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Current practice of allergy diagnosis and the potential impact of regulation in Europe

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Abstract

In the European Union (EU), the regulatory framework regarding diagnostic allergen extracts is currently in the process of being implemented at the national level. Due to these regulations, the initial and periodic renewal expenses for the registration of diagnostic allergen extracts may render extract production unprofitable. Consequently, many extracts may be at risk of removal from the market. The current survey, which was conducted by a task force of the European Academy of Allergy and Clinical Immunology, aimed to assess the current practice of allergy diagnosis in Europe. This survey revealed that skin tests continue to be the main diagnostic procedure and are used as the first option in almost two-third of all types of allergic diseases and in 90% of individuals suffering from respiratory allergies. Therefore, there is a need to ensure the availability of high-quality allergen extracts to maintain the common diagnostic procedures used by EU professionals. To reach this goal, it is necessary to align efforts and establish active partnerships between manufacturers, relevant scientific societies, consumer organizations and authorities to maintain the availability of these diagnostic tools.

KEYWORDS
allergen extracts, allergy diagnosis, regulation, skin tests

1 | INTRODUCTION

The foundations of allergy diagnosis are threefold: a detailed clinical history, assessment of immunoglobulin E (IgE) sensitization and, in

Abbreviations: EAACI, European Academy of Allergy; EU, European Union; IgE, immunoglobulin E; PSURs, Periodic Safety Update Reports; SPT, skin prick test; TA, test allergen.

some instances, confirmation of the relevance of sensitization by shock organ challenge tests.

To assess allergen sensitization, allergists rely on two-first -line techniques: skin tests (mainly the skin prick test, SPT) and serum allergen-specific IgE tests (sIgE)[1,2] SPTs reveal the presence of mast cell-bound sIgE in the skin, while serum sIgE tests measure free allergen-specific antibodies in the serum. These two complementary approaches have advantages and limitations and are chosen based on their suitability and the experience and the preferences of specialists. The methods can also complement each other in case of ambiguity.[3] Patients whose clinical history cannot be supported by SPT- or sIgE-proven allergen sensitization, may require a second-line test (basophil activation test, BAT)[4] or, eventually, an organ-specific allergen provocation to confirm the clinical relevance of the sensitization. Both SPTs and challenge tests (conjunctival, nasal and bronchial) are performed using allergen extracts. Food SPTs and challenges are mostly performed using native allergens in the form of fresh or frozen foods.

The SPT is an educative test that allows quick screening of potential sensitizations. The results from SPTs are available within minutes. However, in vitro tests require a few hours before results are available; therefore, patients need a second visit, usually on another day. Skin tests not only are used for common allergic conditions but also are essential for the diagnosis of occupational allergies.[5] The sensitivity of SPTs is high[6] but varies due to several factors, including extract composition and potency and the technique used by the performing professional.[7] SPTs are relatively safe. Indeed, severe reactions occur in 0.07% of patients in specialized allergy centres and can usually be predicted.[8] In some cases, particularly in children, venipuncture is avoided when possible. Additionally, the cost of assessing a similar number of allergen sensitizations by serum sIgE is significantly higher than the cost of performing a panel of SPTs. In clinical trials with inhalant allergens, organ provocation tests with allergen extracts are sometimes replaced by exposure to natural allergens, such as pollens or animal dander, in allergen exposure chambers. To diagnose insect venom allergies, isolated natural venom is used as the "extract." As an exception to the use of natural allergens as diagnostic allergen extracts, compounds produced by the pharmaceutical industry are used to diagnose sensitization and allergic responses to drugs.

As described above, allergen extracts are widely used in skin tests for sensitization diagnosis and in organ-specific challenges for allergy diagnosis. Patients with inhalant allergies constitute the majority of patients screened for allergen sensitization in Europe. Consequently, the availability of adequate allergen extracts is crucial. Allergen-specific sIgE tests also use allergen extracts. The quality of allergens used by the manufacturers of sIgE tests is not subject to European Medicines Agency (EMA) regulations.

Since the 1970s, the SPT has been established as the main diagnostic procedure in clinical practice for assessing sensitization as a basis for allergy diagnosis. However, there is a need to ensure the quality of the diagnostic extracts. As such, diagnostic extract quality is a goal of regulatory frameworks.

European regulators recently launched new statutory provisions on diagnostic allergen extracts in Europe.[9-11] Although these provisions should be implemented in each EU country, the initial and periodic renewal expenses for the registration of diagnostic allergen extracts may render the production of these extracts unprofitable. As a consequence, many extracts are at risk of being withdrawn from the market, jeopardizing current clinical practices.[12]

Figure 1 summarizes the major procedures indicated by the European Directive, the EMA Guideline on Allergen Products and the European Pharmacopoeia on Allergen Products as well as some of the estimated costs of the procedures.

The European Academy of Allergy and Clinical Immunology (EAACI) commissioned a task force to evaluate the possible impact of the new regulatory changes on the future of allergy diagnosis. The current report is a result of such a task force. This report has been approved by the members of the EAACI Executive Committee.

The goal of this study was to gain insight on how the diagnostic work-up to assess allergen sensitization and/or clinical reactivity is currently performed in Europe.

2 | METHODS

The task force members designed an online survey to compile information regarding the current practice of allergy diagnosis in European countries and to obtain information on the current status of legislation affecting allergen diagnostic extracts. This survey consisted of 8 questions covering different domains (Data S1), such as the preferential use of diagnostic techniques for major allergy-related conditions and regulatory information on the use of diagnostic allergen extracts in EU countries. Representatives of all the EAACI National Allergy Societies were invited to complete the survey. Descriptive data were collected and summarized.

3 | RESULTS

3.1 | Participating societies

Representatives from the following 31 EAACI National Allergy Societies answered the survey: Albania, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Georgia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and Ukraine.

3.2 | Diagnostic methods

As shown in Table 1, skin testing with allergens, followed by in vitro tests, is the most frequently used initial procedure to evaluate sensitization/allergies for common allergic diseases. In the case of respiratory allergies, skin tests were used in more than 90% of cases; in food allergy and insect venom allergies, skin tests were the first

- TAs for diagnosis are considered medicinal products. Therefore, the assessment and approval of diagnostic allergen extracts follow the European Pharmacopoeia and the EMA Guideline on Allergen Products.
- TAs used in the EU must be registered by national authorities. Every individual TA applied for each test method (eg for skin prick and intracutaneous tests and conjunctival, nasal, and bronchial provocation tests) must be authorized in each EU member state.
- TAs can be registered in a single EU state either via a decentralized registration or via a mutually recognized procedure with a reference member state that has already approved the product.
- Clinical trials are needed to demonstrate safety, sensitivity, and specificity of the TA. The costs of ca. €1.5 million must be calculated.
- The registration cost for each TA is ca. €25 000 (varies by country).
- Development of quality assurance methods and stability studies induce further costs of ca. €3500 per TA batch/year.
- Homologous group formation may authorize more TAs with reasonable costs: one member of the homologous group is selected as the representative species. To a limited extent, data on quality, safety and efficacy can be extrapolated from the representative TA.
- PSURs must be submitted to national authorities every 6 mos during the first 2 y after approval, every 12 mos in y 3 and 4 of the approval, and every 3 y afterwards.
- Depending on the complexity and amount of data, personnel costs of creating a PSUR are estimated to be ca. €10 000.

FIGURE 1 Summary of the regulations of diagnostic allergen extracts and estimated costs for each test allergen (TA) and manufacturer

TABLE 1 Preferred initial diagnostic test performed in allergy work-up in 29 countries (only one answer allowed)

	Skin tests N (%)	In vitro tests N (%)
Respiratory allergy	28 (90.3)	3 (9.7)
Food allergy	20 (64.5)	11 (35.5)
Insect venom allergy[a]	18 (58.1)	12 (38.7)
Atopic dermatitis	17 (54.8)	14 (45.2)
Urticaria	18 (58.1)	13 (41.9)
Total	101 (65.2)	53 (34.9)

[a]One country specified component-specific serum sIgE as the first diagnostic approach.

option in more than half of the cases. Even in conditions not "typically" considered IgE mediated, such as urticaria or atopic dermatitis, SPTs were used as the first diagnostic tool in most instances. When not implemented as the first choice, skin tests were frequently considered as a second option (Table 2). Specific challenges occur especially in respiratory and food allergies (Table 2).

3.3 | National regulations

Information on the national status of the legislation regulating allergen extracts was also requested (Table 3). One-third of the countries stated having recently updated national legislation, one-third had not had recent updates, and one-third of the representatives did not know of the current legislation status. National requirements for compulsory authorization, batch release certification or periodic safety update reports (PSURs) were variable. Among national representatives, 25 of 29 admitted a lack of knowledge on the potential costs of such procedures. Only 6 countries stated they have legislation on the use of noncommercial extracts.

4 | DISCUSSION

The impact of the potential future lack of diagnostic allergen extracts, due to the translation of the European Directive to national regulations, is perceived by the EAACI as a serious threat to current clinical practice.[12] The results of this survey strongly support this perception.

The survey indicates that skin tests continue to be the main diagnostic procedure for the majority of allergy cases in European countries and are used as the first option in almost 2/3 of all types of allergic diseases and in 90% of individuals suffering from inhalant allergies (asthma and rhinitis). Additionally, organ-specific allergen challenges are used in approximately 20% of countries as a part of the diagnostic work-up. For diagnostic challenges of the airways, aqueous extracts of inhalant allergens are needed.

For the extracts considered to be the major causes of respiratory allergies, the diagnostic value has been assessed in clinical trials as part of their clinical development or authorization requirements. However, some less prevalent regional allergens will probably not be subjected to these expensive regulatory procedures and may be withdrawn from the market. Occupational allergens could share the same fate.[5] Food allergen extracts, which are generally not used in therapy and thus do not undergo evaluation in clinical trials, would probably not be available for diagnostic purposes due to the expenses involved in their registration.

The use of alternative diagnostic methods, such as in vitro allergen-specific sIgE or BATs, may not be plausible in many

TABLE 2 Secondary tests used after the initial test of choice (more than one answer allowed)

	Skin tests (%)	In vitro tests (%)	Component diagnosis (%)	Challenges (%)	None (%)	Total (%)
Respiratory allergy	3 (5.5)	28 (50.1)	14 (25.5)	10 (18.2)	0 (0)	55 (100)
Food allergy	8 (12.5)	18 (28.1)	22 (34.4)	16 (25.0)	0 (0)	64 (100)
Insect venom allergy	8 (18.2)	17 (38.6)	18 (40.9)	1 (2.3)	0 (0)	44 (100)
Atopic dermatitis	10 (22.7)	15 (34.1)	14 (31.8)	1 (2.3)	4 (9.1)	44 (100)
Urticaria	6 (16.2)	14 (37.8)	9 (24.3)	0 (0)	8 (21.6)	37 (100)

TABLE 3 National legislation on diagnostic allergen extracts

	No N (%)	Yes N (%)	Do not know N (%)
Updated legislation in your country	10 (34.5)	10 (34.5)	9 (31)
Impact on availability of extracts	14 (48.3)	13 (44.8)	2 (6.9)
Compulsory authorization required	6 (20.7)	17 (58.6)	6 (20.7)
Compulsory batch release certification required	7 (24.1)	12 (41.4)	10 (34.5)
PSUR required	10 (34.5)	6 (20.7)	13 (44.8)
Legislation on the use of noncommercial extracts	20 (69)	6 (20.7)	3 (10.3)

instances due to the increased costs in both public health and private practice.

A striking lack of awareness exists regarding the ongoing implementation of the allergen extract regulations and their economic impact on national societies. A change in legislation will impact diagnostic options in clinical practices before the information regarding its influence on allergy practices has reached allergists and general practitioners.

The current study has several limitations. The information provided by the representatives was clearly subjective and was derived from personal experience; consequently, this information may not be completely accurate. Nevertheless, the information gathered in this study provided a good overview of current practice of allergy diagnosis in Europe. However, there may have been regional differences within the individual countries that complicate the ability to ensure unambiguous answers from the national representatives.

The results of this survey highlighted the importance of European clinicians having access to the following:

1. Availability of glycerinated and standardized allergen extracts for SPTs at reasonable costs.
2. Aqueous allergen extracts to be used for organ-specific challenge tests, such as conjunctival, nasal and bronchial provocation tests.

The EAACI considers that regulation of diagnostic extracts should ensure the following:

1. The manufacturer provides documentation assuring the quality and reliability of the extracts when both therapeutic and diagnostic extracts are produced.
2. The batches of diagnostic/therapeutic allergens and aqueous allergens for challenge tests are uniform in quality and consistency.
3. The facilitation of a scaled regulation, with progressively stringent requirements, of the same extract for skin tests, followed by organ-specific provocation extracts and possibly allergens for therapy.
4. The feasible updating of registration in the case of diagnostic extract modification due to the inclusion of newly identified relevant allergen molecules.

In conclusion, the availability of diagnostic extracts remains a basic requirement to ensure the well-established diagnostic approach to allergic diseases.

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CONFLICTS OF INTEREST

All authors declare that they have no conflict of interests, real or perceived, regarding this manuscript.

AUTHOR CONTRIBUTIONS

All authors participated in the design of the survey, evaluated results and substantially contributed to the discussion and final draft of this manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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