Regulation of allergen products – A global perspective

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. Here, we describe the regulatory systems applicable for AIT products in the European Union and in the 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, including regulatory and economical aspects, for AIT products are apparent and will require further consideration.

Introduction

The availability of medicinal products to provide a reliable diagnosis of clinical allergy and an effective treatment 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) demands 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 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 position paper, 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. Activities and decisions of the responsible regulatory agencies directly influence the availability of products. This
position paper 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 position paper is also likely to be of relevance to all other healthcare professionals dealing with AIT. This EAACI Position Paper is not intended 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 later.

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 a decentralized 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 accommodates 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.

**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.

In the EU, different types of procedures may apply in order to obtain a marketing authorization (see Figure 1). 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, 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). In many cases, the original assessment report will need to be updated by the RMS as considerable time may have passed between the original authorization and the actual start of the MRP to reflect the up-to-date status of the marketing authorization dossier. 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 new allergen products to achieve marketing authorization in multiple EU member states (see also (9–11)).

The Decentralized Procedure 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. Therefore, the result of both, a MRP and DCP, typically is that after positive finalization of a procedure, the product will not be authorized in the entire EU, but only in the RMS and respectively involved countries/CMS. The RMS prepares an assessment report including a list of questions on issues that need to be resolved before authorization can be granted. 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 data is typically not considered to be confidential.

For allergen products, several committees and working parties play crucial 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 most critical 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 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 Reference Member State 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 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 non-EU countries Iceland, Liechtenstein, 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 opinions and provides these to the CHMP and CMDh as well as to the European Commission in related procedures.

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
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.

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 Act and as drug products under the Food, Drug and Cosmetics Act. Multiple other Acts apply
but these two Acts, which have the force of law, are the primary legislation under which the products
are regulated. 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). A separate BLA is issued to each new allergenic product upon approval.

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 (AU, BAU, specific
allergen units, or mass units) and each released lot of a standardized allergen extract meets potency-
related specifications. Non-standardized allergen extracts carry labeled unit (PNU or w/v) that has
not been demonstrated to be associated with 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;
any new allergen product for which licensure is sought is regulated as a biological under the
Investigational New Drug (IND) and BLA regulation. Briefly, the new product is first assessed for
safety and efficacy in clinical trials conducted under an IND Application filed by a sponsor at FDA.
After successful completion of clinical trials, the product is submitted for licensure under a BLA. A
BLA includes an electronic file (dossier) that contains all required information on the quality of the
medicinal product, as well as the clinical, pharmacological and toxicity data. FDA expects that a BLA
will demonstrate that an applicant uses the current state-of-the-art to manufacture a quality product
that is safe, pure and potent. After licensure, changes to the manufacturing process are submitted to
FDA according to a three-tiered supplement system, depending on the nature of the proposed
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 under the categories of clinical, CMC and GMP, application submissions, adverse events and product deviations reporting, labeling and promotion, biosimilar products, and manufacturing facilities inspections. As in other regions of the world, there are changes in regulatory procedures and FDA guidance documents as they are regularly updated to represent current state-of-the-art. 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 may also apply to allergen products, depending on the scope of the guidance. Pharmacovigilance monitoring is required in the U.S. for allergen products under specific regulations for reporting of adverse events. 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, Russia, Japan, China, Indonesia) 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 (19). 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 (20).

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 allergen products of biological origin used for the diagnosis or treatment of allergic diseases which introduced a new policy for the regulation of allergen extracts (21). 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 (22). 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 (23). 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 (24). 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 Suffers 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. 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 (25) 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. While many allergen products have disappeared in some countries (i.e. in Germany and Netherlands), 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 (26–28). 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 (29, 30).

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 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. Just as the regulatory framework, reimbursing for allergen products is very heterogeneous and even more differing between the countries considered. 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 (31).

Complicating matters, in addition to the differences in reimbursement, the fees that are to be paid to the respective National Competent Authorities 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. 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 (32, 33), 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. For example, 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 develop proposals for harmonized regulatory approaches for allergen products within the EU (34).

While for certain types of medicinal products in life-threatening diseases, considerations for application of a life cycle approach are made, this is typically not the case for allergen products. In
such lifecycle approaches, a product will be granted market access based on a reduced set of data available and will be assessed for its benefit-risk balance on an on-going basis post-marketing (35). Similar approaches are being applied in different parts of the world (36), 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 (37). Also, PRIME (38)(derived from priority medicines) has been founded to support in the development of medicines aiming 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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Figure 1: Simplified flowchart of the marketing authorisation procedures in the European Union. For reasons of clarity, some details of the procedures have been omitted in the figure, e.g. timetables for each procedure are differing.
Table 1: Medicinal products to be authorized by the centralized procedure according to [Ref]

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<td>• neurogenerative diseases</td>
</tr>
<tr>
<td>• auto-immune diseases and other immune dysfunctions</td>
</tr>
<tr>
<td>• viral diseases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicines derived from biotechnology processes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Advanced-therapy medicines</th>
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<table>
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<tr>
<th>Orphan medicines</th>
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<tr>
<th>Optional for other medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• containing new active substances</td>
</tr>
<tr>
<td>• that are a significant therapeutic, scientific or technical innovation</td>
</tr>
<tr>
<td>• whose authorisation would be in the interest of public health at EU level</td>
</tr>
</tbody>
</table>
Table 2: Overview on responses of NCAs to selected questions of the questionnaire

<table>
<thead>
<tr>
<th>Requirement for a MA for allergen products</th>
<th>Stage of the production process to be authorized</th>
<th>Named Patient Products marketed</th>
<th>Import of allergen products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia</strong></td>
<td>MA required</td>
<td>Finished Product</td>
<td>If a specific allergen product is not approved in Australia, a prescribing physician may request it for use in an individual named patient under the Special Access Scheme.</td>
</tr>
<tr>
<td><strong>Switzerland</strong></td>
<td>MA required</td>
<td>Formula magistralis Medicinal Products corresponding to NPP</td>
<td>Patients and health professionals are allowed to import medicinal products authorized in a third country by specific rules. This is only possible, when there is no authorized product available in Switzerland. This is not applicable for NPPs.</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>MA required</td>
<td>Finished Product</td>
<td>All products sold in Canada must be authorized for sale in Canada by Health Canada.</td>
</tr>
<tr>
<td><strong>Russia</strong></td>
<td>MA required</td>
<td>Finished Product</td>
<td>Only those therapeutic allergens that have been authorized in Russia are allowed to be imported.</td>
</tr>
<tr>
<td><strong>Japan</strong></td>
<td>MA required</td>
<td>Finished Product</td>
<td>Based on the responsibility of the physician, products may be imported from other countries. Such products are exempt from Relief System for Suffers from Adverse Drug Reactions in Japan.</td>
</tr>
</tbody>
</table>
## Supplementary table 1: Main tasks, composition and legal basis of major committees involved in regulatory procedures in the EU – CHMP and CMDh

<table>
<thead>
<tr>
<th>Committee</th>
<th>Committee for Medicinal Products for Human Use (CHMP)</th>
<th>Co-ordination group for Mutual recognition and Decentralized procedures (CMDh)</th>
</tr>
</thead>
</table>
| **Main Tasks** | • Preparing EMA's opinions on medicines for human use in the centralized procedure and post-authorisation procedures (e.g. variations) to an existing marketing authorisation  
• Arbitration in Mutual Recognition and Decentralized Procedures in cases of disagreement between Member States  
• Execution of referrals initiated in relation to the protection of public health or where Community interests are concerned | • Arbitration in Mutual Recognition and Decentralized Procedures in cases of disagreement between Member States  
• Examination of questions related to marketing authorisations in two or more Member States, including new applications, variations, renewals and pharmacovigilance activities  
• Provide recommendations on the classification of unforeseen variations  
• Support worksharing between Member States |
| **Composition** | • One member and an alternate nominated by each of the 28 Member States as well as Iceland and Norway  
• Up to five co-opted members (experts chosen by Members States or EMA) to provide additional expertise in particular scientific fields | • One representative per Member State and Norway, Iceland and Liechtenstein  
• Member States may appoint an alternate to the CMDh member  
• The European Commission participates on a regular basis as an observer. |
**Supplementary table 2: Main tasks, composition and legal basis of major committees involved in regulatory procedures in the EU – PRAC and PDCO**

<table>
<thead>
<tr>
<th>Committee</th>
<th>Pharmacovigilance Risk Assessment Committee (PRAC)</th>
<th>Paediatric Committee (PDCO)</th>
</tr>
</thead>
</table>
| **Main Tasks** | • Providing recommendations to the CHMP and the CMDh on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems  
• Monitoring the effectiveness of those risk management systems  
• The detection, assessment, minimisation and communication relating to the risk of adverse reactions | • Assess the content of paediatric investigation plans (PIPs) and adopt opinions on them including the assessment of applications for a full or partial waiver and assessment of applications for deferrals  
• Assessing data generated in accordance with agreed PIPs  
• Adopting opinions on the quality, safety or efficacy of a medicine for use in the paediatric population, at the request of the CHMP or a medicines regulatory authority in the EU  
• Providing advice on questions on paediatric medicines, at the request of the Agency’s Executive Director or the European Commission |
| **Composition** | • A chair and a vice chair, elected by serving PRAC members;  
• One member and an alternate nominated by each of the 28 Member States as well as Iceland and Norway  
• Six independent scientific experts nominated by the European Commission  
• One member and an alternate representing healthcare professionals  
• One member and one alternate representing patients associations | • Five members of the CHMP, with their alternates. These members are appointed by the CHMP itself  
• One member and one alternate appointed by each EU Member State that is not represented by the members appointed by the CHMP  
• Three members and alternates representing healthcare professionals  
• Three members and alternates representing patient associations |
Online supplement

Supplementary information on country-specific regulatory approaches for allergen products in the EU

Germany

Allergen products for in vivo diagnosis and therapy are subject to a marketing authorization in Germany. However, there are exemptions from this demand for NPP. In 2005, due to changes in the German Medicinal Products Act (Arzneimittelgesetz) which would have resulted in the obligation for all NPP to obtain a marketing authorization, Germany introduced an exemption for NPP used for therapeutic purposes. As a result of this, therapy allergens manufactured for an individual patient on the basis of an individual prescription were, as was the case before, not required to obtain a marketing authorization. Allergens for therapy are thereby allowed to be placed on the market as NPP on the basis of an individual prescription. This is independent of the co-existence of already authorized products from the same allergenic source. While such NPP are not authorized and are therefore not assessed for their benefit-risk balance, manufacturers of NPP do need to follow specific regulation in terms of manufacturing, e.g. there is a requirement for a manufacturing license and production under Good Manufacturing Practice (GMP). Nevertheless, NPP are not further supervised by the authorities and thus there is no list of marketed NPPs and no information on their market share. However, since 2008 a national regulation (Therapy Allergen Ordinance (TAO)) is in force for all therapy allergens distributed as NPP that are intended to treat the most prevalent allergies (caused by grass pollen (Poaceae), tree pollen (birch, alder, hazel), house dust mites (Dermatophagoides sp.), bee and wasp venom) (1, 2). For such products, a marketing authorization is mandatory without any exemption. For NPPs already marketed before the regulation came into effect there is a transition procedure. They are still allowed to be distributed whilst in a marketing authorization application procedure, in which the quality, safety and efficacy is assessed for each product. Taking into account the data available for the concerned products when the TAO came into force, prolonged transition periods allowing for the conduct of clinical trials are in place, thus allowing the compilation of a full dossier according to the current state-of-the-art to evaluate efficacy
and safety. The implementation of the TAO has resulted in the removal from the market of more than 6400 NPP, for most of which there were no clinical data available. Furthermore, there were a considerable number of products where the reasoning behind the composition was very questionable and was not in line with the recommendations of the medical societies (3), as, for example, seasonal and perennial allergens were combined in a single product.

As allergens for diagnosis are usually produced industrially and supplied in multi-use vials for several patients, allergens for diagnosis require a marketing authorization and cannot be placed on the market as NPP. Requirements for content and the evaluation of the marketing authorization application are very similar to therapeutic allergen products. For new products, full dossiers according to the current state-of-the-art have to be submitted. For established substances, a procedure according to Article 10a of the Directive EC/2001/83 (well-established use) may be applicable (case-by-case decision).

Furthermore, whereas allergens for diagnosis may be manufactured in pharmacies without a marketing authorisation under certain conditions, this is not allowed for allergen products for therapy.

According to the German Medicinal Products Act, allergen products (including test and therapy allergens) under the premises of the TAO or having a marketing authorisation are subject to official batch release by the Paul-Ehrlich-Institute. Therefore, a respective batch may only be placed on the market if it is shown that the batch has been manufactured and tested according to the prevailing standard of scientific knowledge.

**Italy**

In Italy allergen products have been and are largely marketed under the NPP provision, upon request by physicians. These are medicinal products supplied in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for
use by his individual patients. In parallel, as an outcome of classical assessment process with regards
to MRP or DCP (see above), at least three products have been authorized and are marketed.
Manufacturers of allergen preparations in Italy are currently inspected for GMP compliance by the
Italian Medicines Agency (AIFA).

Similarly to other European Member States, in Italy the adoption of Directive 89/342/EEC (4) in 1991
into national law (Decree 13 December 1991 (5)) implied that any allergen product had to comply
with the requirements of the European pharmaceutical legislation. At that time, manufactures were
requested to file a list of existing products according to a number of “families” or “groups” such as
food, pollens of various origin, mites, molds, insects, epithelia and venoms which were identified on
the basis of a “grouping” (not taxonomic) approach with the addition of a few more categories such
as bacteria extracts and chemical preparations (for patch tests). For each applicant the list had to be
integrated with representative dossiers for several allergens for each of the families/groups
mentioned above. For these existing products a transitional period was allowed, provided an
application had been received by the end of April, 1992. More recently the manufacturers were
requested to file a full updated quality section of the dossier concerning the drug substance of
several allergens. According to a specific timeline defined by the Italian Medicines Agency,
manufactures had to submit afterwards a comprehensive set of dossier dealing with quality aspects
but limited to the Drug Substance part. In summary, more than 250 dossiers were scrutinized and
the assessment process confirmed a general overall improvement of the information provided at the
end of the questions and answers steps that were part of the assessment process. Further steps of
the process moving onwards from the evaluation of the drug substance aspects of the dossiers are
currently in progress. For this, decisions on the timeline and the procedure for handling the
assessment of the drug product aspects of the dossiers will be taken by the Italian Medicines Agency
after the conclusion of the assessment step involving the respective drug substances.

There is no batch release requirement for allergen products on the Italian market.
**The Netherlands**

**Brief history**

Before 1993, allergen diagnostics and therapeutics in the Netherlands were not regulated as medicinal products. The adoption of Directive 89/342/EEC (4) in 1992 implied that any allergen product was now subject to the requirements of European pharmaceutical legislation. From December 1992 this was also applied to allergen products already existing on the market in The Netherlands. As a result, all industrially produced immunotherapeutic and diagnostic allergen products needed to be registered as medicinal products based on a full dossier, including quality, non-clinical and clinical information. For the existing products a transitional period was allowed, provided an application had been received by December 1993. In this period the marketing authorisation holder could provide the complete dossier, develop all required analytical methods and especially obtain the required clinical efficacy evidence. The product could be marketed until authorities had irrevocably decided about the MAA (Marketing Authorization Application).

For the majority of the existing products a MAA was received. MAA was generally only sought for the main indications (grass and tree pollens, house dust mite, bee/wasp venom and cat epithelia). By 2003, 10 allergen products had been approved, several rejected and for three products the applications were still pending. Of the latter, one product was eventually approved while the other two were rejected.

**Current regulatory situation**

Currently, the following allergen therapeutics (SCIT) are available as registered medicinal products in the Netherlands: Grass pollen extracts, Tree pollen extracts (*Alnus, Betula, Corylus*), House dust mite extract, Cat epithelia, Hymenoptera Venom (*Vespula and Apis*). All of these were registered following a national MAA procedure of products that were already on the market before 1993. In addition two SLIT grass allergen products have been registered, as new applications received after 2003 (via
Mutual Recognition Procedure). For many other indications (e.g. weed pollen, fungi or horse/dog epithelia allergies) allergen therapeutics are available as Named-Patient Products.

There is no batch release requirement for allergen products on the Dutch market.

Named-Patient Products (NPP)

Directive 89/341/EEC (6) also lays down exemptions from the general requirements of the EEC pharmaceutical legislation. It is under these exemptions (Article 1, par. 4) that the so-called NPP are regulated. These are medicinal products supplied: “ ......in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility ('named patient exemption').”

The current legislation in the Netherlands allows dispensing of non-licensed medicinal products (so-called Named Patient products) only under strict regulation (article 3.17 of the Dutch Regulation medicinal product act.; (7)) meeting several conditions:

1) The doctor has to consider it necessary to treat the patient with that preparation,

2) There is no registered adequate alternative available

3) The doctor should apply in writing to the manufacturer/pharmacist separately for each patient

4) The manufacturer must provide each application to the Dutch Health Care Inspectorate

5) The Inspectorate determines the amount and period it can be given for

6) The manufacturer/pharmacist has to record the number of patients, amount of medicine supplied and adverse events.

The regulation of NPP is under the responsibility of the Dutch Health Care Inspectorate. The Inspectorate has clear instructions concerning all conditions for use of non-registered (allergen) products on her website (8). These include that for each patient a doctor’s declaration is required
and that these are only valid for one year to allow regular evaluation. Furthermore, the manufacturers, wholesalers and pharmacists that have a permission for NPP need to provide an annual overview of the number of patients treated with these. If this number is too large a registration with the MEB or EMA is expected, as the article 3.17 (NPP) regulation is not intended to evade the obligatory Marketing Authorization. In 2009 the inspectorate decided that non-registered allergen therapeutics could only be used in exceptional cases (9). From 2014 the regulation with respect to the dispensing of non-registered allergen products is further enforced (10).

It is noted that the Dutch market for allergen extracts decreased about 30% between 2009 and 2013 (from 50 Million Euro to around 32 million Euro with a similar development in prescriptions) (11). At the same time, the market share of NPP dropped from around 80% to around 52% in 2013. Based on condition 2 of article 3.17 the use of NPP would be limited to allergens for which no registered adequate alternative is available (around 1-2% of total use of allergen therapeutics). Considering this, it is expected that the use of NPP will further decrease and be limited to small categories of patients. Just as for registered allergen products, there is no batch release requirement for NPP allergen products on the Dutch market.

Spain

In Spain, allergen products for both in vivo diagnostics and immunotherapy have been traditionally placed on the market as NPP. Thus, apart from the few products registered by the Decentralized or the Mutual Recognition Procedures, the majority are in use today without any previous marketing authorization and as such, without any regulatory assessment of their quality, safety and efficacy, irrespective of whether they are manufactured by an industrial process or not. Manufacturers are required to hold a manufacturing license and to comply with the GMP guidelines. However, given that a very important aspect of GMP inspections is to make sure that the products are manufactured
According to the approved specifications, assurance of full GMP compliance is difficult in the absence of previous quality assessment.

Consequently, a proposal to regulate allergen products already on the market has been drafted in Spain, which is still pending publication. The proposal has established specific regulatory routes for the different types of products, summarized as follows:

1) Allergens for in vivo diagnostic: in general, most of these products are industrially-manufactured and as such, submission of a full dossier will be expected. After assessment, successful products will receive a full marketing authorization.

2) For specific immunotherapy products, several scenarios are envisaged:

- **bona fide** named-patient products will not need to present a Marketing Authorization Application (MAA), but a communication to the national Competent Authority (AEMPS) before manufacturing may be required. For these products, information on manufacturing history, number of units, etc. should be kept ready for inspection for a specified time;

- specific mixtures for individual patients, prepared from industrially manufactured bulks. In this case, mixtures will only be possible from previously authorized bulks. Authorization of bulks will only be possible after assessment of the relevant quality information. It is intended that the authorization includes those mixtures in which the bulk can be used, hence restricting the mixtures to those previously authorized. Final mixtures prepared on a named-patient basis will be subject to similar requirements than those on the previous point;

- industrially-manufactured finished products will require submission of a full dossier for assessment. The amount of clinical data required for authorization will be determined on a case by case basis.

Finally, a very important aspect of this proposal is that both bulks and allergens for *in vivo* diagnostics will benefit from a highly reduced tax. This was prompted by the restricted market for many of the *in
vivo diagnostic products, which would not make feasible their registration at full tax. Implementation of official batch release is not planned initially, but it cannot be ruled out for the future.

Once the regulation comes into force, no product other than the real NPPs will be expected to be on the market without previous authorization.

Additional approaches in the EU

There are numerous additional approaches by the EU member states. For example, in France, a national decree (12) was implemented in 2004 that resulted in the selection of clinically relevant allergen sources based on published evidence in relation to data available on AIT efficacy for these allergen sources. Only products that contained allergen from these sources were allowed to be placed on the market based on the exemptions allowed by Art. 5 of Directive 2001/83/EC. The appropriate pharmaceutical quality must still be secured for these products.

References

3. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo journal international 2014;23:282-319.


