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In-vivo diagnostic test allergens in Europe: A call to action and proposal for recovery plan—An EAACI position paper

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Abbreviations: AIT, allergen immunotherapy; CMDh, Coordinating group for Mutual recognition and Decentralized procedures-human; COMP, Committee for Orphan Medicinal Products; DA, diagnostic allergen; DCP, decentralized procedure; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; EPT, epicutaneous patch test; EU, European Union; GMP, Good Manufacturing Practice; ICH, International Council of Harmonization; MRP, Mutual Recognition Procedure; MS, Member State; NPP, Named Patient Product; PEI, Paul-Ehrlich-Institut; PSUR, Periodic Safety Update Report; SPT, skin prick test.

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Abstract

Diagnostic allergens are defined as medicinal products in the EU. Marketing authorization by national authorities is necessary; however, diagnostic allergens are not homogeneously regulated in different EU member states. Allergen manufacturers argue with increasing costs forcing them to continuously reduce the diagnostic allergen portfolios offered to allergists. In contrast, EAACI and national European Allergy Societies see the need for the availability of a wide range of high-quality diagnostic allergens for in vivo diagnosis of IgE-mediated allergies not only covering predominant but also less frequent allergen sources. In a recent EAACI task force survey, the current practice of allergy diagnosis was shown to rely on skin tests as first option in almost 2/3 of all types of allergic diseases and in 90% regarding respiratory allergies.

With the need to ensure the availability of high-quality diagnostic allergens in the EU, an action plan has been set up by EAACI to analyse the current regulatory demands in EU member states and to define possible solutions stated in this document: (a) simplification of authorization for diagnostic allergens; (b) specific regulation of special types of diagnostic allergens; (c) new models beyond the current model of homologous groups; (d) simplification of pharmacovigilance reporting; (e) reduction of regulation fees for diagnostic allergens; (f) reimbursement for diagnostic allergens.

Joining forces of allergists, manufacturers and authorities are of high importance to ensure remaining relevant allergens in the EU markets to facilitate a sustainable and comprehensive service for the diagnosis and treatment of allergic diseases.

KEYWORDS

allergen provocation test, European Pharmacopoeia, marketing authorization, regulatory framework, skin prick test, skin test allergens

1 | INTRODUCTION

Skin prick test (SPT) and epicutaneous patch test (EPT) are the most common in vivo methods to diagnose IgE and cellular-mediated allergic reactions in patients with rhinoconjunctivitis, asthma, insect allergy, eczema and other allergic diseases.[1-3] SPT and EPT provide evidence for sensitization and help to confirm the diagnosis of a suspected type I or type IV allergy.[1,2] Intradermal (intracutaneous: ID) tests have similar indications like SPT and follow the same regulatory framework in the EU. Since ID is not as frequently used as SPT, SPT will be used in this position paper as an example for different skin test procedures.

Early diagnosis of allergic diseases is necessary for early treatment to avoid illness progression and unfavourable outcome.[4]

Diagnostic allergens (DAs) contain the specific target antigens causing the allergic reaction and are therefore needed to perform such tests. Skin prick test is regarded to be the primary diagnostic tool to detect type I hypersensitivity reactions as it is minimally invasive, well reproducible, cost-effective and results are immediately available.[1,5-7] In a large multicentre, GA2LEN study in 14 countries a standard protocol and allergen panel for SPT have been established.[6,8]

Skin prick test interpretation utilizes the presence and degree of cutaneous reactivity as a surrogate marker for sensitization within target organs, that is, eyes, nose, lung, gut and skin. Several different allergens can be tested simultaneously because the resulting reaction to a specific allergen is localized to the immediate area of the SPT. Moreover, skin tests are still the first or second option in detecting allergic sensitizations in almost all type I allergic diseases and have been supported by a European Academy of Allergy and Clinical Immunology (EAACI) task force survey investigating the current practice of allergy diagnosis in Europe.[9] Here, the National Allergy Societies in Europe report that diagnoses rely on skin tests as first option in almost 2/3 of all types of allergic diseases and in 90% with regard to respiratory allergies.[9]

Provocation tests such as conjunctival, nasal or bronchial challenges can be used in addition to confirm allergy diagnosis. They provide information on the clinical relevance by provoking a reaction of the target organ to a suspected allergen and as such also require available standardized DAs.[10,11] Similar information is, in most instances, not attainable by any other in vivo or in vitro test.

Regardless of this broad acceptance of skin tests, the quantity of commercially available skin test DAs has been tremendously reduced in European countries since 2004.[12-14]

For example, in the German Paul-Ehrlich-Institut (PEI) database, a total of 1014 marketing authorizations (~52% of available products) for test allergens (744 biological Type I, 270 epicutaneous Type IV) have been lost from beginning 2010 until 05/2019. At the time given (status May 2019), there are 918 (547 biological Type I, 371 epicutaneous Type IV) licensed/marketable test allergens that are allowed to be distributed in Germany; however, it is not known, to which extent these are actually available on the market as some are not required to obtain official batch release by PEI.

This reduction may be due to the fact that the costs for biological standardization, and clinical documentation, and initiation and maintenance of DA-authorizations far exceed their related revenues, forcing manufacturers to significantly limit their allergen portfolios taking out of the market rarely used DAs for economic reasons.[12,15]

Allergen manufacturers argue that offering a comprehensive panel of DAs may be economically disastrous, since most of the costs are fixed and identical for frequently and rarely used DAs, making the latter unequivocally more expensive.[12,13]

2 | REGULATORY FRAMEWORK FOR ALLERGEN PRODUCTS IN EUROPE

In the European Union (EU), allergen extracts used for diagnostic tests (DAs) or therapy have been defined as medicinal products by EU-Directives 89/342/EEC and 2001/83 EC.[16-18]

As such, DAs that are to be used in the EU and are produced by an industrial process are required to obtain a marketing authorization in EU member states. For this, the documentation to be provided by the applicant has to follow the European Pharmacopoeia as well as specific guidelines that represent the current state-of-the-art, such as guidelines developed by committees of the European Medicines Agency (EMA) or the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use.[18-26]

For allergen products, the Guideline on Allergen Products: Production and Quality Issues is of outstanding importance.[19] DAs are medicinal products as they are used to diagnose a medical condition as defined in directive 89/342/EC: "…any substance that is used or administered to human beings […] to making a medical diagnosis".[16] DAs therefore need a marketing authorization, as "no medicinal product may be placed on the market of a Member State (MS) unless a Marketing Authorization (MA) has been issued by the competent authority of that MS" (Art. 6 of[18]).

Exceptions are foreseen for "Named Patient Products" (NPPs) (Art. 5 of [18]) that are confectioned at a physician's request upon prescription for an individual patient. Diagnostic allergens are usually produced and packed in advance and are not specifically made for individual patients on the basis of a physician's prescription; moreover, DA production usually involves industrial steps or is fully industrial and DAs are commonly distributed in multi-dose containers to be used in multiple patients which contradicts the manufacturing of these products as NPPs for individual patients.

Currently, European legal and regulatory framework for medicines is applied by the EU member states heterogeneously to test and therapy allergens: While some member states have largely implemented the need for marketing authorization in DAs, others largely make exceptions (according to Art. 5 of[18]) or allow long transition periods.

This diversity is even more pronounced when looking from a global perspective.[27] The Coordination group for Mutual recognition and Decentralized procedures-human (CMDh) plays a fundamental role with respect to procedural issues in the European Union, including marketing authorization procedures in two or more EU Member States. The CMDh recently published[28] a draft guideline for public consultation to support the harmonization of regulatory approaches on allergen products.[29]

A detailed description and flow chart with the Regulatory framework for Allergen products in Europe have been recently given in.[30]

2.1 | New marketing authorizations for DAs

A DA can obtain marketing authorization via different routes, including procedures concerning only single EU states or procedures resulting in authorizations in several Member States at once. For further information on the respective procedures, reference to Bonertz 2018[30] is made.

Fees applicable in such procedures may also be problematic. In a MRP/DCP, national fees for each involved member state vary from ca. € 712.- to € 55.000.- in different EU states (personal communication from Pharmaceutical Industry, data not fully validated by the authors).

These fees rapidly add up to enormous sums if a wide portfolio of different DAs is registered, thereby strongly limiting companies' commitment to bring DAs to the market. Germany has responded to this situation by reducing the fees for all official acts related to DA directed against rare allergens to one quarter of the previously applicable fee.[31]

In all procedures, clinical trials are needed to demonstrate safety, sensitivity and specificity of the DA.[9] Such studies are of particular importance for allergologists and patients; however, they are time-consuming (planning, implementation and evaluation take up to 2 years) and in a representative setting cost of appr. €1.5 million has been calculated for a single DA.[12]

Based on Good Manufacturing Practice (GMP) (Chapter 6 of the EU GMP guidelines) development of quality assurance methods and stability studies need to be presented in the dossiers with the initial marketing authorization application and require high costs for personnel that is needed to write reports, dossiers etc.[12]

2.2 | Existing marketing authorizations

In some EU countries, DAs have been on the market for a long time with marketing authorization dossiers that were compiled based on quality, safety and efficacy requirements that would not be considered to be state-of-the-art, today.[18-24] However, manufacturing and test methods have been developed and refined over years to yield a product of constant quality. Marketing authorization dossiers need to be kept up to date and, with respect to the quality documentation, need to reflect the state of science in order to stay valid and to market a safe and well-controlled product.

The entire approval documentation must permanently be kept up to date in every member state in which the DA is authorized inducing costs (primarily for personnel) in the range of a six-figure Euro sum per year for a SPT portfolio according to GA2LEN.[8,12,13] Moreover, Periodic Safety Update Reports (PSUR) have to be submitted to the national authorities every 6 months during the first 2 years after approval for a DA, every 12 months in years 3 and 4 of the approval, and every 3 years after that. Periodic safety update reports report adverse events from routine use in the market, clinical trials and publications, allowing the authority to evaluate the risk-benefit potential. Depending on the complexity and amount of data, personnel costs of creating a PSUR can be calculated with ca. €10.000.[12]

Additional processing costs of PSURs by national and European authorities have to be calculated,[12] as well as costs for entering products into the EMA database according to Article 57 §2 of regulation 726/2004.

Stability studies according to GMP must include the continuous control of all relevant quality parameters (e.g. determination of protein content or protein profile or allergenic potency) of a DA product over the time of use of the delivered DA (separately for each different skin and provocation test material).

The main requirements for the pharmaceutical quality of allergen products are stipulated in the European Pharmacopoeia[24] and defined in the "Guideline on Allergen Products: Production and Quality Issues".[19] Both documents reflect the fact that allergen products are produced from biological sources and therefore exhibit a natural variance for parameters such as major allergen content or biological potency. In addition, the guidelines on GMP and Good Distribution Practice were updated and there are new requirements regarding the pharmacovigilance legislation for medicinal products that manufacturers of allergen products have to meet now.

The "Pharmapackage" passed in 2014 is based on Directive 2010/84/EU[32] and contains requirements to protect medicines against counterfeiting. It took pharmacovigilance and safety reporting to a new level. The directive and the regulation (EU) 1235/2010[33] were followed by the commission implementation of regulation EU/520/2012,[34] which stipulates how these requirements have to be implemented, especially regarding the reporting and evaluation of adverse events and the implementation of a pharmacovigilance system.

Furthermore, as most allergen products are authorized nationally and national requirements within the EU member states are still diverging, the paperwork for marketing authorizations in the different countries has to be adapted, a costly and time-consuming process.

Homologous groups formation within the abundance of allergen sources may bring more DAs to authorization with reasonable costs.[21-23] Using this method, one member of the homologous group is selected as the representative species. This choice should be justified considering geographical differences in sensitization patterns and other relevant factors. To a limited extent, data on quality, safety and efficacy can be extrapolated from the representative source to other members of the homologous group.[21-23] Detailed safety studies are only requested for the representative allergen, while post-marketing safety reports are requested for non-representative allergens of the same group.[21-23]

3 | RARE ALLERGIES

Per definition, in the EU a disorder is defined as a "Rare Disease" (also referred to as Orphan Disease) when it affects <1 in 2000 citizens (www.eurordis.org). While an individual disease might be labelled as

"rare," the total number of persons in Europe suffering from one of the over 6000 different identified rare diseases is estimated at over 30 million—thus rare disease patients comprise 6% to 8% of the EU population (www.eurordis.org).

"Rare Diseases are rare, but Rare Disease patients are numerous" (www.orpha.net).

The "Orphan Designation" is conferred by the "Committee for Orphan Medicinal Products" being part of the EMA.

It is linked to a legal procedure that allows for the designation of a medicinal substance with therapeutic potential for a Rare Disease, before its first administration in humans or during its clinical development (www.orpha.net). The exact therapeutic indication is then defined at the time of marketing authorization. This procedure has been established in Europe by the Regulation (EC) No 141/2000 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF).

In this paper, rare allergens are defined as allergens from an allergen source recognized by only moderate to low-sized patient populations. Although allergies to "rare allergens" do not fall under the orphan disease definition of the Committee for Orphan Medicinal Products of the EMA, in allergology the challenges for patients suffering from type I allergies to rare allergens (eg occupational allergens)—hereinafter referred to as "rare allergies"—are similar to the above-mentioned Rare Diseases. While allergies in general are very common, some allergen-specific reactions affect <1 in 100 000 citizens in the EU.[35] In contrast to other diseases, each allergen-specific reaction requires its individual medicinal product (DA) for in vivo diagnosis as well as for allergen immunotherapy (AIT). This makes different rare allergies individual disease entities.[35]

However, orphan drugs always require a centralized European marketing authorization.

The Committee for Medicinal Products for Human Use (CHMP) has recognized the difficulties observed for DAs and therapy allergens in rare allergic diseases and the Rheumatology and Immunology Working Party (a subgroup of CHMP) has drafted a concept paper on a guideline for allergen products development in moderate to low-sized study populations. A guideline to be followed to this concept paper aims to provide adequate and feasible guidance on developmental requirements concerning clinical and quality aspects for allergen products directed at rare allergies. At the writing of this manuscript, this concept paper is in public consultation on the EMA website.[36]

4 | DISCUSSION OF THE EAACI TASK FORCE MEMBERS

In a recent survey of EAACI, the National Allergy Societies of Europe declared the lack of DAs a serious threat to current clinical practice.[9] Skin tests were shown to be the mainstay diagnostic procedure for the majority of allergic diseases and are used as first approach in 90% of patients with suspected inhalant allergies (asthma and rhinitis): organ-specific allergen challenges are regarded to be an important part of the diagnostic work-up.[9]

The below listed recommendations given by this EAACI task force would facilitate better diagnosis and management of allergic diseases in European citizens.

If no changes will be implemented, allergen manufacturers may further streamline their portfolios and delete remaining DAs, so that many rare DAs may no longer be available leading to a dramatic deterioration in allergy diagnosis. Since most of the expenditure for getting and maintaining an authorization is based on a fixed cost independent on the amount of a DA sold, realistic calculations estimate that prices for rarely used in vivo allergen products will increase 20-50 times higher than the prices of frequently used DAs.[12] In consequence, they will be used even less and may eventually as a result of demand and supply no longer be commercially available. In addition, it might be more attractive for manufacturers to acquire MAs for a broader range of DAs in large member states than in smaller EU countries, and the differences in costs for approval across EU member states may lead to the availability of a special DA in one country with its absence in another.

For those DAs remaining, there is cause for concerns that not all in vivo test options like skin prick and intracutaneous tests, conjunctival, nasal and bronchial provocation tests[10,11] will be kept on the market, which is already a problem in several EU member states. Significant price increases are anticipated for the less frequently used provocation test DAs. These price increases would most likely not be covered by current reimbursement leading to the disappearance of these products from the market.

If standardized commercial DA products are missing, physicians may be forced to use non-standardized allergens from naturally available sources (native materials) manufactured for individual patients and applied under their personal responsibility.[37] This completely contradicts the undisputed medical need for medicinal products of proven quality, safety and efficacy and may throw in vivo allergy diagnosis back a century towards the beginning of modern allergology. Furthermore, this approach would impose responsibility for the use of such unregulated material solely to the attending physician. The time-consuming and staff-intensive preparation of non-standardized test allergens under the supervision of the physician him/herself and feared liability issues may lead allergologists to restrain from testing these rare allergens, resulting in underdiagnosis of allergic diseases.[37]

In vitro allergy diagnostics such as serum-specific IgE and basophil activation testing can significantly contribute to the diagnostic information.[38] However, in vitro assays cannot completely substitute the information given by in vivo tests, for example when these are used for allergen-specific changes in the nose or lungs (provocation tests), and therefore remain essential tools in the diagnostic work-up of the allergic patient. In addition, in vitro allergen measures may not be plausible in many instances due to higher costs, both in public health services and in private practice.[9,12]

Diagnostic allergens have to fulfil similar criteria to receive and keep a marketing authorization as mass-market products such as

pain or blood pressure drugs. While the return of investment for developing a mass-market product can be effectively spread across high quantities of sold drugs, DAs are often produced in very low quantities. In less frequent allergies relevant in specific target groups (eg reactive to occupational allergens), only very low numbers of DA packages are sold per batch. Moreover, in rare allergies, clinical study populations are small and may not be sufficient for even one single phase III-study and accepted animal models are missing. It may be argued that not every rare DA is needed; however, it may have serious consequences for an individual patient, for example if an occupational allergy is not properly diagnosed.

Especially niche products for rare DAs would benefit from a harmonized European regulatory environment which takes into account that many of these products are legacy products but have been of consistent quality for many years offering their diagnostic value. EAACI has noted respective CMDh activities and will support such activities that are developing strategies to harmonize the regulatory situation for rare allergen products.

Allergologists, manufacturers and authorities should join forces to make sure that relevant diagnostics stay on the EU markets to ensure a sustainable comprehensive service for the diagnosis and treatment of allergic diseases.

While primarily discussing the situation of DAs in this statement, similar measures may be required for the treatment of rare allergies by allergen-specific immunotherapy.

5 | CONCLUSIONS AND REQUESTS OF THE EAACI TASK FORCE MEMBERS

According to a recent EAACI task force report, the availability of a wide range of high-quality DAs for in vivo diagnoses of IgE-mediated allergies in Europe is of utmost importance for a comprehensive diagnostic approach.[9] The EAACI is representing allergists in Europe and advises the European Commission to initiate measures to ensure adequate diagnosis and treatment of this chronic disease.

The EAACI Task Force Members believe that the following recommendations would improve the situation for in vivo allergy testing:

1. *Simplification of authorization for DAs:* Consideration should be given to develop a special procedure allowing registration of DAs based on a limited set of data (eg by providing a quality dossier and limited clinical data) in contrast to current national, Decentralized (DCP) or Mutual Recognition Procedures (MRP) for full authorizations.
2. *Regulation of special types of DAs:* Data requirements for specific types of allergen products (eg a defined set of DAs for the diagnosis of rare allergies) should be harmonized and legally binding by amending Annex I of Directive 2001/83/EC.

In general, marketing authorization procedures should consider the frequency of the respective allergy (staggered requirements) and clarify whether or not additional guidance is applicable e.g. Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev 1). Requirements in existing guidelines do not reflect realistic possibilities for data generation in rare allergies, where data from small study populations should be considered adequate. The EMA-Committee for Orphan Medicinal Products (COMP) is asked to clarify under which conditions rare allergies (eg allergies to natural rubber latex, wood dusts, etc) are considered to receive an orphan medicine designation.

3. *Homologous groups principle:* The "homologous groups principle" is successfully applied in the regulation of common allergies but most of the rare allergies are not covered by this principle making extrapolation of data impossible for such DAs. It should be considered to develop models beyond the current model of homologous groups to allow extrapolation of some data (quality, non-clinic, clinic) for specific groups of rare DAs.
4. *Pharmacovigilance reporting:* Since DAs have been proven to be exceptionally safe,[39] it appears adequate to reevaluate the requirements on pharmacovigilance reporting for these products. Widening intervals for PSUR reporting is considered to be appropriate and grouping of several DAs according to (3) into single PSURs would greatly reduce the expenses without lowering the safety monitoring for these products.
5. *Fees:* It is acknowledged that fees applicable for national marketing authorization procedures, MRP, DCP and post-marketing procedures are in the competence of the individual EU Member States. However, these fees impede market access for new DAs on a European level. Fee reductions for DAs, especially for products to diagnose rare allergies, may help to maintain these on the market.
6. *Reimbursement:* It is acknowledged that reimbursement of DAs differs between the different European Health Care Systems. Lack of reimbursement is a major obstacle for the development of new as well as the maintenance of established DAs. Therefore, we encourage those organizations responsible for Health Technology Assessment and reimbursement to review and adequately adjust reimbursement considering the medical as well as socio-economic value of DAs.

CONFLICTS OF INTEREST

Dr. Klimek reports grants and personal fees from Allergopharma, grants and personal fees from MEDA/Mylan, personal fees from HAL Allergie, grants from ALK Abelló, grants and personal fees from LETI Pharma, grants from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeut., grants from AstraZeneca, grants from GSK, grants from Inmunotk, outside the submitted work; and Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV GPA, EAACI. Dr. Demoly reports personal fees from

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DISCLAIMER

The views expressed in this position paper 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.

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