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Diagnostic test allergens used for in-vivo diagnosis of allergic diseases are at risk: a European Perspective

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Accepted Article

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Short title:

Diagnostic test allergens are at risk in the EU

Abstract:

In the European Union (EU), allergens used for diagnostic tests (TAs) are defined as medicinal products and have to be registered by national authorities. The current situation is not homogeneous. Existing authorizations need to be kept in the market in some EU states, while others need complete new authorizations requiring clinical trials, quality assurance methods, stability studies, and Periodic-Safety-Update-Reports. Allergen manufacturers argue that offering a comprehensive panel of TAs may be economically disastrous. Expenses for initiation and maintenance of TA-authorizations far exceed their related revenues and manufacturers may be forced to significantly limit their allergen portfolios. The availability of a wide range of high quality TAs is very important for *in vivo* diagnoses of IgE-mediated allergies. Increased regulatory demands induce costs that need to be covered by public health organizations or reimbursed by health insurance companies.

Key words:

bronchial provocation test; conjunctival provocation test; European Pharmacopoeia; nasal provocation test; Skin test allergens

In the European Union (EU), allergens used for diagnostic tests or therapy have been defined as medicinal products since 1989 (1). EU-Directives 89/342/EEC and 2001/83/EC encompasses both diagnostic and therapeutic allergens. As a consequence, diagnostic Test Allergens (TAs) used in the EU have to be registered by national authorities, however, in the case of TAs, this process has not been completed.

The assessment and approval of TAs follows the European Pharmacopoeia and the European Medicines Agency (EMA) Guideline on allergen products (2–5). Thus, every individual TA applied for each test method (e.g., for skin prick and intracutaneous tests, and conjunctival, nasal and bronchial provocation tests) has to be authorized in each EU Member state (4). This development is anticipated to have a tremendous impact on *in vitro* allergy diagnosis in Europe.

Currently, the situation in Europe is not very homogeneous. While some EU Member states such as Germany, Poland and The Netherlands have authorizations for TAs in place, several other countries have no authorized TAs on the market. As a result, new regulatory documents are currently in preparation, for example in Spain (Resolución Alergenos Borrador).

Moreover, the authorization requirements are different in those EU member states that already require approval.

Thus, we face the situation that existing authorizations need to be kept in the market in some EU states, while others need complete new authorizations.

New authorizations

A TA can either be registered in a single EU state, or via mutual recognition procedure with a state that has already approved the product referred to as reference member state or via a decentralized registration.

In all procedures, clinical trials are needed to demonstrate safety, sensitivity and specificity of the TA (6). Such studies are of special value for allergologists and patients, however they are time consuming (planning, implementation and evaluation takes up to 2 years) and costs of ca. 1.5million have to be calculated (for any TA, such as timothy, birch, D. pteronyssinus) in addition to registration costs. The registration costs for the 18 prick TA's recommended as a base screening panel by GA²LEN (7) amount to estimated ca.

12.6Million (calculated for 28 EU member states with costs of ca. 25,000 for each TA) for every manufacturer in the EU (4). However, fees are not harmonized between EU states. Costs may be even higher in Italy (where allergen manufacturers calculate registration costs of 55,000 per TA) and lower in Lithuania (712). In Germany, the fee is 11,250, but for parallel approval of biologically similar (homologous) groups the fee is reduced to 1125. TAs for intracutaneous testing and conjunctival, nasal and bronchial provocation need to be authorized in addition to prick TAs.

In rare allergens, there may not be enough patients for a phase III trial. A solution may be the acceptance of data on quality and efficacy from small study populations, similar to orphan drugs situation. Thus, requirements should be adapted to prevalence levels across Europe. Additional evidence could be provided post-authorization, over the following years.

Development of quality assurance methods and stability studies (6) induce further costs of ca. 3500 per TA-batch/year (4), excluding personnel needed to write reports, dossiers etc. Stability studies according to good manufacturing practice have to include the continuous activity measure of at least 3 batches of a TA product over the time of use of the delivered TA (separately for each different skin and provocation test material).

Allergen manufacturers argue that offering a comprehensive panel of TAs may be economically disastrous, since most of the costs are fixed and identical for "block-buster" and rarely used TAs (4).

Homologous groups-formation may bring more TAs to authorization with reasonable costs (2). Using this method, one member of the homologous group is selected as the representative species. This choice should be justified considering geographical differences in sensitisation 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 (2). 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 (2).

Costs for existing TA authorizations

Once authorization is obtained, it has to be maintained. The entire approval documentation must permanently be kept up to date in every member state in which the TA is authorized inducing costs (primarily for personnel) in the range of a six-figure euro sum (4).

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 TA, every 12 months in years 3 and 4 of the approval, and every 3 years after that. PSURs 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 (4).

Additional processing costs of PSURs (e.g. by the Paul-Ehrlich-Institute) currently range from 1800–2250 for marketing authorization only in Germany, to 3600 in the case of mutual recognition or decentralized procedures if Germany is the reference member state, to 2400 if it is not. The European Commission actually plans to increase the fees for authorities' handling of PSURs in the second draft of the proposal (2013/0222 (COD); 26.06.2013) to 19,500 per PSUR.

According to Article 57 §2 of regulation 726/2004, all existing products must be entered into a new security database at the EMA. For every registration number, the authority estimates about 60 per year for the (unspecified) 'maintenance' of this data (6). According to congruent information by European manufacturers, these additional costs (including personnel expenses for data handling), could add up to 6000 (for registration) and 63,000 (in associated costs) for manufacturers with a large portfolio.

Consequences for patients and allergologists in routine care

Based on these figures, it can be estimated that the expenses for initiation and maintenance of TA-authorizations far exceed their related revenues. Consequences for allergologists and patients are predictable: manufacturers may be forced to significantly limit their allergen portfolios for economical reasons. This has already happened in France, for example, with losses of about three quarters of skin prick TAs since 2004, and in Germany, where 443 authorized TAs were lost in 2013 alone.

For those test allergens remaining, it is unlikely that all needed in vivo test options like skin prick and intracutaneous tests, conjunctival, nasal and bronchial provocation tests (8) will be kept on the market, and significant price increases for the remaining TA's are anticipated. Since most of the expenditure is fixed costs independent of the amount of TA sold, prices for rarely used in-vivo allergen products in particular may need to be 20 to 50 times higher than the price of frequently used TAs (4). In consequence, rarely used TAs may no longer be

commercially offered. In addition, it might be more interesting to license a broader range of TAs in large member states than in smaller countries., and the differences in costs for approval across EU member states may lead to the availability of a special TA in one country with its absence in another.

If standardized commercial products are missing, physicians may be forced to use unstandardized allergens from available natural sources (native materials) not subject to legislative constraints. This may throw in-vivo allergy diagnoses back a century towards the beginnings of modern allergology and return responsibility solely to the attending physician. With the development of in-vitro allergy diagnoses such as IgE-measures and component resolved diagnosis (CRD), and with the advent of basophil activation testing, recombinant allergens will become increasingly more important in allergy diagnosis. However, in vitro assays cannot completely substitute the information given by SPT and other in vivo, allergen-specific challenge tests that remain an essential procedure in the diagnostic work-up of the allergic patient.

Conclusions and requests

The availability of a wide range of high quality TAs for in vivo diagnoses of IgE-mediated allergies within Europe is very important for a comprehensive diagnostic procedure. Increased regulatory demands induce increased costs for TAs that need to be covered by public health organizations or reimbursed by health insurance companies in all European countries.

Thus, we make the following requests for in-vivo allergy testing with TAs within Europe:

- 1) Decentralized (DCP) or mutual recognition European registration processes for new TAs should be slimmed down and streamlined (e.g.with a quality dossier and reasonable clinical data).
- 2) For marketed TAs, national procedures should be harmonized throughout Europe.
- 3) The pharmacovigilance fees for TAs should be reduced.
- 4) The homologous groups principle for TAs should achieve general acceptance.
- 5) In rare TAs, data from small study populations should be accepted (i.e. quality dossier data plus limited clinical data).

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