AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Aspetti salienti della linea guida del CMDh

Giusi Forastiero

16/12/2019

Giornata informativa AIFA sugli allergeni: stato dell'arte e problematiche aperte

16 Dicembre 2019 ore 10:15 - 13:30
AIFA - Via del Tritone 181, Roma

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	X	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	X	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	X	☐	☐	☐ facoltativo

* Giusi Forastiero, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. Per questo intervento non ricevo alcun compenso

What is the problem?

In 2015, EMA recognized that there is severe heterogeneity in the way allergen products are regulated in the EU

Allergen products, both for diagnosis and therapy, are authorised and distributed based on different legal backgrounds

PhV requirements and database entries according to Article 57 could not be followed for allergen products

Allergen Working Group

"CMDh Drafting Group on harmonisation of regulatory approaches for allergens" - Kick off Meeting: Febbraio 2016

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

Scope: "to investigate options to harmonize the regulatory situation for allergen products"

Survey

1° step: Questionnaire regarding the national approaches

- If there are national MAs in your country, how is the marketing regulated?
- Are there Named Patient Products (NPPs) on the market in your country? If yes, please explain how they are regulated.
- Are there differences in the regulation of allergens for diagnosis versus allergens for therapy?
- ...

Key results from the CMDh situation analysis

17 Member States replied to the questionnaire

Authorisation status of allergen products in the Member States in the European Union is heterogeneous

- Allergens are mostly available as NPPs
- No agreed definition on applicability of NPP classification
- National MAs are comparatively old and grouped under a single MA (*Umbrella licenses*)

Unplublished survey for the CMD-h Drafting group on harmonisation of the regulatory approaches for allergens

Key results from the CMDh situation analysis

Lack of harmonisation allows widespread treatment with products of low quality and/or unknown efficacy

Most Member States do not have comprehensive information for these products

Guidance/distinction is required

Different models developed

	Options	Maintenance of current status (unchanged)	Overarching Guideline Step 1	Changes to Annex of Directive 2001/83/EC (in combination with Guideline) Step 2 Option A	New registration approach for allergen products Step 2 Option B
Problem Statement					
No agreed classification on which allergen products should be within the scope of NPP		No clarifications. No changes to heterogenic regulatory approaches.	To be clarified by Guideline.	To be clarified by Guideline.	To be clarified by legislation.
Information on availability and composition not available in many countries		No further harmonisation. Availability of information completely heterogeneous between MS.	Minimal information to be provided to authorities could be defined.	Minimal information to be provided to authorities could be defined.	Depending on requirements of registration approach (e.g. transitional period), harmonisation possible.
Disharmonisation on applicable regulatory approaches, e.g. NPP, full MA, well-established use		No further harmonisation.	Adequate regulatory routes to be clarified by Guideline.	Adequate regulatory routes to be clarified by Guideline.	Regulatory route clarified by new legislation
For some products, current requirements impede MA (e.g. for infrequent allergens). Only very few new authorisations.		No harmonisaton. Predictability of requests by MS difficult for companies. Data requests may not be adequate for respective product.	Adequate (staggered) requirements to be clarified by Guideline.	Clarifications on respective data to be provided to be listed in Annex I.	Clarifications on respective data to be provided to be developed in line with new legislation.
Binding character and remaining flexibility for MS		No changes.	Guideline would improve harmonisation but is legally not obligatory for MS.	Clear legal basis for aligned data requirements.	Clear legal basis for aligned data requirements.
Umbrella authorisations in some countries		Situation remains unchanged.	To be addressed in Guideline (e.g. discuss applicability of combined medicinal products authorisations[1]). Suggestions on approach to move from umbrella to single MA could be addressed.	To be addressed in Guideline (e.g. discuss applicability of combined medicinal products authorisations[1]). Suggestions on approach to move from umbrella to single MA could be addressed.	Depending on requirements of registration approach (e.g. transitional period), harmonisation possible.
Timeframe for realisation of the approach		No changes intended, therefore no timeframe applicable.	Could be realized comparably quickly.	Medium term approach; Changes to Annex could be realized by EC without need for full legal process of changing legislation.	Potentially very long and complicated process.

[1] meaning fixed combination products (acc. to Article 10b) or combination packages (as referenced in NTA) within current legislation.

Draft CMDh-Guideline

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

1 April 2019
2 CMDh/399/2019, Public consultation

3

4 Recommendations on common regulatory approaches
5 for allergen products

6 **Draft**

7 **Table of Contents**

Fine consultazione pubblica
30 agosto 2019

Some key aspects discussed in the guideline

2. Scope

The document is intended to provide principles and guidance for the regulation of medicinal allergen products with the aim to facilitate harmonisation throughout the European Union.

In this regard, applicable regulatory approaches for different classes of allergen products are discussed. This includes products of biological origin (allergen extracts derived from natural source materials) used for allergen immunotherapy (AIT), or for *in vivo* diagnosis of Type I (IgE)-mediated allergic diseases (*e.g.* skin prick test and nasal provocation test), and products intended for the diagnosis of Type IV cell-mediated allergies (*e.g.* patch test based on haptens).

The recommendations developed in this document generally apply to all allergen medicinal products as defined by Directive 2001/83/EC. As such, only medicinal products for Human use intended to be placed on the market in MS that are either prepared industrially or manufactured by a method involving an industrial process are concerned. It applies to all such products, including those for which a new MA is intended, or those that are already marketed with or without a MA.

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Some key aspects discussed in the guideline

74 In this guideline, allergen sources are listed for which a full MA with a full set of data should be
75 requested. It should be noted that this list is not solely based on the prevalence of any given allergy
76 as this cannot be considered as the only indicator for the applicable regulatory approach[3]. Additional
77 factors, such as the number of patients meeting the indication for allergen immunotherapy and/or
78 medical need (*e.g.* severity of the allergy) were taken into consideration. In Annex I and II, allergens
79 responsible for common allergies in MS and for which a MA is currently available or an application is
80 under evaluation in some MS are listed. These annexes will be updated taking into account the
81 scientific and technical knowledge progress.

281 **5.1 Applications according to Article 8(3) of Directive 2001/83/EC**

287 Providing full documentation for the MAA is considered mandatory for AIT products containing
288 allergens derived from sources listed in Annex I.

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Some key aspects discussed in the guideline

Annex I

Marketing authorisation and provision of full documentation according to Article 8(3) of Directive 2001/83/EC is considered mandatory for products containing allergens derived from the following sources that are **intended for allergen immunotherapy or *in vivo* allergen diagnosis:**

- Pollen of the group of sweet grasses of the Poaceae (Gramineae) family, subfamily of Pooideae
- Pollen of the birch group
- Pollen of *Olea europaea* (Olive)
- Pollen of *Ambrosia artemisiifolia*, *Ambrosia trifida* (Ragweed)
- Pollen from *Cupressus* sp. (Cypress)
- Pollen from *Parietaria* sp. (Pellitory)
- The group of house dust mites of the Dermatophagoides genus
- Bee and wasp venom
- *Felis domesticus* (Cat)
- *Arachis hypogaea* (Peanut)

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Some key aspects discussed in the guideline

4.2.2 Well-established use application - Article 10a[7]

Given the complexity of the characterisation of the product, bibliographic applications according to Article 10a of Directive 2001/83/EC are normally not applicable for biologicals[8], however, can be considered in exceptional cases on case by case basis. In exceptional circumstances, where there is an unmet medical need and a full set of clinical data cannot be obtained due to limited patient numbers and where a product has already been in medicinal use in the EU for at least ten years without a regular MA, it could be acceptable, in agreement with the NCA, that the (non)clinical information present in the application only consists of bibliographical data. In those cases, the

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Some key aspects discussed in the guideline

153 **4.2 Recommended approaches for Marketing Authorisation Application**

154 For the MA of allergen products, both for AIT or *in vivo* diagnosis, the requirements for the data to be
155 provided are in principle based on Article 8(3) of Directive 2001/83/EC. However, depending on
156 whether the allergen products are for treatment or diagnosis of common allergies or less
157 common/rare allergies (hence whether the limited number of patients may restrict the feasibility of
158 obtaining clinical data), an alternative legal basis might need to be considered. In any case, it is
159 expected that a full set of data on the quality of the medicinal products as requested by current
160 pharmaceutical legislation and according to guidelines and the European Pharmacopoeia is
161 presented.

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Some key aspects discussed in the guideline

7 Named-patient products (NPP)

7.1 Definition of NPP

A NPP is an allergen product, prepared in accordance with a prescription for an individual patient, identified by the name of the patient and a specific reference code/number. Article 5 of Directive 2001/83/EC establishes that in order to fulfil special needs, NPP may be prescribed for individual patients under the direct responsibility of a physician.

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Some key aspects discussed in the guideline

7.2 Acceptability of NPP

The special provision laid down in Article 5 of the Directive 2001/83/EC should not be used to avoid the general rules foreseen in Article 6 of the same Directive, establishing that no medicinal product may be placed on the market of a Member State unless a MA has been issued by the competent Authorities in accordance with the provisions of Directive 2001/83/EC.

A NPP is a therapeutic option for those patients whose allergies cannot be treated with authorised products. It is more likely that a NPP is used for the diagnosis or treatment of patients sensitized to allergens with a very low prevalence ("rare allergy")[10].

Also, the preparation and use of NPPs should not be applicable once authorised products for the treatment of the same allergy are available on the EU market (*e.g.* where an authorised product for AIT in birch pollen allergy is available, an alternative NPP for birch pollen allergy should not be used). In such situations, MRP should be encouraged and supported in order to make these products available in the individual MS.

If MRP is not possible or not sought by a company, an authorised health-care professional could require the importation of authorised allergen products for personal use.

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Public consultation: received comments

- Implementation and transition periods
- Adequate bridging data
- Grouped marketing dossiers
- Well-established use application for diagnostics
- Definition of “less common and rare”
- Annex review

Next steps

- Presentation of the results and CMDh response to the comments at CMDh Plenary
- Joint meeting RIWP and CMDh drafting group
- Presentation to the stakeholders of the update guideline

CHMP Guideline – Concept paper

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/251023/2018
Rheumatology / Immunology Working Party (RIWP)

Concept paper on a Guideline for allergen products development in moderate to low-sized study populations

Agreed by RIWP	September 2018
Adopted by CHMP for release for consultation	13 December 2018
Start of public consultation	21 December 2018
End of consultation (deadline for comments)	30 June 2019

Next steps

- Presentation of the results and CMDh response to the comments at CMDh Plenary
- Joint meeting RIWP and CMDh drafting group
- Presentation to the stakeholders of the update guideline

Grazie per l'attenzione

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