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REVIEW

Proposals for harmonization of allergens regulation in the European Union☆

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Abstract Allergen medicinal products in the European Union are regulated differently across the different Member States. Thus, whereas in some countries strict quality, safety and efficacy requirements are in place, in others, most allergens are on the market as Named Patient Products, without any regulatory oversight. This situation results on European allergic patients being exposed to totally different standards depending on where they live. Initiatives to correct this situation are needed.

Medicinal products regulation in the European Union

Medicinal products for human use in the European Union (EU) are currently regulated by Directive 2001/83/EC[1] together with its subsequent amendments. Although Directives need transposition into national legislations, the basic requirements are the same in all member states. The Directive is only applicable to those medicinal products manufactured by an industrial process.

Article 2 of Directive 2001/83/EC establishes the need for a marketing authorization, issued by the competent authority, before a medicinal product is placed on the market. However, article 5 allows exceptions from this rule if, for instance, a medicinal product is supplied in response to a specific prescription for use by an individual patient and formulated in accordance with the specifications of an authorized health-care professional. These so-called Named Patient Products (NPPs) can then be placed on the market without a marketing authorization.

There are several procedures for marketing authorization (MA) of medicinal products within the EU: centralized, national, decentralized and mutual recognition.[2] In brief:

- The *centralized* procedure involves one single application to the European Medicines Agency (EMA) and, if successful, one single MA issued by the European Commission valid for the whole European Union. The Annex to *Regulation 726/2004, laying down Community procedures for the authorization and supervision of medicinal products*

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for human and veterinary use and establishing a European Medicines Agency, lists those medicinal products for which the centralized procedure is compulsory.[3] The centralized procedure can also be used voluntarily for other products not listed in the Annex if they are a new active substance or if they can demonstrate a significant therapeutic, scientific or technical innovation.[3] Decisions on the centralized procedure are taken by the Committee for Medicinal Products for Human Use (CHMP).

- A *national* authorization is granted by the competent authority within the concerned member state and is only possible when the medicinal product does not have a MA in any other member state.
- The *mutual recognition* procedure is applied when a medicinal product is authorized within one member state and the marketing authorization holder wants to extend the authorization to one or more member states. Normally, the competent authority where the product was initially authorized acts as reference member state (RMS).
- Finally, the *decentralized* procedure for MA is followed when the applicant intends to commercialize an unauthorized medicinal product in several member states at once. The procedure is similar to the mutual recognition but here a RMS is chosen to do the initial assessment.

Regulatory status of allergen products

Allergen products for both diagnostic and therapy are considered medicinal products according to the definitions in Directive 2001/83/EC and as such, they should be subjected to the same requirements applying to other medicinal products

Allergen products other than those produced by recombinant technologies are not obliged to follow the centralized procedure. As such, none is currently authorized by this route and only a few have been authorized by the decentralized or the mutual recognition processes.[4] Most of the currently used allergen products are within national markets but without a harmonized approach to marketing authorization.[2] Thus, in some member states, umbrella authorizations combining several allergens are given whereas in others, individual MAAs are required and yet in some others (e.g. France) special national provisions are in place to authorize the marketing of NPPs.[4]

Finally, in many cases, allergen products are on national markets as NPPs without any marketing authorization.[4] This means that no assessment of quality, safety and efficacy has ever been conducted on them. Although placing these products on the market as NPPs without any specific requirements has been the rule historically, this approach is difficult to justify today. In fact, due to the evolution in diagnostic and prescription habits, the reality now is that most allergen products are, at least in part, industrially manufactured.

The scenario described above results in a heterogeneous landscape across Europe that creates a number of problems, among others:

- Unequal access of patients across the EU to safe and efficacious treatments.
- Availability of allergen products with different standards even within the same member state, for instance, products under NPP (without any pre-assessment) versus products authorized on the basis of a full MA dossier through the decentralized or mutual recognition procedures.
- Difficulty for taking products from one member state to others due to different regulatory requirements.
- Difficulties in applying the pharmacovigilance legislation for this type of products due, for instance, to the difficulty in grouping products of the same composition.
- Potential removal from the market of essential, but scarcely used, allergen products (mainly for diagnostics) in those member states with more stringent requirements for marketing authorization.

What can be done?

One possible solution would be that legislators recognize the particularities of allergens and establish specific regulations for this type of products, similar to those produced for Advanced Therapy[5] or Herbal Medicinal Products.[6] This however would require developing new legislation at European level, which normally needs long procedures.

In order to mitigate the problems highlighted above, and without prejudice of any potential future change in legislation, the German competent authority took the initiative of presenting a reflection paper for internal discussion at the Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) of the EMA.[7] The CMDh has representatives from all national competent authorities and is in charge of dealing with issues relating to the marketing authorization of human medicines in two or more EU member states in accordance with the mutual recognition or the decentralized procedure. A working group was created to discuss the document and to follow the next steps. Several proposals were agreed by the group for further development.[8]

One important outcome was to request the CHMP the development of a guideline for allergens used in allergies of low prevalence. It is acknowledged that the available EMA guidelines on quality[9] and clinical[10] issues for allergen products set recommendations difficult to fulfil for products intended for rare allergies. For instance, the number of patients normally required for proving efficacy is not possible to achieve on rare conditions; additionally, some of the reagents needed for quality standardization (e.g. sera from allergic patients) can be difficult to obtain in these cases, etc.

These difficulties could be pushing many of these products into the market as NPPs without any regulatory oversight. The aim of this guideline would be to establish tailored requirements that allow clinical development of these products leading, eventually, to a proper MA if appropriate quality, safety and efficacy standards are fulfilled. Work on drafting this guideline for rare allergens is expected to start soon. Defining what a rare allergy is will, undoubtedly, be a difficult task.

The working group also agreed on a questionnaire to collect the regulatory status of allergen products across the EU. Once the information is gathered and analyzed, the group will set to develop recommendations that, if agreed, could help in harmonising the regulatory landscape for allergen

products in the EU. One of the issues that could help harmonisation is to have a clear definition of what a real NPP is. The recommendation would be that all products that do not fit into the agreed definition should only be on the market after an authorization is given. If the same criteria are applied in all member states, industrially manufactured allergen products will be regulated similarly across the EU.

Other areas of work could be: defining a common approach to regulate products for *in vivo* diagnostics, finding standard ways to define products composition, etc.

In summary, coordinated efforts are needed to find suitable regulatory pathways for allergen products within the EU. The special characteristics of these products and their long history of use are not strong arguments for being left out of the stringent regulatory oversight to which all other medicinal products are subjected.

Conflict of interest

The author declares no conflicts of interest affecting this publication.

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