



New guidance on the regulation of allergen products: key aspects and outcomes

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Purpose of review

Key aspects and outcomes from the recently published guidance on the regulation of allergen products are summarized.

Recent findings

A new regulatory guideline has been published to enhance harmonized national approaches on the regulation of allergen products and thereby strengthen the availability of high-quality products across the European Union (EU). As the guideline was developed, critical aspects for allergen products regulation were identified and are discussed in the document, including recommendations on the regulatory procedures to be applied for diagnostics, allergen immunotherapy products and named-patient products.

Summary

The new guidance is expected to provide clarifications on and support harmonization of the regulation of allergen products in the EU.

Keywords

allergen immunotherapy, Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) guideline, in-vivo diagnostics, named-patient products, regulation of allergen products

INTRODUCTION

Across the European Union (EU) there is a plurality of products available for the in-vivo diagnosis of allergic disease (test allergens) and the causal treatment by allergen-specific immunotherapy (AIT). However, the availability of these products throughout the EU varies widely, partly based on different exertion of the legal basis applicable for allergen products, and despite the fact that allergen products are uniformly defined as medicinal products in all EU member states based on the ‘European Medicinal Products law’, the Directive 2001/83/EC [1]. Yet, due to the differing pathways that member states have chosen in the regulation of allergen products, distinct problems have surfaced in recent years, including lack of information on the actual availability of allergen products in the individual EU Member States as well as divergent views on the acceptance of specific regulatory pathways to be applied. Multinational marketing authorization procedures have been successfully completed for some AIT products in recent years, resulting in harmonized assessment and subsequent availability of the products in multiple member states. Yet, diminishing or lack of availability of high-quality allergen products still raises concern amongst physicians on future

capabilities for adequate diagnosing and treatment of patients, especially for non-common allergies [2,3,4[¶]]. As a result, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which is responsible for the examination of questions relating to the marketing authorization of a medicinal product in two or more Member States, has developed the CMDh Guideline *Recommendation on common regulatory approaches for allergen products* (CMDh/399/2019) to enhance the harmonization of regulatory procedures for allergen products and thereby support the availability of high-quality products in all member states [5^{¶¶}].

As this guideline may profoundly impact the market of allergen products, in this review, we will briefly summarize the reasoning that has led to its development and we will highlight some key elements as agreed upon in the document, including

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KEY POINTS

- Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human has created a guideline to provide recommendations on reducing obstacles and heterogeneities identified in the regulation of allergen products in the EU.
- The draft guideline was updated based on a multiplicity of comments received during public consultation.
- The new guidance addresses applicable regulatory approaches for therapy allergens and in-vivo test allergens.
- Clarification is provided on circumstances in which it is considered reasonable to provided allergen products as named-patient products without a marketing authorization.

major points from the public consultation that has precluded the publication of the final version of the guideline.

NECESSITY OF THE GUIDELINE

From a regulatory point of view, allergen products are medicinal products that require a marketing authorization to be distributed. Yet, partly due to historical reasons, they have been regulated dissimilar in some aspects as compared with most other medicinal products. To some extent, this divergence follows reason as these products inherit some unique aspects that will not be relevant for other products. For example, as the source materials that are used in the manufacture of products for allergen diagnosis or AIT are typically derived from natural sources and therefore show considerable variability, assurance of a consistent quality of the medicinal product can be more challenging. This is especially true in relation to the quality and quantity of the active ingredient, notably with respect to the content of relevant allergens and the overall allergenic potency of the product [6,7]. Furthermore, there are allergies to hundreds of differing allergen sources relevant to substantial parts of the population. Yet, the number of patients to a specific allergy is considerably limited in most cases. To account for this, current legislation allows distribution of allergen products without a marketing authorization to individual patients under specific circumstances based on Article 5 of the Directive 2001/83/EC [1]. The use of so-called named-patient products (NPP) allows provision of AIT products to patients with comparably rare allergies for which otherwise no authorized product would be available. Experience from recent years has shown that these NPP-provisions

have not only been used for these rare allergies, but have also been used for bypassing the general requirement for a full marketing authorization also in cases, where it is objectively possible to provide a full set of data from clinical trials to confirm safety and efficacy for the respective product [8[¶]]. In Germany, with the implementation of the so-called therapy allergen ordinance [8[¶]], a requirement for a full marketing authorization for NPP products for AIT of common allergies (sweet grasses with the exception of maize, birch, alder, hazel, house dust mites and insect venoms) has been implemented. Here, more than 6500 AIT products had been previously distributed (some with only marginally differing composition), for most of which no data on the quality, safety or efficacy had been available or independently assessed for their validity by a regulatory body.

While differing approaches have been evident between the EU and the United States [9–12], the heterogeneity observed in the regulation of allergen products within the EU itself results in numerous relevant problems and deficiencies (Table 1). For instance, in some countries it is not fully clear, which NPP products are actually on the market, what their composition is or how they are manufactured and controlled. In part, this results in a situation where patients are treated with products of unknown safety and efficacy.

Table 1. Problems and deficiencies in the regulation of allergen products

Diverging approaches on which regulatory path should be applied to allow market access for individual allergen products
Lack of guidance on when a NPP is a reasonable option
For the majority of the NPPs there is no documentation or independent evaluation on quality, safety and efficacy
Most member states do not have comprehensive information (including on availability, exact composition or pharmacovigilance issues) for NPPs
Circumvention of marketing authorization requirements for AIT and in-vivo diagnostic products to common allergies
Lack of harmonization may allow widespread treatment using products of unknown quality and/or efficacy, with potential impact for the patients
Grouping of several, independent products containing diverse active substances under a single marketing authorization (umbrella authorization)
Heterogeneous approach handicaps efficient use of regulatory procedures (e.g. MRP) to expand availability of products to more countries
Key pharmacovigilance activities cannot be performed at European level as current status does not allow integration of allergen products in respective databases

AIT, allergen-specific immunotherapy; MRP, Mutual Recognition Procedures; NPP, named-patient product.

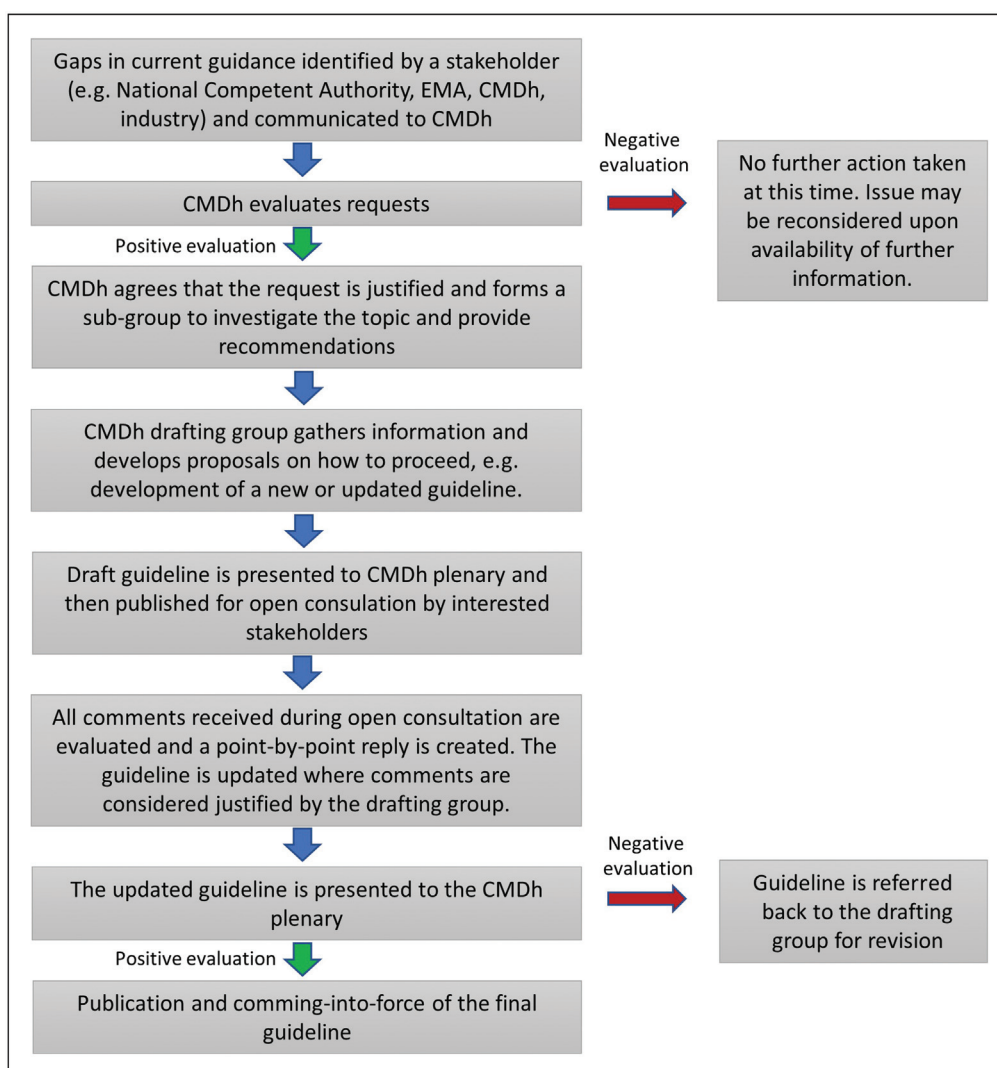


FIGURE 1. Simplified schematic on the development process for a guideline.

It became evident that guidance on the regulatory procedure to be applied as well as an agreed definition on situations where the use of NPP is reasonable was lacking and needed to be developed. Developing such guidance is a multistep process (Fig. 1) and a challenging task, as it needs to consider an environment in which existing marketing authorizations have been lost in some member states (especially due to cost pressure) and there is only limited availability of new products [4*].

REGULATORY PROCEDURES APPLIED FOR DIAGNOSTICS AND ALLERGEN-SPECIFIC IMMUNOTHERAPY PRODUCTS

The new CMDh Guideline CMDh/399/2019 [5**] considers products of biological origin (including extracts from natural source materials) used for AIT and for in-vivo diagnosis of Type I (IgE)-mediated

and Type IV cell-mediated allergies. The guideline basically lists three applications types for marketing authorization (Table 2) that can be appropriate for allergen products. As discussed in the document, it is common agreement that for frequently prescribed products, a full marketing authorization according to article 8(3) of Directive 2001/83/EC should be applicable. For this, a full set of data on quality, safety and efficacy needs to be provided to the regulatory agencies to allow independent assessment of the full benefit–risk-ratio and a consequential decision on the marketing authorization. This means that typically product-specific data from clinical trials in line with current requirements needs to be provided. Where certain allergies are only prevalent in specific regions in Europe (e.g. allergies to birch pollen in Northern and Central Europe or allergies to olive pollen in Southern Europe), the feasibility to conduct clinical trials was considered

Table 2. Relevant application types for marketing authorizations

Application type	Legal basis	Characteristics
Full marketing authorization	Article 8(3) of Directive 2001/83/EC	Full data need to be provided including product-specific data from clinical studies
Mixed marketing authorization	Article 8(3) in combination with Annex I Part II Section 7 of Directive 2001/83/EC	Documentation on pre-clinic and clinic consist of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references
well-established use	Article 10a of Directive 2001/83/EC	Results of pre-clinical tests or clinical trials do not need to be provided if the active substances of the medicinal product have been in well-established medicinal use within the EU for at least 10 years. Efficacy and acceptable safety must be evident from appropriate scientific literature

EU, European Union.

reasonable even under consideration of the regional differences if high numbers of patients are affected. Such full applications, for which a full set of documentation (including clinical data) need to be provided, are considered mandatory for allergens intended for AIT or in-vivo diagnosis and derived from sources as listed in the Annex of the guideline ([5²²] and Table 3).

While the request for a full set of data is reasonable for common allergies, there are many other allergies where the availability of eligible patients for enrollment in clinical trials is so limited that this will make the development of corresponding allergen products impossible if a full clinical dataset would be required. In such cases a ‘Mixed Marketing Authorization’ may be applied. For such an approach, it can be acceptable that data on non-clinical and clinical development is based on a mixture of product-specific reports, studies carried out by the applicant, and bibliographical references.

Table 3. Allergen sources for which a full marketing authorization is required as requested by Annex I of the Guideline Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human/399/2019

Pollen of the group of sweet grasses of the Poaceae (Gramineae) family, subfamily of Pooideae
Pollen of the birch group
Pollen of the Oleaceae group
Pollen from the Cupressaceae group
Pollen from <i>Ambrosia artemisiifolia</i> and <i>Ambrosia trifida</i>
Pollen from <i>Parietaria judaica</i> and <i>Parietaria officinalis</i>
The group of house dust mites of the Dermatophagoides genus
Bee and wasp venom
<i>Felis domesticus</i> (cat)
<i>Arachis hypogaea</i> (peanut)
<i>Prunus persica</i> (peach)

However, the applicant will need to comprehensively justify that the references presented and the data therein is relevant for the product concerned in the individual application.

The threshold for an application under well-established use (Article 10a of Directive 2001/83/EC) is considerably higher. For well-established use, the applicant is not required to provide the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substances of the medicinal product have been in well-established medicinal use within the EU for at least 10 years. Efficacy and an acceptable level of safety must be convincingly documented from scientific literature. This approach is only rarely used for biological products, as the individual characteristics of these products are strongly interdependent with the manufacturing processes applied by the individual manufacturer. As such, it cannot be concluded that any given biological medicinal product will show similar characteristics with respect to safety and efficacy as a product derived from the same source material but produced by a different manufacturer. The CMDh has recently updated the CMDh Questions & Answers on Biologicals [13], where it is stated that bibliographic applications are strongly discouraged. In line with this, the CMDh Guideline argues that such applications should typically not be applied for therapy allergen products. The guideline expresses to some extent a different point of view for in-vivo diagnostics derived from biological sources. The production process for these products is typically less complex as compared with AIT products. For this reason production processes for diagnostics may be more comparable between different products from the same allergen source and bibliographic applications may be considered on a case-by-case basis. However, quantitative and qualitative aspects of product composition have to be considered carefully. Special consideration is

needed for epicutaneous Type IV allergy diagnostics that are not derived from biological sources but often from industrial materials and therefore may allow more direct application of well-established use regulations.

While alternative regulatory pathways as opposed to a full marketing authorization according to Article 8(3) of Directive 2001/83/EC can be followed on a case-by case-basis under specific circumstances, a full set of data on the quality of each medicinal product must be presented in accordance with current guidelines and regulations (including the European Pharmacopeia, ICH- and EMA-guidelines) regardless of the applied regulatory pathway.

In preparation of the guideline, the CMDh Group on Allergen Products collected information on the individual member state's regulatory approaches to allergen products. A major finding from this process was that availability of authorized allergen products is very heterogeneous across Member States. Although procedures are available to extent existing authorizations from one country to others (especially by the so-called Mutual Recognition Procedure, for more information see [12]), they have only rarely been applied for allergen products. The CMDh harmonization guideline provides recommendations on how such procedures may be handled efficiently to encourage marketing authorization holders to actively pursue these routes and thereby support wider availability of allergen products of proven quality, safety and efficacy.

APPLICABILITY OF NAMED-PATIENT PRODUCTS

Although the legal basis for use of NPP is uniformly based on Article 5 of Directive 2001/83/EC, its application is differing widely across Member States. Article 5 establishes that to fulfil special needs, NPP may be prescribed for individual patients under the immediate responsibility of a physician. However, while NPP are manufactured in compliance with regulations according to good manufacturing practice (GMP), further elemental product aspects concerning quality, safety or efficacy are not independently assessed. In most cases, data on the efficacy of the NPP is not available. NPP is considered an option for those patients, for which authorized products are not available due to a low prevalence of the underlying allergy. There is no justifiable rationale for the distribution of such products targeting very common allergies outside of the generally valid regulations applied for other medicinal products. The guideline therefore recommends that NPP should not be used when authorized alternatives for

AIT of the same allergy are available. Importantly, the guideline states that NPP should not be prepared and used for those allergens derived from sources as listed in the document's Annex I (Table 3), being it alone or in combination with other non listed allergens. Member States are requested to develop legally binding frameworks to implement the recommendations as provided.

COMMENTS DISCUSSED DURING PUBLIC CONSULTATION

As part of the advancement of the guideline, the document has been available for public consultation from May 2019 to August 2019. All stakeholders and interested parties were invited to comment and provide suggestions on the guideline. In total, 11 different stakeholders provided a total of 13 general comments (some of which very extensive) and 147 comments specific to the particular phrasing of the guideline. Most sections of the draft guideline were commented on, all comments were considered in detail by the drafting group, and the justifications provided by the stakeholders verified for conclusiveness. For reasons of transparency, the CMDh decided to publish the list of comments as well as the CMDh's response to each individual comment [14[¶]]. Where comments were considered justified, the guideline text was changed or amended accordingly. For this, the CMDh Drafting Group on Allergens discussed the comments in detail and agreed on an updated version of the guideline which was then presented to the CMDh plenary for adoption. Overwhelmingly, comments were supportive of the guideline and underlined its necessity. A considerable number of comments was received on the exact listing of allergens for which submission of a full documentation is considered mandatory. At the time of publication for commenting, the document had contained an Annex II specifically listing allergen products for in-vivo diagnosis for which a full documentation was considered mandatory, thereby effectively extending the list of allergens that was presented in Annex I on both, AIT products and in-vivo diagnostics. It was repeatedly and convincingly argued that feasibility for provision of a full dataset for many products as listed in Annex II is not given. Accordingly, both Annexes were consolidated and Annex II was removed entirely from the document. As a result, most allergens that had previously been listed in that Annex have been removed from the guideline, thereby allowing more regulatory flexibility for these products. Applicability of NPP was addressed by several comments, some arguing that NPP should not be considered inferior to authorized allergen products. However, the CMDh did not

follow this line of argumentation as for NPPs typically neither independently assessed data on efficacy and quality nor an independent assessment of the appropriateness of the stated indications or patient populations as described in the summary of product characteristics are available. In consequence, CMDh states that such a product cannot be recommended over a product where these aspects have been documented and independently assessed resulting in an approved positive benefit–risk-ratio. Therefore, irrespective of the formulation or route of administration, an approved product should be preferred over a non-approved NPP for the treatment or diagnosis of the same type of allergy [14[¶]]. Comments also requested that more information should be provided on scientific aspects of the guideline. In this context, aspects on the applicability of well established use applications were intensely commented. For such applications, most or all parts of the documentation on pre-clinical and clinical aspects can be presented based on bibliographic data as discussed above. As an important aspect, the CMDh guideline states that adequate bridging data must be provided in case that bibliographic data are to be used to support safety and efficacy of a respective product. The wording in the new CMDh guideline was amended to clarify that particular data is required for extrapolation as to justify that the respective bibliographical references are actually relevant for the allergen product in the application. Moreover it need to be kept in mind that this CMDh harmonization guideline is not a scientific but a regulatory guideline and details on the content and extensiveness of such bridging data are not discussed in the document. Further clarifications on such scientific aspects are expected to be provided by the EMA guideline resulting from the Concept paper on a Guideline for Allergen Products Development in Moderate to Low-Sized Study Populations [15].

CONCLUSION

Considering the situation of allergen products as it has dynamically evolved over recent decades, it is an unrealistic expectation to solve all pending challenges for allergen products by the simple implementation of a regulatory guideline. It is the authors opinion that such a guideline cannot reasonably achieve this and considerable challenges, for example with respect to clinical studies in children [16], remain. Yet, important steps are taken with the coming into force of the document as it gives clear advice on many critical aspects, including the choice of the respective regulatory procedures and the applicability of NPP in the EU. Throughout its

development, the patients' needs have continuously been the clear priority. As such, it can be challenging to weigh the necessity and benefit of documented quality, safety and efficacy against low-threshold realistic approaches to make a product needed by the patients available in the first place (e.g. by NPP).

The CMDh has agreed to maintain the CMDh Allergen Group as an ad-hoc group to support the member states in the implementation of the guideline. As such, this group will be available, upon request, to provide advice and further support the harmonization of allergen product regulation.

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Conflicts of interest

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