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Challenges in the implementation of EAACI Guidelines on Allergen Immunotherapy: A global perspective on the regulation of allergen products

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Abstract

Regulatory approaches for allergen immunotherapy (AIT) products and the availability of high quality AIT products are inherently linked to each other. While allergen products are available in many countries across the globe, their regulation is very heterogeneous. First, we describe the regulatory systems applicable for AIT products in the European Union (EU) and in the United States (US). For Europe, a depiction of the different types of relevant procedures, as well as the committees

involved is provided and the fundamental role of national agencies of the EU member states in this complex and unique network is highlighted. Furthermore, the regulatory agencies from Australia, Canada, Japan, Russia, and Switzerland provided information on the system implemented in their countries for the regulation of allergen products. While AIT products are commonly classified as biological medicinal products, they are made available by varying types of procedures, most commonly by either obtaining a marketing authorisation or by being distributed as named patient products. Exemptions from marketing authorisations in exceptional cases, as well as import of allergen products from other countries, are additional tools applied by countries to ensure availability of needed AIT products. Several challenges for AIT products are apparent from this analysis and will require further consideration.

Introduction

The availability of medicinal products to provide a reliable diagnosis of clinical allergy and effective treatment(s) is of critical importance for patients with suspected or proven allergy. Products for allergen immunotherapy (AIT) have been approved by national competent authorities in different regions of the world. However, the regulatory landscape governing the approval of these products is enormously heterogeneous – both within the European Union (EU) and even more so when looking globally – thereby rendering it extremely complicated and challenging to develop a harmonized, international approach to regulating these products.

Pharmaceutical companies are increasingly focused on global strategies to develop and market their products. It is therefore very important to understand the current regulatory situation for allergen products from an international perspective, as this will have a direct impact on the availability of these medicinal products to patients throughout the world. Certain regulatory patterns can be observed on a global scale. For example, whereas AIT was previously mainly used and placed on the market on the

basis of expert opinions with limited regulatory oversight, the requirements for high quality clinical data for granting market access have greatly increased during the last 20 years. In the EU, legislation applicable for new and existing products (1, 2) has been in force since 1989 demanding that allergen products are registered as medicinal products with corresponding requirements for clinical data. The development of the guidelines on Good Clinical Practice (GCP) in the conduct of clinical trials has been the main driving force for the specific requirements in the legislation. In the EU, the Clinical Trials Directive (3) implemented GCP as a mandatory requirement for the conduct of clinical trials. Since 2004, EU member states have needed to apply the provisions on GCP established by this Directive. For AIT products, this has resulted in the performance of numerous state-of-the-art, randomized, double-blind, placebo-controlled trials in recent years as documented by the US and European databases on clinical trials (4, 5). However, due to the seasonal nature of many allergic diseases and the protracted immunological processes induced by AIT, clinical trials can be very time consuming and costly, particularly if a disease modifying effect is the intended indication as defined by the respective European Medicines Agency (EMA) Guideline (6). In this systematic analysis, we provide an overview on how products for the *in vivo* diagnosis of allergies, as well as for AIT, are regulated in different regions of the world. Approval of allergen products involves large and complex regulatory networks directing the independent assessment of allergen therapeutics and providing guidance on how to determine whether or not a specific product shows a favorable risk-benefit profile. Moreover the activities by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) displayed formidable achievements in the last decades. While they already led to the harmonization of various aspects related to medicinal products development and authorisation (e.g. Guidelines on quality and (non-)clinical development as well as regulatory guidance on a common format for the submission of marketing authorisation dossiers), other aspects of regulatory procedures remain heterogeneous. Activities and decisions of the responsible regulatory agencies directly influence the availability of products. This analysis has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on

Regulatory Aspects of Allergen Immunotherapy (AIT) and is part of the EAACI AIT Guidelines. The primary audiences are expected to be clinical allergologists and regulators, but the document is also likely to be of relevance to all other healthcare professionals dealing with AIT. As the focus of this EAACI systematic analysis is to describe the regulatory situation and heterogeneity observed, it is not intended to advise on solutions to the situation described and is not to be seen as a regulatory guidance document.

International and national regulation of allergen products

The regulatory system in the European Union

In the EU, allergen products are defined as medicinal products according to Directive 2001/83/EC (7). As stated in this Directive, therapeutic allergen preparations are considered medicinal products as they are substances or combination of substances presented as having properties for treating or preventing disease in human beings. Furthermore, any substance or combination of substances that may be used in or administered to human beings to obtain a medical diagnosis are also considered medicinal products. This includes *in vivo* diagnostic test allergens, including skin prick tests, provocation tests, intradermal tests and epicutaneous tests. Where such products are prepared industrially or manufactured by a method involving an industrial process, these medicinal products fall within the scope of the above mentioned Directive. Generally, these products are required to obtain a marketing authorization in order to be placed on the market. Some exemptions apply, which will be discussed below.

The EU has a unique combination of national regulatory agencies that work together in a network to regulate market access of medicinal products. Each member state of the EU holds its own national competent authority. The EMA (8), is an agency that is responsible for the coordination of several types of procedures related to the marketing authorization of medicinal products, including the centralized procedure. Furthermore, EMA hosts a number of independent scientific committees that are deeply

involved in the assessment of specific aspects or types of medicinal products as well as the development of scientific guidelines that are then used for a standardized assessment of the medicinal products.

Procedures and assessment of marketing authorization applications

It should be noted that the scientific assessment of all marketing authorizations, post-marketing authorization procedures (i.e. variations to a marketing authorization) as well as the development of the guidance and opinions in scientific advice procedures is actually performed by the national competent authorities. To this end, for centralized procedures, there is a call for countries that are willing to act as Rapporteur (or Co-Rapporteur) in a procedure. The scientific assessment itself occurs in the national competent authorities of those countries that are acting as Rapporteur or Co-Rapporteur; assessment reports are subsequently presented and discussed within the EMA's respective committees where a collective opinion is adopted by all members.

In the EU, different types of procedures may apply in order to obtain a marketing authorization (see Figure 1A and 1B). For certain products, depending on manufacturing and/or medical indication, the **centralized procedure** is mandatory for marketing authorization (Table 1). This type of procedure is therefore applied when marketing authorization is sought for recombinant allergen products. However, in the EU, there are currently only marketing authorizations for products derived from natural sources and neither products for the diagnosis of allergens nor products for AIT have yet been authorized by the centralized procedure. Most allergen products, for which marketing authorizations exist within the EU, have been authorized via a **National Authorisation Procedure**. In such a case, a pharmaceutical company applies for marketing authorization in one member state only. Consequently, after finalization of the procedure, the product is only authorized in the respective country. In contrast to the agreed timelines for multinational procedures (as described below), the national procedures are executed under national timelines and these vary among countries. If the company then decides to apply for marketing authorizations in additional member states, the **Mutual Recognition Procedure** (MRP) has to be applied. In this procedure, the country in which the marketing authorization has

already been granted acts as so-called Reference Member State (RMS) and will provide the assessment report that led to the original authorization of the product to those countries in which an authorization is sought (Concerned Member States, CMS). Often, the original assessment report will need to be updated by the RMS in case that considerable time has passed between the original authorization and the actual start of the MRP to reflect the up-to-date status of the marketing authorization dossier. The procedure itself typically takes 90 days, only where no consensus among member states is reached, the procedure will last 150 days due to arbitration by CMDh. An important drawback of this approach is that two procedures (national authorization followed by MRP) are conducted sequentially in the MRP, thereby prolonging the timeframe from initial submission of a marketing authorization application and eventual market access in intended countries. A speedier alternative is the **Decentralized Procedure (DCP)**, which is the preferred route for allergen products without preexisting national marketing authorisation to achieve such authorization in multiple EU Member States (see also (9–11)).

Overall, the DCP allows the decision and potential approval to be reached within a shorter timeframe as there is no requirement for a national authorization to precede the DCP. To initiate a DCP, an applicant will request the national competent authority (NCA) in a country of their choice to act as coordinating authority (RMS), which will then be leading the assessment and coordinating the procedure. If the requested authority agrees to be RMS, the company submits an application for marketing authorization to the RMS and all involved member states, which are selected by the applicant. For DCP, the procedure can be closed by the RMS at different time points as soon as consensus is reached by RMS and CMS. This can happen at Day 105, Day 150, or Day 210 of the procedure. Where necessary, the procedure will be stopped in a so-called *clock-off period* at Day 105 to allow the applicant to respond to issues raised in the procedure. In case arbitration by CMDh is needed, the CMDh adopts its final position by Day 270. The result of both, a MRP and DCP, typically is that after positive finalization of a procedure, the product might not be authorized in the entire EU, but only in the RMS and respectively involved countries/CMS that the applicant decided to include in

the procedure. The RMS prepares an assessment report including a list of questions on issues that need to be resolved before authorization can be granted. For both, MRP and DCP, the CMS comment on the assessment report, which may result in additional issues to be raised. Next, the assessment report as well as the list of outstanding issues is provided to the applicant to allow for resolution of these issues. The RMS then reassesses the updated documentation and, in agreement with the CMS, a decision is made on whether or not the medicinal product can be approved. In case there is disagreement between the RMS and the CMS on issues that may potentially harm the patients (“potential serious risk to public health” (12)), the procedure may be referred to the Co-ordination group for Mutual recognition and Decentralized procedures – human (CMDh) (see below) and possibly to the Committee for Medicinal Products for Human Use (CHMP) for arbitration (see also (10, 11)).

For all marketing authorization procedures, a public assessment report is prepared (either by the CHMP (for CP), the RMS (for MRP and DCP) or the respective national competent authority (for national procedures)) upon granting of a marketing authorization, thereby publicly documenting the assessment for a concerned medicinal product. However, those parts of the dossier that are confidential will not be included in the public assessment report. This is typically the case for specifics of the manufacturing process. Clinical and non-clinical data are typically not considered to be confidential.

For allergen products, several committees and working parties play important roles in the different phases of development, marketing authorization, and post-marketing authorization procedures (Supplementary tables 1 and 2).

The networks of institutions and committees involved in procedures resulting in the marketing of a medicinal product in the EU and resultant procedures (variations to an existing marketing authorization, pharmacovigilance monitoring, etc.) are complex. We will therefore give an overview of the major committees playing a role in regulatory procedures for allergen products in Europe.

The Committee for Medicinal Products for Human Use (CHMP) and related committees

The CHMP is the committee at the EMA responsible for preparing opinions on issues with respect to medicines for human use. In centralized procedures, the CHMP assesses the marketing authorization application and gives a recommendation on whether or not a specific product may be approved. The final decision on this will then be made by the European Commission (EC) on the basis of the opinion provided (13, 14). The opinion by the CHMP is prepared within the European regulatory framework and based on scientific criteria allowing a conclusion on the benefit-risk balance using the information provided by the applicant concerning quality, safety and efficacy of the medicinal product. A recommendation for marketing authorization is only made where this balance is favorable. In addition to the initial marketing authorization procedure, the CHMP is also responsible for a number of post-authorization activities, such as changes to an existing marketing authorization (variation) (14).

For Mutual Recognition and Decentralized Procedures, the CHMP plays an important role in situations where the member states involved in a specific procedure (including the RMS as well as the Concerned Member States) do not come to an agreement concerning the marketing authorization of a specific product. This may, for example, be the case where a CMS raises issues of potential serious risk to public health while the RMS does not share this concern. In such circumstances, the CHMP will arbitrate and take a decision on whether or not a concern should be upheld (which results in a recommendation to deny a marketing authorization) or whether the presented issues are not profoundly affecting the benefit-risk balance in a negative way (which would typically result in the approval of a specific product by the RMS and CMS).

Another very important aspect of the CHMP's responsibilities is the provision of scientific advice during all phases of a products life-cycle, e.g. during clinical development and after marketing authorisation. In addition, CHMP is responsible for the development of scientific guidance for the pharmaceutical industry. These guidelines, although not directly mandatory from a legal perspective, reflect the scientific or regulatory state of the art and are typically applied by the regulatory agencies of the EU Member States. Accordingly, applicants should follow these guidelines or provide comprehensible justifications in case deviations from these documents are intended. As a part of its mandate, the

CHMP has established a number of working parties, which provide expertise in particular scientific fields. These working parties are composed of European experts selected from the national competent authorities. On varying issues, the CHMP will ask these working parties to contribute to the development of specific guidelines or to the assessment of marketing authorisations and EMA scientific advice procedures – for example the Safety Working Party (SWP) for specific non-clinical issues or the Biologics Working Party (BWP) for quality issues concerning biologicals, including allergens from natural and recombinant sources (15).

The Co-ordination group for Mutual recognition and Decentralized procedures – human (CMDh)

The CMDh is not a committee of the EMA but is associated to the Heads of Medicines Agencies (HMA), which is a network of the Heads of the National Competent Authorities in the European Economic Area (EU and the non-EU countries Iceland, Liechtenstein and Norway). The CMDh was set up by Directive 2004/27/EC (16) and plays a fundamental role with respect to procedural issues in Mutual Recognition and Decentralized procedures. Based on its mandate as given in this directive, the committee has developed guidance on all aspects of MRP and DCP and discusses issues that arise in ongoing procedures. As stated previously, these types of procedures have steadily risen in relevance for allergen products in recent years. As described above for CHMP's role in CP, an unresolved potential serious risk to public health issue in a marketing authorization procedure with disagreement between RMS and CMS will first result in discussion of the relevant issues at CMDh. Only if the disagreements remain unresolved in the CMDh, the issue is passed to the CHMP for arbitration. Accordingly, in addition to procedural questions, the CMDh is also involved in scientific issues.

Role of the Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC is responsible for assessing and monitoring safety issues for human medicines. These responsibilities include the detection, assessment, minimization and communication of safety issues such as adverse reactions observed for specific medicinal products (17). For this, the PRAC prepares

recommendations and provides these to the CHMP and CMDh as well as to the EC in related procedures. Yet, for allergen products, the role of PRAC is currently limited as most issues relating to pharmacovigilance are presently still handled by the member states.

The Paediatric Committee (PDCO)

As part of a valid marketing authorization application, European legislation (in this case Paediatric Regulation (EC) 1901/2006 (18)) mandates that an applicant for the marketing authorization of a medicinal product and therefore also for allergen products for therapy and in-vivo diagnosis, must provide a paediatric investigation plan (PIP) that has been assessed and approved by the PDCO of the EMA. This plan is provided by the applicant during development of the medicinal product to delineate how data on the clinical efficacy and safety of a specific product will be generated in children to support the authorization and use of this medicine in this population group. For certain classes of medicines, the requirement to submit a PIP is waived due to the fact that these classes of medicines are likely to be ineffective or unsafe in paediatric populations, are intended for conditions that occur only in adults, or will not result in a significant therapeutic benefit compared to existing treatments in paediatric populations. As allergen products typically do not fall in any of these categories, an approved PIP is mandatory for these products and, if missing, will prohibit authorization even at the national level. However, a deferral can be requested where it is appropriate to conduct clinical studies in adults prior to initiating studies in the paediatric population (19). Such deferrals are often granted for allergen products. Yet, the requirement to perform clinical studies in paediatric populations has resulted in varying difficulties in reality as recruiting can be profoundly difficult and ethical issues arise.

National specifics on regulatory issues for allergens in Europe

Allergen products are regulated according to European law since 1989 (1, 2). The implementation of the European Directive 2001/83/EC (7) crucially advanced the legal framework for allergen products so that it is basically harmonized in the EU. Yet, there is still a high level of heterogeneity in how EU member states regulate market access for this type of products. For most parts, this is due to specific

regulations such as Article 5 of above mentioned Directive that allows member states to place specific allergen products, especially named patient products (NPP), on the market without the requirement of a marketing authorization. Furthermore, while implementing the particulars of the European Directive 2001/83/EC into national legislation, many member states adapted or elaborated this legislation by specific national law such as ordinances or decrees. Some examples are provided in the supplementary section of this document to demonstrate the spectrum of approaches on how allergens are currently regulated in the EU. For reasons of brevity, there are specifics in additional EU member states that are not covered by this review.

Allergen products in the US

Allergen products in the US are regulated as biological medicinal products under the Public Health Service (PHS) Act and as drug products under the Federal Food, Drug and Cosmetics Act (FD&C Act) Additional Acts (laws) contain important provisions for regulation of biological products and drug products, but the PHS Act and FD&C Act and their related amendments are the primary laws under which biological products are regulated. In addition, FDA is authorized or required under these laws to issue Federal Regulations. Federal Regulations, which have the force of law, detail requirements on how to comply with US law. Products administered to man for the diagnosis, prevention, or treatment of allergies, are defined by Federal Regulation as Allergenic products (hereinafter referred to as allergen products). Allergen products licensed in the US include sterile injectable allergen extracts for diagnosis and immunotherapy, allergenic extracts in sublingual tablet formulations for treatment of certain allergies, and allergen patch tests. Generally, there are no differences in the regulation of allergens for diagnosis versus therapy. Allergen products require a marketing authorisation termed a Biologics License Application (BLA).

US-licensed allergen extracts are either “standardized” or “non-standardized”, depending on the labeled units. Standardized extracts are labeled in units tied to biological activity and each released lot

of a standardized allergen extract meets potency-related specifications. Non-standardized allergen extracts carry labeled units (PNU or w/v) that do not correlate to potency. US-licensed allergen products that are not aqueous extracts do not carry the designation of standardized or non-standardized.

Separate BLAs are assigned for each of the existing standardized allergenic extracts, but non-standardized allergen extracts from each manufacturer are licensed under one BLA. That BLA includes every non-standardized extract manufactured by a specific license holder, regardless of extract type. Therefore, a specific license holder's BLA for non-standardized allergenic extracts could encompass many different products. The model for non-standardized allergen extracts is historical. Entities seeking a BLA for a previously unlicensed allergen product or a licensed allergen product with a new clinical indication must demonstrate that their products are safe and effective for their intended use in accordance with requirements specified under laws and regulations for BLAs. . Briefly, in general the allergen product is first assessed for safety and efficacy in clinical trials conducted under an IND Application that a sponsor submits to FDA. FDA may also accept data from foreign studies not performed under IND provided certain requirements are met. After successful completion of clinical trials, the product is submitted for licensure under a BLA. BLAs are submitted electronically using the harmonized eCTD format. The BLA contains all required information on the quality of the medicinal product, as well as all clinical, pharmacological and toxicity data. FDA expects that a BLA will demonstrate that an applicant manufactures a quality product in accordance with current Good Manufacturing Practices (cGMPs) that is safe, pure and potent. After licensure, changes to the manufacturing process are submitted to FDA according to a three-tiered supplement and annual report system, depending on the nature of the proposed changes. FDA regulations and guidance discuss reporting requirement for post-approval changes. NPPs are not marketed in the US, and the marketing of allergen products manufactured in pharmacies is not permitted.

Guidance documents provide FDA's current thinking on implementation of regulations or law. FDA Guidance documents span a wide range of topics including: design, production, labeling, promotion,

manufacturing, and testing of regulated products; processing, content, and evaluation or approval of submissions; or inspection and enforcement policies. As in other regions of the world, changes in laws and regulations occur and FDA updates guidance documents as necessary to insure that approaches to compliance with applicable laws and regulations are current. These changes then apply to a wide range of FDA-regulated products, including allergen products, regardless of their use in therapy or diagnosis. ICH guidance documents are used for the same purpose as FDA guidance and apply to allergen products, depending on the scope of the guidance. Pharmacovigilance monitoring is required in the U.S. for allergen products, and specific regulations for reporting of adverse events exist. Periodic Safety Update Reports are also required for licensed products. During the conduct of clinical trials, adverse events are also reported in the IND annual report.

Allergen products in selected parts of the world

General regulation of allergen products

Allergic diseases affect people all over the world. Hence, allergen products are available in many countries and yet there is little information available on how such products are regulated on a global scale. We therefore developed a questionnaire in which national competent authorities from a selection of countries were asked to provide information on the regulation of allergen products in their countries. Responses were received from the NCAs in Australia, Canada, Japan, Russia and Switzerland as well as feedback on selected questions from China and Indonesia. The responses to the questionnaire received give an impression of such regulation from various areas of the world. Table 2 displays some key findings extracted from the responses to the questionnaire. Some general observations can be made from the responses received. For example, it becomes clear that as in the EU and US, allergens are considered biological medicinal products in most countries (Australia, Canada, China, Indonesia, Japan, Russia) and typically allergen products are not in general exempted from the requirement for a marketing authorization. Such authorizations are issued for the finished product. Furthermore, the basic regulatory frameworks typically do not differentiate between therapy and test allergens. Nevertheless, although allergen products are considered as biological medicinal products,

some countries have implemented specific regulations for this type of products. For example, Switzerland has implemented an allergen ordinance in December 2009 allowing for a simplified authorization procedure for test and therapy allergens from natural sources (20). In this ordinance, specifics on the requirement on data to be provided for marketing authorization are laid down individually for test and therapy allergens. Among other addressed issues, there are details provided on the requirements for data from clinical studies for both groups of allergen products. Additionally, Swissmedic published a guidance document on the simplified authorization of allergen products (21).

In Canada, there are currently two regulatory authorization pathways for allergen extracts in place. Firstly, there are so-called 'Grandfathered Products'. These products were approved under a framework that was applicable before 2012. In this framework, there are two main types of allergenic extracts to be considered: non-standardized and standardized extracts. Non-standardized allergenic extracts are further divided into extracts derived from pollen or non-pollen materials. Currently, for these non-standardized products, one authorization is given for all pollen products and one authorization is given for all non-pollen products per company. In contrast, for standardized allergenic extracts, one authorization is given to each product per company. In addition, Health Canada follows the FDA standards for the Standardized Allergenic Extracts.

Secondly, in November 2012, Health Canada published a guidance document entitled Regulatory Framework for Unauthorized New Allergenic Products of Biological Origin used for the Diagnosis or Treatment of Allergic Diseases which introduced a new policy for the regulation of allergen extracts (22). All Allergen Extracts approved after the introduction of the new Framework in 2012 are regulated and authorized under the same regulatory authorization pathway as other Biologic Drugs. Each product requires its own authorization. As stated in the response provided by Health Canada, the agency is currently examining options for aligning these two pathways.

Named patient products

As is the case within the EU, the regulation and acceptance of named patient products differs widely globally. For example, according to the Russian legislation it is allowed to produce medicinal products on the basis of a prescription only in cases where authorized substances are used in the production process. However, according to the NCA in Russia, no authorized allergen drug substances are currently available on the Russian market, only finished products. Therefore no NPPs can be produced based on a prescription for an individual patient. In Switzerland, the Swiss Therapeutic Products Law defines so-called 'formula magistralis' medicinal products which are exempt of a marketing authorization. These medicinal products have to be manufactured upon a specific prescription by a physician which would potentially also be feasible for allergens. The information on the actual availability of such products on the market lies at the regional Cantonal Health Authorities.

Contrasting with the previous examples, Australia, Canada and Japan generally do not allow NPPs to be placed on the market. However, while NPPs are not available as such in Australia, practitioners there may obtain so-called Authorized Prescriber status for allergens under a special program, the Authorized Prescriber program (23). This may be applied in cases where patients require access to medicines or medical devices that have not been approved for supply by the Australian agency. For those countries for which NPPs are allowed on the market, specific information on the number and type of NPPs on the market is often non-available to the NCAs responsible for the marketing authorization and monitoring of the authorized allergen products.

Import of allergen products

Non-availability of authorized allergen products may result in crucial gaps in the provision of needed products to patients. To overcome this, some countries allow alternative routes for such products to be made available. In addition to the above mentioned Authorized Prescriber program, Australia also applies a so-called special access scheme (24). For this, the import and/or supply of a specified unapproved therapeutic good (or class of unapproved therapeutic goods) to specific patients (or classes of recipients) with a particular medical condition can be granted upon request of a prescribing physician. The decision on such requests is taken on a case-by-case basis, and is based on the clinical

information supplied by the doctor. Any approval or rejection is limited to the named patient only for a defined dose and duration of therapy and does not allow supply to another patient and is not tantamount to progression to general marketing. Also, extemporaneous compounding by pharmacies is permitted for individual patients on prescription-based orders of treating physicians but is not an avenue for general marketing to other patients. In Switzerland, patients and health professionals are allowed to import medicinal products authorized in a third country by specific rules (25). This is only possible, when there is no authorized product available in Switzerland. This is not applicable for NPPs. In Japan, based on the responsibility of the physician, allergen products are allowed to be imported from other countries. However, these products are then exempt from Relief System for Sufferers from Adverse Drug Reactions. In Russia, the import of therapeutic allergen products is allowed for those products that are also authorized within the Russian Federation. In Canada, all products to be sold must be authorized for sale by Health Canada. China allows the import of certain allergen products from overseas, adding to the domestic products registered there. Apart from the exceptions described above, manufacturing of allergen products in pharmacies without marketing authorization is not allowed in any country replying to the questionnaire.

Post-authorization requirements for allergen products

All countries stated that there are post-authorization requirements such as pharmacovigilance monitoring in place (for example Risk Management Plans and/or Periodic Safety Update Reports) for authorized allergen products. In Canada, in addition, each lot of a biological medicinal product is subject to the Lot Release Program before sale. The risk-based Lot Release Program covers both pre- and post-market stages and derives its legislative authority from section C.04.015 of the Food and Drug Regulations. Products are assigned to one of four evaluation groups, with each group having different levels of regulatory oversight (testing and/or protocol review) based on the degree of risk associated with the product. The graded risk-based approach to testing and oversight allows the Biologics and Genetic Therapies Directorate of Health Canada to focus ongoing testing on products for which enhanced surveillance is indicated such as vaccines and blood products. The criteria used to determine

the appropriate Evaluation Group include, but are not limited to, the nature of the product, the target population, the lot testing history in the Directorate, and the manufacturer's production and testing history.

Regulations for specific types of allergen products

As was previously described for the EU and the US, there is no particular regulation or guidance in place in any country that responded to our questions for allergen challenge products, for example for food challenge. Typically they are considered to be diagnostic allergen products and are treated as such.

Moreover, thus far there are no authorizations for recombinant allergen product or for peptides derived from allergen sequences anywhere in the world. Special requirements are applicable in some countries for such products, for example, in Switzerland, an administrative ordinance for human medicines with new active pharmaceutical ingredients (26) must be followed.

Current regulatory challenges for allergen products and unmet needs

Recent years have shown tremendous rearrangements in the allergen market and consequently the availability of allergen products. In some countries, many AIT products have disappeared, for example due to novel regulations such as the therapy allergen ordinance in Germany (27) or the enforcement of Directive 89/342/EEC in the Netherlands (2) (see online supplementary for further information) or reimbursement issues. For other products, state-of-the-art clinical and quality data has been generated resulting in the development and even marketing authorization of a new generation of products (28–30). Although such positive developments are observed, other aspects may be more ambivalent. Several recommendations have been made by academia to improve thoroughly standardized definitions for future trial in AIT and should be consequently followed (31, 32).

It should be noted that this is a dynamic situation and the ongoing developments in this field will continue to reshape the allergen market fundamentally.

Several issues have surfaced in recent years that are thought to be key triggers of the current developments. Overall, the requirements on the data that must be provided to successfully apply for a marketing authorization have risen significantly in the last 20 years. There has been a clear shift towards products with proven quality, safety and efficacy, which has also been evident in some cases for previously authorized products. Randomized, double-blind placebo controlled studies according to current GCP-regulation are required as the current state-of-the-art approach. Products for which such proof is not provided will not be approved for marketing. Furthermore, it has become evident in recent years that the distribution of products as NPP for in vivo diagnosis and AIT for highly prevalent allergies is neither necessary nor desirable. The data to be generated for documentation of clinical efficacy and safety as well as proof of adequate manufacturing of these products should be provided and independently assessed. In contrast, while for highly prevalent allergies it is feasible to conduct randomized double blind placebo controlled studies, for allergens with a lower prevalence this may not be possible due to insufficient recruiting of patients.

In addition, considering the (non-)availability of allergen products, it should be distinguished between a potential lack of newly developed products (e.g. for allergies with low prevalence) and the withdrawal of products from the market due to the decision of companies to cease marketing. Consequently, while certain causes resulting in these two scenarios are overlapping (e.g. economic profit to be expected with respect to reimbursement), they are differing in other aspects. For example, the requirement to provide GCP-compliant clinical data on efficacy and safety as requested by Directive 2001/83/EC will not necessarily affect products for which a marketing authorization has already been issued.

Economic considerations influencing the availability of allergen products

As several factors are influencing the current and future availability of allergen products, pricing and reimbursing are among those most commonly discussed. As with the regulatory framework, reimbursement for allergen products is very heterogeneous with even more differences between countries. Decision making on reimbursement is often based on national procedures for so-called

Health Technology Assessments (HTA). However, in many countries, HTA is not performed by the same authorities that are responsible for marketing authorisation and the assessments are based on different criteria. This can result in potentially diverging opinions on one medicinal product between HTA and the assessment in a marketing authorisation procedure. However, it should be noted that regulators involved in scientifically assessing the medicinal products are neither in a position nor are they commissioned to include considerations on reimbursement in their decision making on a marketing authorization application (33). Complicating matters, in addition to the differences in reimbursement, the fees that are to be paid to the respective NCAs involved in a marketing authorization procedure (as well as post-marketing procedures such as variations to an existing marketing authorization) in national procedures, MRP and DCP are defined on a national level, resulting in enormous differences in the magnitude of fees. Furthermore, these national fees may add up to considerable sums, thereby enticing companies to market their product in a selected number of countries, limiting the availability of products in countries not considered for marketing authorization. Adding up to the fees applicable for marketing authorization itself, there are national fees to be paid in each country where a variation to an existing marketing authorization is applicable as well as fees for pharmacovigilance activities. Besides, in many cases fees do not consider the economic attractiveness of a specific product and therefore do not distinguish between, for example, a commonly prescribed therapy allergen and a test allergen for diagnosis of an allergy with low prevalence, thereby likely intensifying the focus of pharmaceutical companies on allergen products for the most prevalent allergies. However, some countries have implemented measures to account for the specific characteristics of allergen products. For example, in Switzerland, the fees raised for allergen products are differentiated for allergens for therapeutic and diagnostic purpose (the latter ones with a fee reduction of 90%). Variation fees are also reduced by 50% for both therapeutic and diagnostic allergens in comparison to other medicinal products.

Future perspectives

Considering the current position, companies are tending to focus on a core group of allergens. While it is reasonable that products for rare allergies that are of insufficient quality or have no or very little data on clinical efficacy are disappearing from the market, this is problematic for patients who require them and where there is no adequate alternative. This situation is especially evident for allergen products for *in vivo* diagnosis. Consequently, strategies to counteract this development, for example with regard to the regulatory management of such products may be needed. However, to do sufficient justice to this topic and its significance, it requires separate discussion elsewhere.

Furthermore, the situation concerning the heterogeneity of the regulatory status of allergen products worldwide and in the EU is deeply rooted in their regulatory history, as for decades these products have been managed on a national level only. Resulting diverseness is evident, for example, in the applicability and prevalence of use for NPPs in the EU. In contrast, while NPPs are not marketed as such in the US, it has been reported that products are frequently mixed at the physician's office. Although respective guidance has been developed for this approach (34, 35), there is a lack of evidence to support the efficacy of the individual mixtures used. Moreover, the EU is an evolving structure with the decision of the UK to leave the EU and several countries having joined the EU in the last decades. The latter ones have had the challenge of integrating their own national regulations and medicinal products available on their markets into the regulatory system of the EU. In light of these differences, companies are faced with the challenge to keep their products (and manufacturing processes) standardized during development as well as post-marketing in a global distribution setting.

Some of the issues concerning allergen products and their availability have resulted in activities by responsible European committees. Due to problems resulting from the regulatory disharmony observed in the EU, for example with respect to pharmacovigilance obligations, the CMDh has started an activity to work on proposals for harmonized regulatory approaches for allergen products within the EU (36).

For certain types of medicinal products in life-threatening diseases, considerations for application of a life cycle approach are made where a medicinal product can be authorized based on less

comprehensive data than normally required if the public health benefit of their immediate availability to patients outweighs the risk (39). However, this is typically not the case for allergen products. In such lifecycle approaches, a product will be assessed for its benefit-risk balance on an on-going basis post-marketing (37). Similar approaches are being applied in different parts of the world (38), although they are often criticized, especially because products within such a lifecycle approach are made available with insufficient data to fully determine a benefit-risk ratio at the time of market access.

Several projects are in place targeted at supporting manufacturers in developing effective and safe medicinal products, for example the Innovative Medicines Initiative (40). Also, PRIME (41)(derived from priority medicines) has been founded by the EMA to support in the development of medicines aimed at currently unmet needs. With respect to allergies, there are several fields, where medical need can currently not be adequately addressed with authorized medicinal products (e.g. in oral immunotherapy of food allergies) and where such programs may be of benefit for future developments.

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Disclaimer

The views expressed in this review are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the respective national competent authorities, the European Medicines Agency or one of its committees or working parties.

Authors' contributions

This paper was drafted by Bonertz A, Hoefnagel M, Timon M, Slater J, Rabin R, Bridgewater J, Pini C and Vieths S. It was revised following critical review by Roberts G, Pfaar O, Bonini S, Sheikh A and then

by all the co-authors. The EAACI task force developing the manuscript was chaired by Vieths S. Coordination of authors' contributions was done by Bonertz A. This study is part of the EAACI AIT guidelines project, chaired by Muraro A and coordinated by Roberts G.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

References

1. The Council of the European Communities. COUNCIL DIRECTIVE of 3 May 1989 amending Directives 65 /65 / EEC, 75 / 318 / EEC and 75 / 319/ EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products: Official Journal of the European Communities.
2. The Council of the European Communities. Council Directive 89/342/EEC of 3 May 1989 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, 1989: Official Journal of the European Communities.
3. 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, 2001: Official Journal of the European Union.
4. European Medicines Agency. EU Clinical Trials Register. <https://www.clinicaltrialsregister.eu> (Dec 16, 2016).
5. U.S. National Institutes of Health. ClinicalTrials.gov. <https://clinicaltrials.gov/> (Dec 16, 2016).
6. 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.
7. The European Parliament and Council. Directive 2001/83/EC. The community code relating to medicinal products for human use, 2004: Official Journal of the European Union.
8. European Medicines Agency (EMA). <http://www.ema.europa.eu/ema/>.
9. Lorenz AR, Luttkopf D, Seitz R, Vieths S. The regulatory system in europe with special emphasis on allergen products. *International archives of allergy and immunology* 2008;**147**:263-275.
10. Kaul S, May S, Luttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy* 2011;**66**:753-764.
11. Kaul S, Englert L, May S, Vieths S. Regulatory aspects of specific immunotherapy in Europe. *Current opinion in allergy and clinical immunology* 2010;**10**:594-602.
12. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). 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, 2009.
13. European Medicines Agency (EMA). The European regulatory system for medicines: A consistent approach to medicines regulation across the European Union, 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47#.

14. The European Parliament and Council. Directive 2004/726/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human and veterinary use and establishing a European Medicines Agency, 2004: Official Journal of the European Union.
15. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) and Biologics Working Party (BWP). Mandate, Objectives and Rules of Procedure for the CHMP Biologics Working Party (BWP), 2005.
16. European Parliament and the Council. Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2004: Official Journal of the European Union.
17. The European Parliament and Council. Regulation (EU) No 1235/2010 amending, as regards pharmacovigilance of medicinal products for human use, 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, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, 2010: Official Journal of the European Union.
18. 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, 2006: Official Journal of the European Union.
19. European Commission. Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies, 2014: Official Journal of the European Union.
20. Der Institutsrat des Schweizerischen Heilmittelinstituts. Verordnung des Schweizerischen Heilmittelinstituts über die vereinfachte Zulassung von Allergenpräparaten, 2009.
21. Swissmedic. AW-Verwaltungsverordnung Vereinfachte Zulassung von Allergenpräparaten, 2014. <https://www.swissmedic.ch/zulassungen/00153/00189/01878/index.html?lang=en>.
22. Minister of Health. Regulatory Framework for Unauthorized New Allergenic Products of Biological Origin Used for the Diagnosis or Treatment of Allergic Diseases, 2012. http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/allergenic_allergenes_2012-
23. Australian Government - Department of Health Therapeutic Goods Administration. Authorised prescribers. <https://www.tga.gov.au/form/authorised-prescribers> (Dec 14, 2016).
24. Australian Government - Department of Health Therapeutic Goods Administration. Special access scheme. <https://www.tga.gov.au/form/special-access-scheme> (Dec 14, 2016).
25. Verordnung über die Bewilligungen im Arzneimittelbereich. AMBV, 2001.
26. Swissmedic. AW-Administrative ordinance Instruction Authorisation of human medicines with new active pharmaceutical ingredients and major variations, 2014. <https://www.swissmedic.ch/zulassungen/00153/00189/01878/index.html?lang=en> (Oct 19, 2016).
27. Bonertz A, Kaul S, Ruoff C, Vieths S. Die Umsetzung der Therapieallergene- Verordnung bei der spezifischen Immuntherapie. Eine Bestandsaufnahme. *AL* 2014;**37**:395-402.
28. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. *The Journal of allergy and clinical immunology* 2016;**137**:444-451.e8.

29. Pfaar O, van Twuijver E, Boot JD, Opstelten DJE, Klimek L, van Ree R et al. A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study. *Allergy* 2016;**71**:99-107.
30. Didier A, Worm M, Horak F, Sussman G, Beaumont O de, Le Gall M et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *The Journal of allergy and clinical immunology* 2011;**128**:559-566.
31. Pfaar O, Demoly P, van Gerth Wijk R, Bonini S, Bousquet J, Canonica GW et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;**69**:854-867.
32. Pfaar O, Bastl K, Berger U, Buters J, Calderon MA, Clot B et al. Defining pollen exposure times for clinical trials of allergen immunotherapy for pollen-induced rhinoconjunctivitis - an EAACI position paper. *Allergy* 2016.
33. Eichler H-G, Hurts H, Broich K, Rasi G. Drug Regulation and Pricing--Can Regulators Influence Affordability. *The New England journal of medicine* 2016;**374**:1807-1809.
34. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I et al. Allergen immunotherapy: a practice parameter third update. *The Journal of allergy and clinical immunology* 2011;**127**:S1-55.
35. Daigle BJ, Rekkerth DJ. Practical recommendations for mixing allergy immunotherapy extracts. *Allergy & rhinology (Providence, R.I.)* 2015;**6**:1-7.
36. Final Minutes for the meeting on 16-18 November 2015, (Version 4). EMA/CMDh/808330/2015, 2015.
37. Breckenridge A, Mello M, Psaty BM. New horizons in pharmaceutical regulation. *Nature reviews. Drug discovery* 2012;**11**:501-502.
38. Fujiwara Y. Evolution of frameworks for expediting access to new drugs in Japan. *Nature reviews. Drug discovery* 2016;**15**:293-294.
39. The European Parliament and Council. COMMISSION REGULATION (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004, 2006: Official Journal of the European Union.
40. Goldman M, Seigneuret N, Eichler H-G. The Innovative Medicines Initiative: an engine for regulatory science. *Nature reviews. Drug discovery* 2015;**14**:1-2.
41. European Medicines Agency. PRIME: priority medicines.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac058096f643.