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Recommendations on common regulatory approaches for allergen products

Draft

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1. Introduction

It is known that the authorisation status of allergen products in the Member States (MS) in the European Union (EU) is heterogeneous. Previous information provided from several MS revealed that allergen products, both for diagnosis and therapy, are authorised and distributed in these MS based on different legal backgrounds. This also became evident in relation to the integration of allergen products into the European Union reference dates (EURD) list and the corresponding requirement for the submission of Periodic Safety Update Reports (PSUR). The current heterogeneous authorisation status of allergen products leads to a situation in which unique, specific entries in the Article 57 database are currently impossible[1].

In some MS, the majority of allergen products have historically been distributed in response to a *bona fide* unsolicited order without a marketing authorisation (MA) according to Article 5 of the Directive 2001/83/EC as a medicinal product for use by an individual patient (named patient product, NPP). While for new products a MA and a full dossier are required, for the majority of the NPPs there is no documentation or independent evaluation on quality, safety and efficacy. Some MS tightly monitor NPPs, but most do not have comprehensive information (including on availability, exact composition or pharmacovigilance issues) for these products. Importantly, there is no agreed definition at EU level on what constitutes a named patient product for allergens.

The majority of the authorised allergen products have national MA according to Article 6 of Directive 2001/83/EC, although most of these national MAs are comparatively old, which is reflected in the contents of the respective dossiers. In addition, within certain MS there are single MAs for each individual allergen product, whereas in others several products containing diverse active substances are grouped under a single MA (*e.g.* grass pollens, tree pollens, or several intracutaneous diagnostic allergens; so-called umbrella authorisations[2]). In certain MS which enforce the requirement to provide full documentation for existing allergen products (including quality data and clinical data), only a minority of the products could meet the current standards. Therefore, lack of harmonisation may allow widespread treatment using products of unknown quality and/or efficacy, with potential impact for the patients.

Current requirements for MAs cannot be met for some allergen products, such as for infrequent allergies or some diagnostic allergens. There is only limited availability of new products and existing authorisations have been lost in some MS (*e.g.* due to pharmacovigilance fees, maintenance costs). Umbrella authorisations result in reduced costs, but have associated regulatory problems, *e.g.* with respect to pharmacovigilance monitoring performed at EU level.

Although there is some scientific guidance available on the requirements for MA for allergen products (*e.g.* Guideline on Allergen Products: Production and Quality Issues

[1] Key pharmacovigilance activities, especially signal detection and assessment of PSUR, cannot be performed at European level without defined single entries in the database according to Article 57(2) of Regulation (EC) No 726/2004, as amended.
See 'Data submission of authorised medicines in the European Union' http://www.ema.europa.eu/

[2] Umbrella authorisations means multiple independently distributed medicinal products that are authorised within one single marketing authorisation with one corresponding marketing authorisation number

(EMEA/CHMP/BWP/304831/2007) and Guideline on the Clinical Development of Products for specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006)), specific guidance for rare or infrequent allergies (where there may be only few patients with the respective allergy available for clinical studies) is currently lacking. Furthermore, regulatory guidance is needed with respect to the heterogeneity observed in the regulation of allergen products. While for frequently prescribed products a full MA according to Article 8(3) of Directive 2001/83/EC should be applicable, for other products alternative approaches can be applied.

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

There are different views on the question of when a NPP may be a reasonable option compared with a MA for allergen products, with guidance required for the best choice to achieve market access. It should be noted that the epidemiology of allergy among different MS/regions is a critical issue (*e.g.* allergy to olive pollen in the Mediterranean region, birch tree pollen in Northern Europe, or *vice versa*) and should be taken in consideration for a harmonized approach, both in the scope of NPPs, the need for an MA and data requirements for an MA for allergy products.

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.

This guideline will not cover any medicinal allergen products manufactured using recombinant DNA technology, consisting of synthetic peptides, DNA or RNA constructs and/or cell preparations.

[3] For example, the prevalence of an allergy does not give any information on the eligibility of a patient for AIT or the frequency of use of respective products, as the prevalence does not consider severity of symptoms.

3. Legal basis

The legal basis of applications for MA for allergen products can be found in Directive 2001/83/EC which lays down the legal and regulatory framework for allergen products used both for immunotherapy and *in vivo* diagnosis of allergic diseases.

The legislation provides in Article 1 of Directive 2001/83/EC a definition of Allergens as medicinal products both for diagnostic and therapy use as follows: (b) *'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent*.

As a result, for such medicinal products that are either prepared industrially or manufactured by a method involving an industrial process (Article 2 of Directive 2001/83/EC), a MA should in principle be foreseen for allergen products to be placed on the market.

Depending on the legal basis under which an application is submitted, the requirements for a marketing authorisation application (MAA) dossier can be found in Annex I of Directive 2001/83/EC, as amended.

In addition, the following guidelines should be taken into account:

- Guideline on Clinical Evaluation of Diagnostic Agents (CPMP/EWP/1119/98/Rev 1)
- Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease (CHMP/EWP/18504/2006)
- Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007)

Applicants should also refer to all other pertinent EU and ICH guidelines, including but not limited to:

- Good Clinical Practice (ICH topic E6)
- Statistical Principles for Clinical Trials (ICH topic E9)
- Choice of Control Group in Clinical Trials (ICH topic E10)
- Structure and Content of Clinical Study Reports (ICH topic E3)
- Guideline on Clinical Trials In Small Populations (CHMP/EWP/83561/2005)

4. General approaches on allergen products

4.1 Overview of current marketing authorisation status for allergen products

While this section describes approaches currently applied by different MS on the regulation of allergen products, not all of these approaches should be understood as recommendations. Recommended approaches for MAA are discussed in section 4.2.

a) Single MA for each individual allergen product
   - one active substance (or mixture provided in single container) with a defined strength (*e.g.* test allergen Birch and test allergen Hazel would be two separate MAs).

b) Allergen products grouped into a single MA according to:
   - homologous or non-homologous allergen group[4]:

[4] As described in the Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007)

- one MA for different members of a specific family (*e.g.* grass pollens or tree pollens)
- pharmaceutical form:
  - one MA for different strengths of an active substance as single allergen extract or a mixture of extracts (*e.g.* increasing dosage vials for a specific immunotherapy)
  - one MA for a set of test allergens (*e.g.* separate and non-related allergen extracts in a testing 'kit' for diagnosis of specific allergies)

c) Control of industrially-manufactured bulks[5]

In some MS, the quality of the industrially-manufactured allergen bulks is controlled and approved by the responsible National Competent Authority (NCA), and sometimes specific mixtures are prepared from these allergen bulks for individual patients. While this ensures suitable quality of the allergen products, manufactured to GMP with subsequent supply as NPPs, appropriate dosing, safety and efficacy of these products is not documented on a product-specific basis.

4.2 Recommended approaches for Marketing Authorisation Application

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

Some MS have issued 'umbrella' authorisations for groups of allergen products, although this is not covered by current legislation. As stated in the Notice to Applicants, a key principle of the acquis is that there must be a MA for each medicinal product that is put on the EU market. In support of harmonisation, MS are encouraged to provide options to marketing authorisation holders (MAH) to transfer their existing umbrella MAs to individual MAs with minimal requirements on the contents of the individual marketing authorization application dossiers. As such, this transfer should be briefly justified for the individual MAs and may be handled administratively without the need for scientific reassessment of the documentation. Sufficient product-specific information should be provided in the dossiers in such a procedure. It could be agreed by commitment of the MAH that such information can be amended at later times where it is not available at the time of separation of the existing umbrella MA into individual authorisations.

It should be noted that the choice of the legal basis and the route of authorisation is the responsibility of the applicant. However, the text below is provided as guidance concerning general expectations for the authorisation of allergen products for AIT or *in vivo* diagnosis.

4.2.1 Applications according to Article 8(3) of Directive 2001/83/EC

a) *Stand-alone application*

[5] In some processes, a product is stored as an industrially-manufactured bulk at the latest manufacturing stage before the product is filled into its final container, e.g. upon prescription for an individual patient.

For the authorization of allergen products used for therapy or *in vivo* diagnosis of common allergies, typically the data to be provided is expected to meet the current requirements based on Article 8(3) of Directive 2001/83/EC. The dossier should include (besides Modules 1 and 2) a complete Module 3 in line with current guidance, including the Guideline on Allergen Products: Production and Quality Issues (EMEA/CHMP/BWP/304831/07) and Ph. Eur. Monograph on Allergen Products (1063), as applicable. The (non)clinical information should include complete Modules 4 and 5 and is expected to be in line with the relevant guidelines.

b) *"Mixed application"*[6]

Some medicinal products present specific features such that certain requirements of the MAA dossier (as laid down in Part I of Annex I of Directive 2001/83/EC) need to be adapted. This situation may apply in particular to allergen products used for therapy or *in vivo* diagnosis of less common and rare allergies. For authorization of such allergen products, there may be a challenge in recruiting a sufficient number of subjects to obtain clinical data meeting the requirements as requested by current guidelines. In line with Annex I Part II Section 7 of Directive 2001/83/EC, it can be acceptable in such cases that Modules 4 and/or 5 consisting of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references, are provided. For the bibliographical data to be provided as part of the mixed MA, bridging data should be presented to justify that these data are relevant for the allergen product in the application.

Generally, for applications according to Article 8(3), a Paediatric Investigation Plan (PIP) as requested by Regulation (EC) No 1901/2006 is required. However, it should be noted that the Paediatric Committee (PDCO) has the possibility to agree on a waiver, deferral, or bibliographical data to fulfill PIP requirements where sufficiently justified.

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 authorisation is based on well-established medicinal use within the European Union (in accordance with the requirements set out in the Annex I to Directive 2001/83/EC, Part II.1).

For this it needs to be demonstrated that the active substance(s) of a medicinal product in the claimed therapeutic indication has/have been in well-established medicinal use within the Union for at least ten years, with a recognized efficacy and an acceptable level of safety. Adequate bridging data should be provided only to justify that the bibliographical data, presented to support safety and efficacy of the active substance(s), are relevant for the allergen product in the application.

[6] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use, as amended. Annex I Part II Section 7.

[7] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use, as amended. Annex I Part II Section 1.

[8] CMDh Questions & Answers Biologicals, CMDh/269/2012, Rev.1, July 2016

Where non-biological drug substances are concerned in products for the diagnosis of Type IV allergies, well-established use applications under Art. 10a or applications according to Article 10(3) of Directive 2001/83/EC can be applied where the requirements as stated are fulfilled.

In case the bibliographical data are insufficient to support a MA and additional (non)clinical data are needed, the application should follow the mixed Article 8(3) MA procedure (see 6.2 above).

4.2.3 Combination packs

It is recognized that diagnosis of allergies may require several diagnostic allergen products, however it should be noted that the combination of active substances, where active substances are included in separate pharmaceutical forms and presented in a combination pack, cannot be considered as fixed combination according to Article 10 b of Directive 2001/83/EC. Therefore, applicability of Article 10 b of Directive 2001/83/EC (so-called fixed combination) is not considered appropriate to allow distribution of multiple independent products within one combined package.

Note that the possibility of combination packs containing distinct medicinal products would only be possible in very exceptional circumstances, which must be considered on a case by case basis, where the marketing of distinct medicinal products in the same package may be indispensable for public health reasons[9]. Such reasons cannot be related to convenience or commercial purposes and should be agreed upon with the NCAs.

4.2.4 Support of Mutual Recognition Procedures (MRP) and Decentralized Procedures (DCP)

Where authorisation of a new allergen product for AIT or *in vivo* diagnosis of allergies is intended in several MS, a DCP should be used.

Otherwise, in cases where the authorised products are already available in several MS or in a single MS within a national authorisation, MRP should be applied to extend the existing MA to additional MS.

This approach has been rarely used in the past, due to diverging requests on the detail of documentation by MS, as well as due to the high coordinative and documentary efforts needed. As a high number of authorised products are potentially eligible for MRP, this would result in an extraordinary regulatory effort for NCA and MAH alike. To support and enhance such procedures, CMS and RMS should agree on the applicable legal basis for MRP (*e.g.* full/stand-alone, mixed, or well-established use applications) and on the products concerned before the procedure starts.

While each product does require a product-specific MRP and MA according to current requirements, the procedures could be, potentially, combined by a lead procedure, followed by a coordinated approach for the additional products. For the lead procedure, the usual procedural steps should be used and a full assessment report should be created, which could be used as framework for the following additional products and would only need to be amended where product-specific aspects are concerned. This approach should be flagged to the MS in advance. Alternatively, the MRPs for the individual products could be organized and conducted in parallel with the same timetable to reduce the organizational burden.

[9] Notice to Applicants – Volume 2A - Procedures for marketing authorisation - Chapter 1 Marketing Authorisation

It is expected that a full set of data on the quality of the medicinal products is provided. However, in some specific cases not all such data will be available as the underlying national authorisation may be comparably old and available data in the existing dossiers may not be in full compliance to the current state of the art. This may primarily concern products related to non-common/rare allergies where respective batches are not produced regularly. Upon agreement with the RMS and CMS on a case-by-case basis, it can be acceptable to include a commitment to provide additional data obtained from the next batches that are produced and to include these data into the dossier at that time post-authorisation. Such an approach should only be taken where it is plausible that batches are not produced on a regular basis. In any case, available data should allow a reasonable understanding of the product and the process, but could then be fully completed at later time points based on such a commitment.

It is noted that allergen products for immunotherapy may fall within the scope of the centralised procedure according to Article 3 of Regulation (EC) No 726/2004.

5. Medicinal products for allergen immunotherapy (AIT)

Allergen specific immunotherapy is the only known allergy therapy which is able to activate immunomodulatory mechanisms and thus to treat the overreacting immune-system in a disease modifying way (*i.e.* not only symptomatically suppressing allergic symptoms). When allergic rhinitis/rhinoconjunctivitis is (i) left untreated, or (ii) is only treated by symptomatic medication based on pharmacotherapy, or (iii) is treated by immunotherapy products lacking efficacy, there is a risk to escalate to more serious conditions, *e.g.* asthma, which can be a chronic and life-threatening disease. Although the concept of specific immunotherapy is known, efficacy is product-dependent as allergen concentration, composition of the product, administration route, intervals and number of applications may vary for each individual product, even if derived from the same source material. Thus each product must be evaluated individually to prove quality, efficacy and safety.

AIT products are authorised in the MS mainly through national procedures or are supplied in response to a *bona fide* unsolicited order without MAs according to Article 5 of Directive 2001/83/EC. Some of the existing authorisations have been extended to additional MS through MRP. In addition, products authorised through DCP have become available in several MS recently.

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

Typically, products for AIT should be authorised by a MAA as required by Article 8(3) of Directive 2001/83/EC to fully document the quality, efficacy and safety of the concerned product. Specific guidance relevant to allergen products should be followed, where available (see section 4.2.1). This is particularly important for the treatment of common allergies or in indications bearing a high risk for severe adverse events (*e.g.* certain food allergens).

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

Where authorised products are available in a MS for the treatment of specific allergies against a particular allergen source, applicability of NPPs for the same active substance and indication is not considered to be appropriate. Where a MA is already granted in a MS, the recognition of existing MAs via MRP should be followed in order to expand access to additional MS. If products are authorised in one MS, these should not be routinely imported and used as NPPs in another MS.

However, where MRP is not possible, importation can be considered as an alternative. Transition periods should be applied by MS to support transition from NPPs to authorised products.

5.2 Mixed marketing authorisation application – Article 8(3)

While full data as required by Article 8(3) of Directive 2001/83/EC should typically be presented where possible, the concept of mixed MA according to Annex I, Part II, Section 7 of Directive 2001/83/EC can be applied where this is considered reasonable. Under consideration of the biological nature of allergen extracts, bibliographical references should be product-specific.

5.3 Well-established use application – Article 10a

An application according to Article 10a (well-established use) of Directive 2001/83/EC for AIT products should only be accepted under exceptional circumstances as detailed in 4.2.2. This legal basis may be used in exceptional cases 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 on the EU market for at least ten years without a regular MA. The quality of AIT products as biological medicinal products with regard to identity, purity and potency is dependent on the respective manufacturing process and thereby severely limits transferability of data from bibliographical sources.

6. Allergen products for *in vivo* diagnosis

It is noted that different types of medicinal products for *in vivo* diagnosis of allergies are available, including skin prick tests, provocation tests, intracutaneous tests and epicutaneous tests. The level of evidence available and risk for adverse events among distinct types of diagnostics may differ as, for example, there may be less data available for a given bronchial provocation diagnostic as compared to the respective skin prick test. As stated above, the requirements for the data to be provided as required by Article 8(3) of Directive 2001/83/EC apply for *in vivo* diagnostics of allergies. However, depending on the products concerned, an alternative legal basis might need to be considered.

6.1 Applications according to Article 8(3) of Directive 2001/83/EC

For the authorisation of allergen products used for *in vivo* diagnosis of common allergies, the data to be provided is expected to meet the current requirements based on Article 8(3) of Directive 2001/83/EC. The dossier should include (besides Modules 1 and 2) a complete Module 3 in line with the Notice to Applicant and current Guideline on Allergen products: Production and Quality Issues (EMEA/CHMP/BWP/304831/07), Ph. Eur. Monograph on Allergen Products (1063) and available Ph. Eur. Monographs on specific starting material, where applicable. The (non)clinical information should include complete Modules 4 and 5 and is expected to be in line with the Guideline on Clinical Evaluation of Diagnostic Agents CPMP/EWP/1119/98/Rev. 1.

Providing full documentation is considered mandatory for diagnostic allergen products containing allergens derived from sources as listed in Annex I and Annex II, unless sufficiently justified.

6.2 Mixed marketing authorisation application – Article 8(3)

Considerations as stated in section 4.2.2 apply. This may be relevant in particular to allergen products used for *in vivo* diagnosis of less common and rare allergies.

6.3 Well-established use application – Article 10a

In cases where there is a clinical need to have the allergen products available for diagnosis and no complete data are available due to the difficulty to recruit an adequate number of sensitized patients, it can be considered that an authorisation procedure according to Article 10 (a) of Directive 2001/83/EC is followed provided requirements for demonstration of the well-established medicinal use can be fulfilled (see section 4.2.3).

6.4 Special considerations on Type IV allergy diagnostics

While allergen products for the diagnosis of Type I allergies are derived from biological source materials (*e.g.* pollen, animal dander, foods), products for the diagnosis of Type IV allergies are typically derived from chemical substances or mixtures thereof (*e.g.* synthetic substances, formaldehydes, metals such as nickel). However, the considerations as stated above also apply for allergens used for Type IV allergy diagnosis. As the source materials used for the production of Type IV allergy diagnostics are often derived from industrial source materials outside of a pharmaceutical scope (*e.g*. chemical starting materials) , quality requirements should consider this accordingly, *e.g.* that GMP requirements may not be applicable to the source material itself, but only after reception of the material at the manufacturer and accompanying designation as a source material to be used in the manufacturing process for the active substance of a medicinal product.

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.

This preparation is generally manufactured in authorised production sites according to GMP and therefore its manufacture, control and batch release are under the responsibility of the Qualified Person.

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].

NPPs containing active substance(s) derived from the same source material present in products with a MA and available on the national market should not be prepared and used, as the quality, safety and efficacy of these NPPs have not been assessed by a NCA. Considering the complexity of

[10] It is noted that due to a common pathophysiology, allergies cannot be considered rare as defined in the legislation for orphan diseases (for which a marketing authorisation is in any case mandatory), since their frequency is considerably above 5 cases in 10.000 population. However, allergen immunotherapy is indicated only in a small proportion of the allergic population according to medical guidelines, due to the high prevalence of mild symptoms in respiratory allergies.

establishing the equivalence between two biological products containing similar active substances (*i.e.* allergens extracted from the same species), these parameters cannot be considered demonstrated for the NPP simply based on extrapolation from an authorised product derived from the same source material.
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.

Therefore, the preparation of a NPP and use of NPP provision should be considered only in exceptional situations when no alternative medicinal products are available on the EU market. Also, and as discussed above, the use of NPP provisions is not considered to be justified for preparations containing allergens derived from sources as listed in Annex I and II.

Companies that currently market allergens as NPPs should consider applying for a MA as requested in the specific sections above, with temporary use of NPP only to complete ongoing therapies where agreed to by the NCA. MS can implement common or national approaches to develop legally binding frameworks to enhance such changes. Transition periods may be applied by MS to support transition from NPPs to authorised products.
Allergen products or allergens listed in Annexes I and II are expected to be placed on the market with a MA and should not be mixed as part of NPPs.
In order to demonstrate that the preparation of NPPs do not represent a potential bypass of the demand for MA, the finished product (in contrast to a possibly pre-manufactured bulk) should generally not be manufactured in advance with respect to the doctor's prescription.
It is the physician's responsibility to monitor the patient during the therapy, in order to evaluate the safety and efficacy of the NPP prescribed. As specific documentation requirements are applicable (e.g. on manufacturing aspects according to GMP or on safety aspects according to GVP), all relevant information according to these regulations should be promptly available for respective inspections.

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)

Annex II

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 *in vivo* allergen diagnosis:**

- Pollen from *Artemisia vulgaris* (Mugwort)
- Pollen from *Fraxinus excelsior* (Ash)
- Pollen from *Castanea* sp. (Chestnut)
- Pollen from *Platanus* sp.(Plane)
- Milk from *Bos taurus* (Cattle milk)
- Egg from *Gallus domesticus* (Chicken egg)
- Fish
- Olive
- *Prunus persica* (Peach)
- Shellfish
- Soy
- Tree nuts
- *Secale cereale* (Cultivated rye)
- *Triticum aestivum* (Cultivated wheat)
- *Canis familiaris* (Dog)
- Latex