

REVIEW ARTICLE

Regulatory environment for allergen-specific immunotherapy

S. Kaul, S. May, D. Lüttkopf & S. Vieths

Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Division of Allergology, Langen, Germany

To cite this article: Kaul S, May S, Lüttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy* 2011; DOI: 10.1111/j.1398-9995.2011.02552.x

Keywords

efficacy of allergen products; European Medicines Agency; immunotherapy; Named Patient Products; quality of allergen products; regulation of allergen products; specific immunotherapy.

Correspondence

Stefan Vieths, PhD, Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Division of Allergology, Paul-Ehrlich-Str. 51-59, D-63225 Langen, Germany.

Tel.: +49 6103 77 2000

Fax: +49 6103 77 1240

E-mail: viest@pei.de

Accepted for publication 9 January 2011

DOI:10.1111/j.1398-9995.2011.02552.x

Edited by: Thomas Bieber

Abstract

Products for specific immunotherapy (SIT) are medicinal products according to the European Regulations. To obtain a marketing authorization (MA) within the European Community, the quality, safety and efficacy have to be proven. During the development phase of a medicinal product, applicants have the opportunity to apply for scientific advice by national competent authorities or the European Medicines Agency (EMA) to compile a suitable development plan for the examination of quality and performance of nonclinical and clinical trials. Moreover, a paediatric investigation plan has to be submitted to the Paediatric Committee of the EMA and has to be approved before submission of an application for MA. Several regulatory procedures exist for obtaining a MA in the European Community. The national procedure leads only to marketability in one country whereas the Mutual Recognition, the Decentralized and Centralized Procedures (CP) are intended for MA in several or all member states of the European Union. The CP is mandatory for certain medicinal products, for example for drug substances derived by biotechnological processes such as recombinant allergens. Named Patient Products for SIT are a specialty because they are manufactured on the basis of an individual prescription and marketed without a MA.

After its introduction 100 years ago (1, 2), allergen-specific immunotherapy (SIT) has been used for decades mainly based on expert opinions rather than on scientific evidence, and the applied products were not standardized. However, knowledge was increasing on the basis of clinical studies even if these included only a limited number of patients and were often uncontrolled. In the course of time, the number of

placebo-controlled studies increased; however, a wide variety of study designs hampered the comparability of results obtained in such clinical trials. Until the late 1980s, some products for SIT obtained national marketing authorizations (MAs) but the majority of products were used as Named Patient Products (NPPs) (3).

In 2001, the European Directive 2001/83/EC (4) was released, which defines the community code of medicinal products for human medicines within the European Union (EU). Moreover, the Directive 2001/20/EC (5) introduced the regulations for Good Clinical Practice (GCP) as mandatory for all clinical trials. These regulations increased the evidence-based knowledge on SIT. Finally in the last few years, guidance documents of the European Medicines Agency (EMA) (6) and scientific publications (7–9) launched a basic study design for clinical trials with allergen products for SIT, enhancing the quality and comparability of such trials.

For quality issues, guidance on allergen extract quality was introduced in the mid-1990s and was mainly unchanged until 2008. During this time, molecular and clinical allergology developed quickly, for example the use of modern proteomics and physicochemical techniques in the characterization

Abbreviations

CHMP, Committee for Medicinal Products for Human Use; CMD(h), Co-ordination Group for Mutual Recognition and Decentralized Procedures (Human); CMS, Concerned Member State; CP, Centralized Procedure; CT, clinical trials; DCP, Decentralized Procedure; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; MA, marketing authorization; MAH, marketing authorization holder; MRP, Mutual Recognition Procedure; MS, Member State of the European Union; NPP, named patient product; Ph. Eur., European Pharmacopoeia; RMS, Reference Member State; SAWP, Scientific Advice Working Party; SCIT, subcutaneous immunotherapy; SIT, specific immunotherapy; SLIT, sublingual immunotherapy.

of allergen products (10, 11) or the use of recombinant allergens in the standardization of allergen products (12) and as medicinal products in clinical trials (13). These developments led to the revision of existing and to the development of new documents (14, 15). In addition, a large catalogue of guidance documents for biotechnological products in general has been released by the EMA (16–22). The present article compiles the state of the art in the regulatory field concerning allergen products for SIT.

Guidance documents applicable to products for specific immunotherapy

Different types of documents are relevant for the development and MA of products for SIT. The first type of documents consists of laws, regulations and ordinances published in the Official Journals of the European Community or of the EU Member States (MS) (Table 1A). They have to be followed by the pharmaceutical companies and are the basis for every regulatory decision of the authorities. The general 'key' document is the Directive 2001/83/EC for medicinal products for human use that has been amended several times (4). European Directives are not per se legally binding in the MS but have to be implemented in the national legislation of each MS within a certain period of time. By contrast, European Regulations, for example the Regulation (EC) No 1901/2006 on medicinal products for paediatric use (26), are directly legally valid in all MS. Furthermore, the pharmaceutical rules laid down in the European Pharmacopoeia (Ph. Eur.) are obligatory in all MS. The Ph. Eur. contains general chapters on e.g. pharmaceutical methods and reagents, which apply to several medicinal products but also monographs on special medicinal products such as allergen products (14).

The second type of documents comprises 'Guidelines', 'Notes for Guidance' and 'Points to Consider' published by the EMA giving more detailed recommendations and suggestions but they are not legally binding (Table 1B). Some of these documents are not only approved by EMA but are also adopted by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use activities are aimed at achieving harmonization of such requirements between the European Community, USA and Japan. Thus, these documents reflect the scientific state of the art and are in general applied by authorities. Therefore, applicants should follow the recommendations of such guidelines and need to provide thorough justification if they deviate from requirements laid down in such documents.

Lastly, position papers of scientific societies and other publications (Table 1C) reflect or contribute to the current scientific state of the art but are not necessarily considered in decisions of regulatory authorities.

Scientific advice

During the development phase of a medicinal product, applicants may apply for scientific advice by national competent

authorities or the EMA. Pharmaceutical companies are invited to submit a request for scientific advice early in the development of a medicinal product and additionally during further development if required. Questions concerning product quality and/or performance of nonclinical and clinical trials may be addressed. On the national level, the scientific advice procedure may differ between MS; however, in general, the applicant should provide a briefing document and a list of questions. The competent authority will decide whether to reply by a written response or during a scientific advice discussion meeting.

Scientific advice by the EMA follows a regulated procedure. The applicant submits a request for scientific advice including briefing documents and a list of questions. The Scientific Advice Working Party (SAWP) selects representatives of two MS as co-ordinators. In a presubmission meeting with representatives of the EMA and sometimes including the chosen co-ordinators, formal issues of the application will be reviewed as well as clarity of questions and quality of the briefing document. After submission of final versions of the documents including a complete list of questions and the position of the applicant, the two co-ordinators independently provide first written reports that will be discussed by the SAWP. In case of significantly deviating opinions of the two co-ordinators, or if the opinion of the SAWP differs widely from the applicants' position, a discussion meeting with the applicant will be scheduled. At the end of the procedure, the SAWP provides a joint report to the Committee for Medicinal Products for Human Use (CHMP) that will approve and release the final opinion.

Clinical trials

To obtain data on efficacy and safety of a product, clinical trials conducted according to GCP (5, 41) have to be performed. The EMA hosts the 'EudraClinicalTrials (EudraCT)' database and provides a unique identifier study number (EudraCT-number) to each study. All relevant data of a study are recorded in this database and are accessible for all European competent authorities. However, the approval of a clinical trial is not within the responsibility of the EMA but of the national competent authorities. Thus, a multinational clinical trial requires national approval by the competent authority in each country involved in the trial. If one country refuses the approval, the clinical trial can still be conducted in all other countries that granted approval. The study design of clinical trials for SIT should comply with the current state of the art. In this regard, especially the EMA 'Guideline on the Clinical Development of Products for SIT for the Treatment of Allergic Diseases' (6) is of high relevance. Guidance provided in this document covers the whole clinical development plan including early studies (Table 2), dose-finding studies (Table 3) and confirmatory studies (Table 4). Moreover, guidance is provided for insect venom and food allergy, purified allergens, cross-reacting allergens, comparability studies and safety evaluation. Some publications also deal with the design of clinical studies with products for SIT (7–9). In general, the same issues are covered and similar advice

Table 1 Selection of European documents relevant for the development and marketing authorization of products for SIT

(A) Legally binding documents

- Directive 2001/83/EC of the European Parliament and of the Council on the community code relating to medicinal products for human use. (4)
- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use. (5)
- Commission Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. (23)
- Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. (24)
- Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a EMA. (25)
- Regulation 1901/2006/EC on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (26)
- European Pharmacopoeia, in particular: Monograph on Allergen Products (14)

Guidance on	Documents
(B) Not legally binding but strongly recommended to follow	
Quality	• EMA Guideline on Allergen Products: Production and Quality Issues (CHMP/BWP/304831/2007) (15) • ICH Topic Q 5 B. Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA Derived Protein Products (CPMP/ICH/139/95) (16) • ICH Topic Q 5 C. Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. 1996;CPMP/ICH/138/95 (17) • ICH Topic Q 5 D. Note for Guidance on quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products (CPMP/ICH/294/95) (18) • ICH Topic Q 5 E. Note for Guidance on Quality of Biotechnological/Biological Products subject to Changes in Their Manufacturing Process (CPMP/ICH/5721/03) (19) • ICH Topic Q 6 B. Note for Guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96) (20) • ICH Topic Q 7. Note for Guidance on Good Manufacturing Practice for active pharmaceutical Ingredients (CPMP/ICH/4106/00) (27) • ICH Topic S 6 C. Note for Guidance on quality of biotechnological products: stability testing of biotechnological/biological products (CPMP/ICH/138/95) (21) • EMA Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: quality issues. (CPMP/BWP/ 3207/00/Rev1) (22)
Nonclinical development	• ICH Topic M 3 (R2). Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95) (28) • ICH Topic S2 (R1). Note for Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. (EMA/CHMP/ICH/126642/2008) (Draft) (29) • ICH Topic S2A. Note for Guidance on Genotoxicity: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals. (CPMP/ICH/141/95) (30) • ICH Topic 2B. Note for Guidance on Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (CPMP/ICH/174/95) (31) • ICH Topic S4. Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing (CPMP/ICH/300/95) (32) • ICH Topic S5 (R2). Note for Guidance on the Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (CPMP/ICH/386/95) (33) • ICH Topic S6. Note for Guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95) (34) • EMA Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95) (35) • Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity' (EMA/CHMP/SWP/81714/2010) (36) • EMA Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr) (37) • EMA Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications (EMA/CHMP/SWP/169215/2005) (38) • EMA Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00) (39)

Table 1 (Continued)

Guidance on	Documents
Clinical development	• ICH Topic E 1. Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95) (40) • ICH Topic E 6 (R1). Note for Guidance on GCP (CPMP/ICH/135/95) (41) • ICH Topic E 9. Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96) (42) • ICH Topic E 11/Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99) (43) • EMA Guideline on the Clinical Development of Products for SIT for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006) (6) • Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99) (44) • EMA Standard Paediatric Investigation Plan (EMA/PDCO/737605/2009) (Revision 2) (45) • EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMA/CHMP/203927/2005) (46)
(C) Contributing to scientific state of the art	
• WHO Position paper. Allergen immunotherapy: Therapeutic vaccines for allergic diseases (47) • EAACI Immunotherapy position paper (48) • WAO taskforce statement. Recommendations for standardization of clinical trials with Allergen SIT for respiratory allergy (7) • WAO Position Paper. Sub-Lingual Immunotherapy (8)	

CHMP, Committee for Medicinal Products for Human Use; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; ICH, International Conference on Harmonization; SIT, specific immunotherapy.

is given in the guideline and the scientific publications. However, for some issues such as clinical trials for efficacy in patients with allergic asthma, necessity of a baseline period, and medication and symptom scoring recommendations are diverging. However, authorities will mainly adhere to the regulatory guideline. In general, the authorities will not accept any arbitrarily defined scoring system but will request justification of the chosen scores and values, or validation, if possible. The publications about clinical trial methodology with products for sublingual specific immunotherapy (SLIT) provide additional recommendations for special aspects of the sublingual route e.g. regarding application duration and dosing regimens (8, 9).

Table 2 European Medicines Agency (6) 'Guideline on the Clinical Development of Products for specific immunotherapy (SIT) for the Treatment of Allergic Diseases' Guidance for early studies

- Classical phase I studies in healthy individuals are not appropriate for allergen products
- Tolerability studies should be performed in individuals allergic to the allergen in question
- Tolerability studies should provide data on safety and tolerability with regard to the maximum-tolerated dose and a suitable dose escalation scheme
- If new substances are included in the drug product (e.g. new adjuvants), clinical trials in healthy subjects may be necessary
- Pharmacokinetic studies are not possible for products of SIT
- Formal pharmacodynamics studies are not possible for allergen products
- To show the effect of SIT on the immune system laboratory parameters such as changes in allergen-specific IgG levels, T-cell reactivity and/or cytokine production should be measured in phase II or III trials

The draft Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (49) aims at ensuring harmonized quality requirements for clinical trials and hence may further facilitate subsequent MA application strategies of pharmaceutical companies in the EU.

Paediatric investigation plan

According to the Regulation 1901/2006/EC on medicinal products for paediatric use (26), each application for MA has to contain a Paediatric Investigation Plan (PIP) approved by the Paediatric Committee (PDCO) of the EMA. The PDCO is mainly an independent scientific committee that was established according to Art. 3 of the Regulation 1901/2006/EC (26). This Article defines that the EMA shall fulfil the secretariat functions for the PDCO and that an appropriate co-ordination between the PDCO and the Committee for Medicinal Products for Human Use, the Committee for

Table 3 European Medicines Agency (6) 'Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases' Guidance for dose-finding studies

- Should be performed after establishing a tolerated dose range
- Dose-response relationship for clinical efficacy should be established
- Short-term treatment with different doses in several study arms
- Possible endpoints: Provocation tests and/or clinical endpoint (symptom/medication score)
- Laboratory parameters (changes in allergen-specific IgG levels, T-cell reactivity and/or cytokine production) are not accepted as endpoints, provide only supportive information

Table 4 European Medicines Agency (6) 'Guideline on the Clinical Development of Products for SIT for the Treatment of Allergic Diseases' Guidance for confirmatory studies of SIT on allergic rhinitis/rhinoconjunctivitis

Guidance on	Rational
Randomized placebo-controlled and double-blind design	• Absolute necessary owing 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 may influence the study outcome, main inclusion criteria are provided • Patients with allergic asthma may be included for obtaining safety data. However, for efficacy assessment on asthma, separate trials should be conducted and specific guidance for asthma therapy should be followed
Baseline period	• 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
Symptom and medication scores	• Methods to score symptoms and medication, necessity to define rescue medication and the influence thereof on symptoms
Primary endpoints	• Combined symptom/medication score preferred as primary endpoint, because severity and frequency of symptoms and use of rescue medications are strictly interdependent, and symptom score and medication score as co-primary endpoints are also possible
Clinical relevance	• 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
Secondary endpoints	• Provision of a list of possible secondary endpoints
Measurement of allergen exposure	• Necessary because of 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

SIT, specific immunotherapy.

Orphan Medicinal Products, their working parties and other scientific advisory groups should be ensured. Since in Germany in 2008 a new ordinance for preparations for SIT (50) was released, which led to a large number of MA applications by 1 December 2010 (please refer to section 'Named Patient Products and new regulatory approaches'), the PDCO published a 'Standard PIP for Allergen Products for SIT' that was revised recently (45). The PDCO is convinced that products for SIT should only be given a paediatric indication if a disease-modifying effect has been demonstrated by sustained efficacy after 3 years of treatment followed by 2 years without treatment. Moreover, the PDCO is of the opinion that until now a proven disease-modifying effect in adults cannot be extrapolated to children. Therefore, a procedure was defined to obtain clinical data as a basis to justify such an extrapolation and to reduce the number of long-term efficacy clinical trials in children. Each applicant has to propose one reference allergen product to be evaluated for disease-modifying effect in adults and in children. If these studies in children and adults show comparable results, it will be assumed that long-term efficacy can be extrapolated from adults to children and subsequently short-term trials in children will be sufficient for other allergen products with demonstrated long-term efficacy in adults. Until such evidence is available, long-term studies are to be proposed in the PIP for

all allergen products but should be deferred until the data of the reference product are available to avoid unnecessary clinical trials in children. Moreover the Standard PIP provides a standard study design containing the key binding elements that must be fulfilled for acceptance by the PDCO.

National marketing authorization procedure

The national MA procedure depends on the national legal framework of each MS. For example, in Germany especially the German Medicinal Products Act (Arzneimittelgesetz) (51) is applicable. A national MA procedure is only possible if the medicinal product does not have a MA in any MS. The resulting national MA is only valid in the respective MS. However, a national MA can be extended to other EU countries via the Mutual Recognition Procedure (MRP).

Mutual Recognition Procedure

The MRP is the procedure of choice if a MA already exists in one or more MS of the European Community to achieve expansion to additional EU countries. The applicant asks the competent authority of one MS in which a national MA exists to act as Reference Member State (RMS). The RMS co-ordinates the procedure and sends its assessment report of

the product to all MS in which approval is planned, the so-called Concerned Member States (CMS). If all CMS agree on the assessment report, the procedure will be finalized within 90 days. The CMS have the possibility to comment on the RMS's assessment report and to ask for supplementary data as well as to refuse the approval of the MA application in case of concerns that the product may harm the patients ('potential serious risk to public health') (52). If one or more CMS have such concerns, the RMS schedules a 'break-out-session' in which the applicant has the chance to comment on the objections. If consensus is reached during the 'break-out-session', the procedure can be finalized during the designated 90 days period. If potential serious risks to public health remain a referral to the Co-ordination Group for Mutual Recognition and Decentralized Procedures (Human) [CMD(h)], follows which is another option to reach agreement within 60 days. The discussion often results in several changes to the Summary of Product Characteristics (SmPC). If after the CMD(h) referral, still one or more CMS are of the opinion that it is not possible to grant a MA, the final decision on the authorization of the product will be made by CHMP where the arbitration procedure takes place. If a MA is refused by the CHMP, the medicinal product will also lose its already-existing national MA(s), e.g. in the RMS. In case of a successful MRP, the medicinal product will obtain a national MA in each CMS.

Decentralized Procedure (DCP)

If the medicinal product has no MA in any European MS but is intended to be marketed in more than one MS, the DCP is applicable. The procedure is very similar to the MRP but the dossier is assessed by all MS in parallel and the RMS is freely selectable by the applicant. The competent authority of the RMS prepares the assessment report and provides it to all CMS. The CMS are invited to comment on the assessment report. If no consensus on the assessment report is reached, the referral/arbitration procedures are the same as in the MRP. In case of a positive outcome, the medicinal product will obtain national MAs in each involved MS.

Repeat use

If after a successful MRP or DCP a pharmaceutical company wants to expand the authorization to further MS, a second MRP, the so-called repeat use procedure, is utilized. The marketing authorization holder (MAH) chooses one MS with an existing MA as RMS and the following procedure is similar to the MRP.

Centralized Procedure (CP)

In contrast to the aforementioned procedures, the MA granted in the CP is not a collection of national MAs but is granted by the European Commission and is valid in the entire Community. If a medicinal product fulfils the requirements of the Regulation (EC) No 726/2004 (25), a CP is mandatory. These requirements are: developed by biotechnological processes,

containing a new active substance, being innovative or orphan, or intended as drug for the indications of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases, immune dysfunctions and viral diseases. Other medicinal products may be marketed by the CP if the applicant is able to justify a significant therapeutic, scientific or technical innovation. Thus, products for SIT consisting of recombinant allergens have to be authorized via the CP due to the biotechnological manufacturing, whereas therapeutic and diagnostic products consisting of allergen extracts of natural biological materials will be rated as long-established active substances and therefore the national, MRP or DCP applies to such products.

For the CP, the application dossier is submitted to the EMA. The CHMP chooses two MS to act as rapporteur and co-rapporteur. They are responsible for independently providing assessment reports to the CHMP. These assessment reports are the basis of a discussion within the CHMP involving representatives of all MS. During the procedure, there is a possibility for the applicant to eliminate deficiencies notified in a list of questions and to clarify further outstanding issues. The CHMP has to provide its opinion within 210 days to the Commission which will decide about granting the MA.

An overview of all procedures is given in Fig. 1.

Named Patient Products and new regulatory approaches

Allergen products are classified as medicinal products (53) and even NPPs which are manufactured on the basis of an individual prescription are normally manufactured by procedures involving industrial processes. Since 2004 (54), Art. 2 of Directive 2001/83/EC (4) defines that all medicinal products manufactured by procedures involving an industrial process require a MA. As a consequence, in principle allergen products require a MA. However, according to Art. 5 of the Directive 2001/83/EC (4), exemptions are possible. Thus, the marketing of NPPs without a MA is still common practice in many European countries (3).

For example, in 2005 the German Medicinal Products Act (Arzneimittelgesetz) (51) introduced a national exception from the requirement for MA for therapy allergens manufactured for an individual patient on the basis of an individual prescription. If this exemption had not been included, almost all therapeutic NPPs would have been subjected to the requirement of obtaining a MA as a result of the change in the scope of the Directive 2001/83/EC (Art. 2) and subsequently the national legislation, from then including products where an industrial process is involved. The purpose of this activity was to provide SIT also to patients with rare allergies or sensitized to rare combinations of allergens. For this kind of products, it is very difficult or even impossible to perform clinical trials and it is not profitable to obtain a MA. However, this exception applies to NPPs derived from all allergen sources.

Therefore, to ensure that products for the treatment of highly prevalent allergies have a MA, Germany recently enacted the Therapy Allergens Ordinance (TAO) (50, 55) in force since 14 November 2008. Up to now, grass species of the *Poaceae* family (except *Poa mays*), early flowering trees (birch,

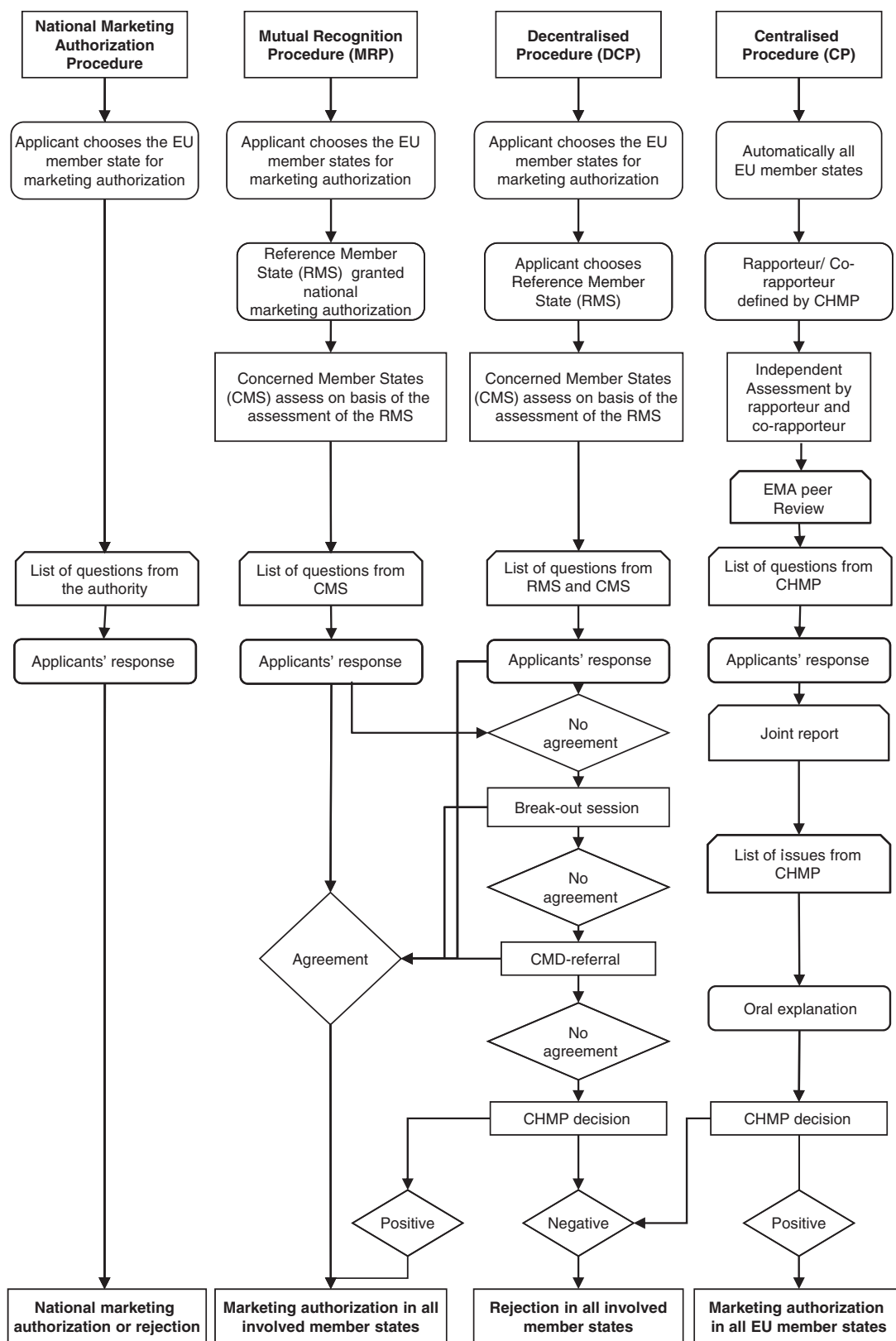


Figure 1 Flowchart for regulatory procedures.

alder and hazel), house dust mites (*Dermatophagoides* sp.), bee and wasp venom are defined as allergen sources for highly prevalent allergies. This list may be amended in the future if further allergens (e.g. ragweed) will reach a higher prevalence than today. All preparations including one of the defined allergens as single allergen or in a mixture are subject to the TAO. Until May 2009, all manufacturers had to notify products for which they wanted to apply for a MA. Some of these preparations were withdrawn in the meantime, but for the majority, an application for MA was submitted until 1 December 2010. As it was expected that up to December 2010 clinical data would be sparse for these products, long optional transition periods were included to allow performing the necessary clinical trials to generate appropriate data on efficacy and safety.

A second group of preparations was also notified in May 2009, which should remain on the market for a maximum of 3 years (i.e. until 14 November 2011) to finalize ongoing treatments. Products of both groups are subjected to official batch release of the bulk material since October 2009.

Other European Countries like Italy, Spain, Portugal or France are also in the act of releasing regulations for NPPs. The Italian Authority has recently requested a quality documentation of all products that are currently on the market and plan for the future to demand clinical data (C. Pini, Presentation at the EAACI [European Academy of Allergy and Clinical Immunology] Congress 2010). The French authority uses a different approach. The exemptions of Art. 5 of the Directive 2001/83/EC (4) were implemented by a special decree (56). Clinically relevant allergen sources were defined by a working group by means of published evidence for efficacy in SIT. Only products containing extracts of these allergen sources are permitted for marketing. These preparations have to demonstrate an adequate pharmaceutical quality. In contrast to other regulatory approaches in the field of biologicals, this approach is not product specific.

It is expected that all these activities will have a relevant impact on the market for allergen products within the EU.

Assessment of marketing authorization application – quality part

For SIT with licensed allergen preparations, two therapy systems exist: the subcutaneous (SCIT) and the sublingual (SLIT) application. For SCIT, aqueous suspensions with the allergen extract fixed to an adsorbent and preparations of two components i.e. a freeze-dried component that has to be dissolved in an aqueous solution are used. SLIT is carried out with drops, tablets or 'oral lyophilisates'.

Allergens may also be transformed in so-called allergoids by chemical modification. Allergoids are characterized by a reduced allergenicity while the immunogenicity is maintained.

Besides the preparations containing native or modified allergen extracts, allergens produced by recombinant DNA technology are a third option coming up for the treatment of allergies. In the recent EMA Guideline on allergen products: Production and quality issues (15), quality recommendations regarding structural integrity, impurities and determination of potency especially of hypoallergenic derivatives of aller-

gens were implemented. In addition, the general EMA guidance documents for biotechnological products (16–22) have to be followed.

The quality of an allergen preparation as well as its use for a special type of application is essentially determined by two factors. One basic prerequisite is the batch-to-batch consistency of the product. The second main point is the stability of the finished product and its preliminary stages. The stability of the preparation limits the usability of the finished preparation for therapy before opening the container as well as in case of multi-dose containers, its shelf life after opening the container.

In general, in the manufacturing process of allergen preparations for therapy, a distinct production stage is defined as drug substance. The drug substance preferably is a stable preparation at the latest step before mixing or formulation and in many cases it is lyophilized. The drug product is manufactured from the drug substance involving e.g. formulation steps, standardization to the nominal strength and/or adsorption to aluminium hydroxide. If applicable, a number of drug substances from different allergen sources are mixed to be processed into one drug product. The shelf life of the drug product is influenced by the stability of its components. The component with the shortest shelf life determines the drug product's shelf life.

The demand for batch-to-batch consistency and stability of products requires manufacturing procedures and test methods suitable for the purpose. Their selection is within the responsibility of the manufacturer. The Ph. Eur. is a collection of recognized pharmaceutical practice e.g. regarding the quality, testing, storage, dispensing and designation of medicinal products and the substances used in their manufacture. Processes used for the manufacture and methods used for the examination of a medicinal product have to comply with the requirements of the Ph. Eur. Only if there are no respective regulations, national pharmacopoeias of other MS may be used. Methods not found in a pharmacopoeia or methods of a pharmacopoeia that are modified by the manufacturer have to be validated. Generally, the manufacturer has to ensure that the method is suitable for the intended purpose. The Ph. Eur. monograph 'Allergen Products' (14) contains the acceptance criteria and methods allergen preparations for diagnosis and therapy have to meet. Furthermore, additional requirements may be applicable, for instance Ph. Eur. monographs on dosage forms like parenteral or oromucosal preparations.

The panel of methods to characterize allergen extracts was broadened first in May 2009, when the 'Guideline on Allergen Products: Production and Quality Issues' (15) came into effect, replacing the 'Note for Guidance on Allergen Products' (57). Increased standards were set for the quality of allergen products as reflected by the development in standardization, characterization, and control of allergen preparations. For the first time, the quantification of individual allergens was included and methods therefore such as ELISA, mass spectroscopy and potency testing were inserted in the catalogue of characterization methods for allergen extracts.

Significant progress was achieved in the molecular characterization of allergoid preparations and in projects aiming at the development of immunoassays discriminating between

native and modified allergen preparations (e.g. ELISA systems suitable for quantifying the biological activity by using animal IgG antibodies). On the basis of these developments, quality demands for chemically modified allergen extracts were increased (15).

Moreover quality requirements were generally increased in 2010, when the revised version of the Ph. Eur. monograph 'Allergen Products' was published (14) as

- 1 the presence of relevant allergen components in the protein profile must be verified where possible, and the choice of relevant components to be tested for must be justified,
- 2 the protein content must be within 80–120% of the stated content, unless otherwise justified and authorized,
- 3 if the biological potency can be determined, the test for protein content has also to be performed as a batch-to-batch consistency test. The protein content has then to be within 50–150% of the stated content,
- 4 the permitted activity range is narrowed down to 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,
- 5 individual allergens must be 50–200% of the stated amount of each relevant allergen component, determined by a suitable method, and
- 6 the monograph applies for the first time also to NPPs.

Assessment of marketing authorization application – nonclinical part

A MA will only be granted if the risk/benefit ratio of the respective product is judged positive. Data for this evaluation originate from nonclinical and clinical studies. Nonclinical studies mainly provide data on safety but can also contribute to pharmacological data. In general, the nonclinical development plan should follow the recommendations of the ICH Topic M3 Guideline (28). However, as environmental exposure to constituents of native allergen extracts (e.g. pollen proteins) is unavoidable, an abridged toxicological programme may suffice if thoroughly justified by the applicant. It is assumed that at least the absence of generic toxicity and the local tolerability should be shown for each product e.g. by performing a repeated dose toxicity study using the intended application route. Moreover, in such a study, the effect on reproductive organs can be investigated. If the drug substance differs from the natural form [e.g. chemically modified allergens, (allergoids)] more extensive toxicological studies are necessary. For example, in such cases, it has to be excluded that any genotoxic potential has been elicited by the manufacturing process. For allergens produced by biotechnological processes, the general EMA guideline ICH Topic S6 (34) is applicable.

Assessment of marketing authorization application – clinical part

The independent evaluation of clinical data includes the main question whether or not the clinical development programme is in accordance with current state of the art (see section 'Clinical trials'). Moreover, several general requirements are

laid down in EMA guidelines e.g. the need of normally two pivotal studies for proving efficacy (44) and a minimal number of treated patients for a sufficient safety basis (40).

A critical issue is the proof of efficacy. Since up to now the mechanism of SIT is not fully understood and at present none of the immuno-modulatory effects of SIT (e.g. changes in IgG- and/or IgE serum levels, T-cell reactivity and cytokines) has been shown to be predictive for the clinical outcome, such laboratory parameters cannot be used as primary endpoints. Nevertheless, some laboratory parameters should be measured to show the pharmacodynamic effect of the product. Provocation tests such as nasal, bronchial or conjunctival provocation as well as provocation in an allergen challenge chamber are currently not accepted as primary endpoint for pivotal studies because data on the correlation to the clinical response during natural allergen exposure are required for validation. Thus, results of these tests can only be used as primary endpoint for dose-finding studies or as secondary endpoint in pivotal trials. As a consequence, in confirmatory studies, efficacy has to be shown on clinical outcome measured by symptom and medication scores during natural allergen exposure. As the use of rescue medication has an impact on symptom severity, the primary endpoint has to reflect both symptom severity and the intake of rescue medication. A positive evaluation requires (i) a statistically significant difference between placebo group and the group on active treatment and (ii) a demonstration that the observed effects represent a clinically relevant improvement for the patient. Up to now, no validated symptom score, medication score or combined score has been published, and thus for each primary endpoint chosen, the clinically relevant effect has to be defined and justified by the applicant, ideally before performing the study (6). The last step in clinical assessment is to weigh the clinical benefit against the risk to sustain adverse events and the severity of possible adverse events. Thus, depending on the possible adverse events, the clinical effect to obtain a positive benefit/risk ratio may be clearly higher than the clinically relevant effect.

For products containing recombinant allergens, the clinical evaluation will be very similar to allergen extracts (58). However, by using allergen extracts, there is a greater possibility that the patient is treated with all allergens relevant for the individual allergy, whereas this possibility is reduced if only a single allergen molecule or a mixture of a defined number of molecules is used. Therefore, the individual sensitization pattern should be measured in clinical trials with recombinant allergen molecules to justify the composition of the product and the selected study population (6).

Concluding remarks

Marketing authorization processes are complex with many different regulatory documents and institutions involved. In case of allergens, several new documents came into effect recently to define the state of the art for allergens as biomedicines. The requirements for characterization of both product quality and clinical effects have been increased. It is expected that these developments will lead to relevant changes in the field of SIT within the next years.

References

- Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572–1573.
- Freeman J, Noon L. Further observation on the treatment of hay-fever by hypodermic inoculation of pollen vaccine. *Lancet* 1911; 2:814–817.
- Kroon AM. The EAMG position on the regulation of existing products for treatment with special reference to named patient products (NPPs). *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf AM* 2003; **94**:7–14.
- The European Parliament and Council. Directive 2001/83/EC. The community code relating to medicinal products for human use. *OJ* 2004;**L31**:67–122.
- The European Parliament and Council. Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *OJ* 2001;**L12**:24–44.
- European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases. 2008, CHMP/EWP/18504/2006.
- Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;**62**:317–324.
- Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R et al. Sub-Lingual Immunotherapy. World Allergy Organization Position Paper 2009. Chapter 11: Methodology of Clinical Trials in Sublingual Immunotherapy. *Allergy* 2009; **64**(Suppl. 91):51–59.
- Casale TB, Canonica GW, Bousquet J, Cox L, Lockey R, Nelson HS et al. Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009;**124**:665–670.
- Himly M, Nony E, Chabre H, Van Overtvelt L, Neubauer A, van Ree R et al. Standardization of allergen products: 1. Detailed characterization of GMP-produced recombinant Bet v 1.0101 as biological reference preparation. *Allergy* 2009;**64**:1038–1045.
- Reuter A, Lüttkopf D, Vieths S. New frontiers in allergen standardization. *Clin Exp Allergy* 2009;**39**:307–309.
- Chapman MD, Ferreira F, Villalba M, Cromwell O, Bryan D, Becker WM et al, CREATE consortium. The European Union CREATE project: a model for international standardization of allergy diagnostics and vaccines. *J Allergy Clin Immunol* 2008;**122**: 882–889.
- Pauli G. Clinical trials with recombinant allergens. Research studies?. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M* 2009;**96**:257–264.
- Monograph on Allergen Products, European Pharmacopoeia 01/2010:1063.
- European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) and Biologics Working Party (BWP): Guideline on Allergen Products: Production and Quality Issues. 2008. EMEA/CHMP/BWP/304831/2007.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic Q 5 B/Note for Guidance on quality of biotechnological products: Analysis of the expression construct in cell lines used for production of r-DNA derived protein products. 2005; CPMP/ICH/139/95.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic Q 5 C/Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. 1996; CPMP/ICH/138/95.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic Q 5 D/Note for Guidance on quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products. 1997; CPMP/ICH/294/95.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic Q 5 E/Note for Guidance on Quality of Biotechnological/Biological Products subject to Changes in Their Manufacturing Process. 2005; CPMP/ICH/5721/03.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic Q 6 B/Note for Guidance on specifications: test procedures and acceptance criteria for biotechnological/ biological products. 1999; CPMP/ ICH/365/96.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S 6 C/Note for Guidance on quality of biotechnological products: stability testing of biotechnological/ biological products. 1995; CPMP/ICH/ 138/95.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and Biotechnology Working Party (BWP): Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: quality issues. 2003; EMEA/CPMP/BWP/ 3207/00/Rev1.
- The Commission of the European Communities. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. *OJ* 2003; **L159**:46–94.
- The Commission of the European Communities. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. *OJ* 2003;**262**:22–26.
- The European Parliament Council. Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *OJ* 2004;**136**: 1–33.
- The European Parliament Council. Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *OJ* 2006; **378**:1–19.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic Q 7/Note for Guidance on Good Manufacturing Practice for active pharmaceutical Ingredients. 2000; CPMP/ICH/ 4106/00.
- European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic M 3 (R2)/Note for Guidance on

- Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. 2009; CPMP/ICH/286/95.
29. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S2 (R1)/Note for Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. Draft. 2008; EMEA/CHMP/ICH/126642/2008.
 30. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S2A/Note for Guidance on Genotoxicity: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals. 1996; CPMP/ICH/141/95.
 31. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S2B/Note for Guidance on Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals. 1998; CPMP/ICH/174/95.
 32. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S4/Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing). 1999; CPMP/ICH/300/95.
 33. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S5 (R2)/Note for Guidance on the Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility. 1994; CPMP/ICH/386/95.
 34. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic S6/Note for Guidance on pre-clinical safety evaluation of biotechnology-derived pharmaceuticals. 1998; CPMP/ICH/302/95.
 35. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines. 1998; CPMP/SWP/465/95.
 36. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity'. 2010; EMA/CHMP/SWP/81714/2010.
 37. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on repeated dose toxicity. 2010; CPMP/SWP/1042/99 Rev 1 Corr.
 38. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). EMA Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications. 2008; EMEA/CHMP/SWP/169215/2005.
 39. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products. 2001; CPMP/SWP/2145/00.
 40. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic E 1/Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety. 1995; CPMP/ICH/375/95.
 41. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic E 6 (R1)/Note for Guidance on Good Clinical Practice. 2002; CPMP/ICH/135/95.
 42. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic E 9/Note for Guidance on Statistical Principles for Clinical Trials. 1998; CPMP/ICH/363/96.
 43. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Topic E 11/Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. 2001; CPMP/ICH/2711/99.
 44. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP). Points to Consider on Application with 1. Meta-Analysis; 2. One Pivotal Study. 2001; CPMP/EWP/2330/99.
 45. European Medicines Agency (EMA). Standard Paediatric Investigation Plan (EMA/PDCO/737605/2009) (Revision 2), 3 March 2010.
 46. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling. 2009; EMEA/CHMP/203927/2005.
 47. Bousquet J, Lockey RF, Malling HJ. WHO Position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;**53**(Suppl. 44):1–42.
 48. Malling HJ, Weeke B. EAACI Immunotherapy position paper. *Allergy* 1993;**48**(Suppl. 14):9–45.
 49. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Draft Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. 2008; EMEA/CHMP/BWP/534898/2008.
 50. Verordnung über die Ausdehnung der Vorschriften über die Zulassung der Arzneimittel auf Therapieallergene, die für einzelne Personen auf Grund einer Rezeptur hergestellt werden, sowie über Verfahrensregelungen der staatlichen Chargenprüfung (Therapieallergene-Verordnung). Bundesgesetzblatt I 2008; **51**:2177–2178.
 51. Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz). Bundesgesetzblatt I 2005; S 3394 amended by 15. AMG Novelle. Bundesgesetzblatt I 2009;**43**:1990–2020 and 69:3578.
 52. Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC – March 2006 (2006/C 133/05). *OJ* 2006;**C133**:5–7.
 53. The Council of the European Communities. Directive 89/342/EEC extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens. *OJ* 1989;**L142**:14–15.
 54. The European Parliament and Council. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *OJ* 2004;**L136**:34–57.
 55. May S, Kaul S, Lüttkopf D, Vieths S. Regulation, role and future of named patient products in Germany. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf AM* 2009; **96**:193–197.

56. Ministère de la santé et des solidarités. Décret n° 2004-188 du 23 février 2004 relatif aux allergènes préparés spécialement pour un seul individu et modifiant le code de la santé publique. *OJ* 2004;**50**:4101 texte n° 30.
57. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP) and Biotechnology Working Party (BWP). Note for guidance on allergen products. 1996; CPMP/BWP/243/96, replaced by EMEA/CHMP/ BWP/304831/2007.
58. Elferink AFA. Clinical trials with recombinant allergens – a regulatory perspective. *Arb Paul Ehrlich Inst Bundesinstitut Impfstoffe biomedizinische Arzneimittel* 2009;**96**:266–299.