract throughout modification. However, the authors stressed that the mass spectrometric method used produces only qualitative results. Thus, it is primarily suitable for reporting the allergen composition on a batch-to-batch basis, if quantitative data are not required.

Last but not least, comprehensive studies aiming at the development of discriminatory immunoassays for hypo-allergenic recombinant as well as allergoid preparations were reported by Fiebig *et al.* [22^{••}]. Positive discriminatory ELISA systems for allergoids were developed,

Table 1 Summary of the most important differences between the 'Note for Guidance on Allergen Products' (CPMP/BWP/243/96) [15] and the 'Guideline on Allergen Products: Production and Quality Issues' (EMA/CHMP/BWP/304831/2007) [15***] regarding quality requirements for allergen products**

Issue	Note for Guidance on Allergen Products (CPMP/BWP/243/96) [16]	Guideline on Allergen Products: Production and Quality Issues (EMA/CHMP/BWP/304831/2007) [15**]
Grouping	Taxonomic families: Extrapolation of stability data and data on efficacy and safety among members of the same taxonomic families possible	Concept of homologous groups [7*]: Grouping based on structural similarity/cross-reactivity of allergens. Extrapolation of data on quality, safety and efficacy from the representative of a homologous group to other members possible to a limited extent
Allergen mixtures	No restrictions	Allergen mixtures should be prepared from individual extracts from single source materials. Source materials should not be mixed prior to extraction Potency testing should be performed for each individual active substance prior to mixing Mixing of allergens restricted
Recombinant allergens	Not addressed	Emphasis on structural integrity and consistency of folding and impurities from media or host cells Correlation between quantity of individual recombinant allergen and biological activity must be shown – ELISA methods with specific animal antibodies may be used as potency tests For hypoallergenic preparations, a discriminatory test to distinguish between molecules with high and low IgE-binding capacities
Potency assays	Measurement of total allergenic activity should be performed preferably by IgE inhibition For allergoids/adsorbed products, potency does not need to be determined, documentation of adsorption and/or modification is sufficient	Nonmodified allergen extracts: total allergenic activity should be determined by a competitive IgE-binding test Allergoids: discriminatory test or combination of immunological tests to distinguish between native and modified form required (e.g. discriminatory immunoassay or mass spectrometry) If products are defined on the basis of relevant allergens, correlation with allergenic activity must be demonstrated Relevant individual allergens may be determined by immunological methods with specific animal antibodies
Sera pools	Not addressed	Pools should be composed of sera from 10 to 15 individuals (consideration of geographically different sensitization patterns) Detailed quality requirements are included
Stability	Demonstration of potency of allergoids/adsorbed products not required ≥30% of the stated allergenic activity should be maintained at the end of shelf life	Potency of allergoids/adsorbed preparations has to be demonstrated by in-vivo or validated alternative in-vitro tests. For potency, limits defined in the monograph on allergen products apply For allergen extracts, stability studies of finished products manufactured with active substance at the end of its shelf life should be performed (cumulative stability data)
Safety and efficacy	Covered together with quality requirements, very limited guidance included	Separately covered in EMA/CHMP/EWP/18504/2006 [5**] (see Table 3)

Table 2 Comparison of the most important differences (indicated in bold) between the two last versions of the Monograph on Allergen Products of the European Pharmacopoeia

Tests	Ph. Eur. 6th edition 2008 (6.0) 01/2008 : 1063 [19]	Ph. Eur. 6th edition 2010 (6.6) 01/2010 : 1063 [18**]
Sterility	Allergen products intended for parenteral, bronchial and conjunctival administration comply with the test for sterility	Allergen products presented as parenteral preparations, eye preparations, inhalation or preparations for skin testing comply with the test for sterility
Microbial contamination	Not addressed	For nonsterile pharmaceutical preparations and substances for pharmaceutical use of nonsterile 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, unless otherwise justified and authorized If the biological potency can be determined, 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 determined by suitable methods corresponds to that of the in-house reference preparation (IHRP)	The protein profile determined by suitable methods corresponding to that of the IHRP. The presence of relevant allergen components is verified, where possible. The choice of relevant allergen components to be tested for must be justified
Antigen profile	The antigens are identified by means of suitable techniques using antigen-specific animal antibodies	Not addressed
Allergen profile	Relevant allergenic components are identified by means of suitable techniques using allergen-specific human antibodies	Relevant allergenic components are identified by means of suitable techniques using allergen-specific human or animal antibodies
Total allergenic activity	The activity is 50–200% of the stated amount as assayed by inhibition of the binding capacity of specific immunoglobulin E antibodies or a suitable equivalent in-vitro method	The activity is 50– 150% of the stated amount as assayed by inhibition of the binding capacity of specific immunoglobulin E antibodies or a suitable equivalent in-vitro method
Individual allergens	50–200% of the stated amount, determined by a suitable method	50–200% of the stated amount of each relevant allergen component , determined by a suitable method

which are suitable for quantifying the biological activity of hypoallergenic allergoid derivatives by using animal IgG antibodies. A large panel of monoclonal antibodies has provided the means to distinguish between the folded form (nBet v 1, rBet v1) and a recombinant folding variant (rBet v 1-FV) of Bet v 1. The design of these potency assays is reported to be suitable for quantifying biological activity of low IgE-binding derivatives as well as for demonstrating batch-to-batch consistency and thus addresses the demands of the ‘Guideline on Allergen Products: Production and Quality Issues’ (EMEA/CHMP/BWP/304831/2007) [15**].

Efficacy and safety

After its description in 1911 [1,2], SIT was used based for decades on expert opinions derived from retrospective evaluation of individual patient’s treatment. The first prospective clinical studies included only a small number of patients and were often uncontrolled. The number of placebo-controlled studies increased in the 1990s but the studies were often of low quality, for example regarding the inclusion and protection of clinical trial subjects, the control of the investigational medicinal product, the notification of adverse events, etc. and clinical trials were only approved by ethic committees. To overcome these problems, in 2001 Directive 2001/20/EC [4] was released to implement good clinical practice in all clinical trials and to subject the approval of clinical trials to authorization by the national competent Authorities. While formal issues were now regulated, the methods and experimental designs used in clinical trials on SIT remained very heterogeneous. SIT was regarded as an established treatment of allergic diseases caused by inhalational allergens and insect venoms on the basis of the evidence available so far [23–25] and the official recommendations for practitioners were regularly up-dated [26,27]. For medicines aiming at the reduction of allergic symptoms such as antihistamines and corticosteroids the mechanisms of action are clear. The existing guidelines for their development [28,29] focus on the evaluation of the reduction of existing allergy symptoms, for example during the relevant pollen season. In contrast, SIT is aiming at a disease modifying effect by modulating the immune system but the mechanism of action is up to now not fully understood. Therefore, the existing guidelines on products for the treatment of allergic symptoms were not applicable to clinical trials with SIT and scientific societies as well as regulators came up with recommendations on the design and outcome measurements of SIT in clinical trials. In 2007, Canonica *et al.* [30] published such recommendations as a statement of a World Allergy Organization (WAO) taskforce. In parallel the European Medicines Agency developed the ‘Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases’ (EMA,

Table 3 Important issues regarding the design of clinical studies for SIT addressed by the WAO taskforce [30] and the EMA [5]**

Issue	Addressed problems
Randomized placebo-controlled and double-blind design	Absolutely necessary due to variability in individual clinical responses, unpredictability and variability of allergenic exposure, and subjective nature of symptom assessments
Selection of study population	Specialties of polysensitized patients, co-morbidities, disease severity, main inclusion criteria
Symptom and medication scores	Methods to score symptoms and medication, necessity to define rescue medication and the influence thereof on symptoms
Combined symptom/medication score	Preferred as primary endpoint, because severity and frequency of symptoms and use of rescue medications are strictly interdependent
Secondary endpoints	Provision of a list of possible endpoints
Measurement of allergen exposure	Necessary due to variability and influence on symptoms
Statistical aspects	Main criteria are listed
Several special problems with clinical trials on SIT	Different routes of administration, studies in children, long-term and preventive effect, etc.

EMA, European Medicines Agency; SIT, specific immunotherapy; WAO, World Allergy Organization.

CHMP/EWP/18504/2006) [5**]. Most issues addressed in this guideline are the same as in the WAO taskforce statement [30] (Table 3 [5**,30]); however, in some cases, diverging advice is provided. The main differences are listed in Table 4 [5**,30]. In general, it can be deduced that the EMA guideline does not accept any arbitrarily defined scoring system or level of score improvement for concluding clinically relevant efficacy but requests a justification of the chosen values until validated scoring systems exist and the influence of a specific reduction in this score on the patient's well being has been evaluated. Moreover, the EMA guideline implemented some issues of regulatory importance such as insect venom allergy; different claims for efficacy depending on study duration (treatment of allergic symptoms; sustained clinical effect; long-term efficacy and disease modifying effect; curing allergy); additional statistical aspects (e.g. evaluation time points, interim analysis); purified allergens; cross-reacting allergens and comparability studies.

In 2009, a WAO position paper on sublingual immunotherapy was published addressing in one chapter the methodology of clinical trials in sublingual immunotherapy [31]. In addition, in 2009, Casale *et al.* [32*] published recommendations for appropriate sublingual immunotherapy clinical trials. In general, the suggestions in both publications are similar to the ones outlined in the WAO taskforce statement [30]; however some special aspects of the sublingual route are addressed, some issues like dosing regimens and phase I and II studies are added and some issues are discussed in more detail, for example symptom severity. Moreover, Casale *et al.* [32*] provide a slightly different approach to assign values to the different rescue medications based on data from studies in which the rescue medications were compared for their relative efficacy in allergic rhinitis. Unfortunately, neither the studies used nor the method how to transmit these data to the values provided are mentioned. In contrast, in the WAO position paper [31] no scoring system for rescue medication is adduced but it is pointed

out that up to now no standardized methods exist, and that there is still need for a consensus on standardized symptom and medication scores.

Specific requirements for clinical trials in children are only shortly addressed in the above-mentioned publications. Mentzer summarized the regulatory aspects of clinical trials in children in general with regard to the need of special paediatric studies, target population, clinical trial design and the risk-benefit assessment in the paediatric population [33]. According to the Regulation 1901/2006/EC on medicinal products for paediatric use [34], each application for marketing authorization has to contain a Paediatric Investigation Plan (PIP) approved by the Paediatric Committee (PDCO) of the EMA. With regard to the large number of marketing authorization applications according to the German Therapy Allergen Ordinance [35] the PDCO published a Draft Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy which was revised recently [36*]. A standard study design is provided and it is emphasized that products for SIT in children must have proven long-term efficacy. The PDCO is of the opinion that until now long-term efficacy data obtained in adults can not be extrapolated to children and defined a procedure to obtain clinical data as basis to justify an extrapolation. Further studies in children should be deferred until these data are available. As long as these data are lacking, long-term efficacy studies are demanded in children. If the extrapolation studies will show the validity of extrapolation, short-term studies in children are sufficient; however, they have to be deferred until long-term efficacy data for adults are available for the specific product.

Named Patient Products

According to the Directive 2001/83/EC as amended [4] all medicinal products manufactured by an industrial process require a marketing authorization. Since allergen

Table 4 Differences between the recommendations of the WAO taskforce [30] and the EMA [5**] regarding the design of clinical studies for SIT

Issue	WAO taskforce statement [30]	EMA guideline [5**]
Patients with asthma	Bronchial symptoms must be included in patients with symptoms from the lower airways if a claim for asthma is requested for the trial	Patients with allergic asthma may be included for obtaining safety data and for exploring effects on asthma in trials of specific immunotherapy on allergic rhinitis/rhinoconjunctivitis. However, for a claim of efficacy in asthma separate trials should be conducted and specific guidance for asthma therapy should be followed
Baseline period	The unpredictability and variability of allergenic exposure to pollen allergens and the fluctuations in the levels of indoor allergens make the use of a baseline period undesirable, or at least not mandatory, as it is time-consuming and expensive	For assessing the disease severity for inclusion, retrospective scoring suffers from memory bias. A prospective baseline period has the advantage of a controlled collection of symptoms with knowledge of the allergen exposure and therefore is recommended whenever possible
Medication score	Each dose of: nasal, ocular, oral antihistamines and bronchodilator: 1 point, inhaled or nasal corticosteroids: 2 points, Daily use of an oral corticosteroid: 3 points	No score is provided. The applicant has to provide a scoring system and has to justify this on the basis to the approximated relief of symptoms, as well as the magnitude and duration of effect and to the kind of symptoms affected by each drug
Combined symptom/medication score	Each score accounts approximately for half of the clinical burden of the disease. It is recommended that a combined symptom + medication score be utilized as the primary outcome measure	So far, no validated system for balancing symptom and medication score exists. Different approaches to combine symptom score and intake of rescue medication are possible. The method to combine both scores has to be prespecified and justified
Clinical relevance	The minimal clinically relevant efficacy should be at least 20% higher than placebo	Regardless of the choice of the primary efficacy parameter, the applicant should provide a definition of a clinically meaningful effect in the primary efficacy endpoint and the basis for choosing this value

EMA, European Medicines Agency; SIT, specific immunotherapy; WAO, World Allergy Organization.

products are defined as medicinal products [37] and the production of nearly all allergen products involves an industrial step, a marketing authorization is generally required. However, the use of Named Patient Products (NPPs) manufactured on the basis of an individual prescription and marketed without a marketing authorization is still common practice in many European countries although they are mostly industrially prepared [3]. In line with the exemptions possible according to Art. 5 of the Directive 2001/83/EC [4], the German Medicinal Products Act (Arzneimittelgesetz (AMG)) [38] introduced a national exemption from the requirement for marketing authorization in 2005 for therapy allergens which are manufactured for a patient on the basis of an individual prescription. This exemption was introduced to enable manufacturers to produce therapy allergens for patients with rare allergies or sensitized to rare combinations of allergens because for such products clinical trials are very difficult to perform. To prevent the marketing of unauthorized products for the treatment of highly prevalent allergies Germany has recently enacted the Therapy Allergen Ordinance [35,39*]. This ordinance demands a marketing authorization for all NPPs derived from grass pollen, early flowering trees pollen, house dust mites, and bee and wasp venom, regardless if produced as single allergen preparation or included in mixtures. After a short transition period the manufacturers had to notify for products which they wanted to apply for a marketing authorization and products to remain on the market for not longer than 3 years to finalize ongoing treatments. All bulk preparations of these products were subjected to official batch testing at the latest from 1 October 2009. Applications for marketing authorization have to be submitted until 1 December 2010, but only a clinical development plan has to be enclosed and long transition periods are allowed to perform the necessary clinical trials and generate appropriate data on efficacy and safety.

France used another approach to implement the exemptions in Art. 5. A new decree [40] was released to implement registration of NPPs. The applicants had to provide the National Authority with a list of preparations which they would keep on the market. A working group defined a list of ‘clinically relevant allergens’ for which sufficient evidence for efficacy in SIT has been published, and only these allergens are allowed to stay on the market provided that the pharmaceutical quality is adequate (C. Pini, Presentation at the EAACI Congress 2010). In contrast to other regulatory approaches in the field of biologicals, this approach is not product-specific.

Other countries such as Spain or Italy have also initiated activities to achieve a better control of NPPs. The Italian Authority has recently requested a quality documentation of all products which are currently on the market

in Italy (C. Pini, Presentation at the EAACI Congress, 2010).

Recombinant allergens

During the last years not only native or modified allergen extracts were used for the development of allergen products but also allergens produced by recombinant DNA technology. Research has been performed on single allergen molecules, mixtures of allergen molecules, hypoallergenic variants, and fusion constructs containing several allergens or allergens fused to peptides with adjuvant or immune modulating properties. Moreover, synthetic peptides derived from allergen sequences have been used. Most of these approaches have been evaluated in clinical trials [9^{••},41]. With some recombinant allergens phase III studies were conducted and the first applications for marketing authorization are expected in the near future. As recombinant allergens are biomedicines produced by biotechnological processes, a marketing authorization for EU Member States is only possible via the centralized procedure at the EMA [42]. Thus, a detailed regulatory framework exists consisting of several guidelines released by committees of the EMA and often adopted by ICH [7[•],43–49]. These guidelines cover quality and nonclinical issues in general, but do not address specifics of recombinant allergens. Therefore, allergen-specific guidance addressing recombinant allergens was included in the recent EMA guidelines on quality and clinical development of allergen products [5^{••},15^{••}]. For quality recommendations regarding structural integrity, impurities and determination of potency especially of hypoallergenic derivatives of allergens were implemented (see Table 1). Compared with allergen extracts the active substance of recombinant allergen products are much better defined, characterized, and standardized. Moreover, with recombinant allergens it is possible to include each allergen molecule in its optimal concentration with very high batch-to-batch consistency. This is not possible in allergen extracts, due to the natural different expression of the individual allergen molecules in allergen source materials (e.g. pollens).

In general, the clinical evaluation will be very similar to allergen extracts [50]. However, by using allergen extracts for SIT the patient is treated with a broad variety of allergens, whereas the spectrum of allergens is reduced by using single allergen molecules or mixtures containing a limited number of components. Therefore in the clinical guideline [5^{••}] the importance of measuring individual sensitization patterns is emphasized to justify the included allergens in the product and the selected study population for this product. By using allergen extracts the possibility is enhanced that the patient is treated with all allergens relevant for the individual allergy; however, the patient is also treated with a variety

of allergens, nonallergenic proteins and other components not relevant for the individual allergy. By using a mixture of single allergens this disadvantage can be overcome and a product can be developed reflecting the sensitization pattern of the individual patient [51[•]]. However, such treatment with patient-tailored immunotherapy is very difficult to achieve within the existing regulatory framework, as current documents demand the authorization of finished products and do not offer an approach to authorize individualized recombinant allergen products. Thus, today it is only possible to market products containing a predefined number of allergen molecules relevant to the majority of patients. Growing experience from determining the individual sensitization patterns and treatment of allergies with recombinant allergens may enhance the request of patient-tailored immunotherapy in the near future.

Conclusion

Recently implemented increased demands for quality will lead to increased characterization and standardization of allergen products. However, as completely new requirements such as potency tests for allergoids or hypoallergenic recombinant allergens are introduced, the regulatory changes represent a challenge to manufacturers who will have to develop novel assays to meet the needs.

A similar challenge for manufacturers results from the recent documents offering relevant guidance on the conduct and outcome measurements of SIT clinical trials. As a result harmonization in the assessment of allergen products will be increased, and a reliable measurement of efficacy and a better comparability of the efficacy and safety of the individual products throughout Europe will be achieved. On the one hand, this will result in more certainty for the manufacturers regarding the acceptance of clinical trial results by Authorities but on the other hand complexity and costs of clinical trials will clearly increase. Especially the demands for clinical trials in children are difficult to meet and will in addition be very time-consuming. The demands raised by the Standard PIP on allergen products [36[•]] are still a matter of debate.

A reduced use of NPPs without quality control will most likely result from the recently initiated regulatory activities in Europe. Moreover, at least in Germany use of NPPs lacking product specific clinical data will be diminished for the most prevalent respiratory and insect venom allergies. Some European countries may follow this approach.

An appropriate regulatory framework for quality testing and clinical evaluation of recombinant allergens has been established and gives relevant advice to manufacturers. Recombinant allergen technology provides the possibility to diagnose the sensitization pattern of an individual

patient on the basis of the individual allergens and raises the desire of patient-tailored products for SIT. A regulatory approach to achieve the possibility to develop and use such products with a patient-tailored mixture of recombinant allergens needs to be established.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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