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CHALLENGES IN THE IMPLEMENTATION OF EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

A GLOBAL PERSPECTIVE ON THE REGULATION OF ALLERGEN PRODUCTS

∞ Supplementary materials ∞

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SUPPLEMENTARY INFORMATION ON COUNTRY- SPECIFIC REGULATORY APPROACHES FOR ALLERGEN PRODUCTS IN THE EU

Germany

Allergen products for *in vivo* diagnosis and therapy are subject to a marketing authorization in Germany. However, there are exemptions from this demand for NPP. In 2005, due to changes in the German Medicinal Products Act (*Arzneimittelgesetz*) which would have resulted in the obligation for all NPP to obtain a marketing authorization, Germany introduced an exemption for NPP used for therapeutic purposes. As a result of this, therapy allergens manufactured for an individual patient on the basis of an individual prescription were, as was the case before, not required to obtain a marketing authorization. Allergens for therapy are thereby allowed to be placed on the market as NPP on the basis of an individual prescription. This is independent of the co-existence of already authorized products from the same allergenic source. While such NPP are not authorized and are therefore not assessed for their benefit-risk balance, manufacturers of NPP do need to follow specific regulation in terms of manufacturing, e.g. there is a requirement for a manufacturing license and production under Good Manufacturing Practice (GMP). Nevertheless, NPP are not further supervised by the authorities and thus there is no list of marketed NPPs and no information on their market share. However, since 2008 a national regulation (Therapy Allergen Ordinance (TAO)) is in force for all therapy allergens distributed as NPP that are intended to treat the most prevalent allergies (caused by grass pollen (*Poaceae*), tree pollen (birch, alder, hazel), house dust mites (*Dermatophagoides sp.*), bee and wasp venom) (1, 2). For such products, a marketing authorization is mandatory without any exemption. For NPPs already marketed before the regulation came into effect there is a transition procedure. They are still allowed to be distributed whilst in a marketing authorization application procedure, in which the quality, safety and efficacy is assessed for each product. Taking into account the data available for the concerned

products when the TAO came into force, prolonged transition periods allowing for the conduct of clinical trials are in place, thus allowing the compilation of a full dossier according to the current state-of-the-art to evaluate efficacy and safety. The implementation of the TAO has resulted in the removal from the market of more than 6400 NPP, for most of which there were no clinical data available. Furthermore, there were a considerable number of products where the reasoning behind the composition was very questionable and was not in line with the recommendations of the medical societies (3), as, for example, seasonal and perennial allergens were combined in a single product.

As allergens for diagnosis are usually produced industrially and supplied in multi-use vials for several patients, allergens for diagnosis require a marketing authorization and cannot be placed on the market as NPP. Requirements for content and the evaluation of the marketing authorization application are very similar to therapeutic allergen products. For new products, full dossiers according to the current state-of-the-art have to be submitted. In very specific cases and for established substances (e.g. for diagnosis of certain type IV allergies), a procedure according to Article 10a of the Directive EC/2001/83 (well-established use) may be applicable (case-by-case decision).

Furthermore, whereas allergens for diagnosis may be manufactured in pharmacies without a marketing authorisation under certain conditions, this is not allowed for allergen products for therapy.

According to the German Medicinal Products Act, allergen products (including test and therapy allergens) under the premises of the TAO or having a marketing authorisation are subject to official batch release by the Paul-Ehrlich-Institute. Therefore, a respective batch may only be placed on the market if it is shown that the batch has been manufactured and tested according to the prevailing standard of scientific knowledge.

Italy

In Italy allergen products have been and are largely marketed under the NPP provision, upon request by physicians. These are medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual

patients. In parallel, as an outcome of classical assessment process with regards to MRP or DCP (see above), at least three products have been authorized and are marketed. Manufacturers of allergen preparations in Italy are currently inspected for GMP compliance by the Italian Medicines Agency (AIFA).

Similarly to other European Member States, in Italy the adoption of Directive 89/342/EEC (4) in 1991 into national law (Decree 13 December 1991 (5)) implied that any allergen product had to comply with the requirements of the European pharmaceutical legislation. At that time, manufactures were requested to file a list of existing products according to a number of “families” or “groups” such as food, pollens of various origin, mites, molds, insects, epithelia and venoms which were identified on the basis of a “grouping” (not taxonomic) approach with the addition of a few more categories such as bacteria extracts and chemical preparations (for patch tests). For each applicant the list had to be integrated with representative dossiers for several allergens for each of the families/groups mentioned above. For these existing products a transitional period was allowed, provided an application had been received by the end of April, 1992. More recently the manufacturers were requested to file a full updated quality section of the dossier concerning the drug substance of several allergens. According to a specific timeline defined by the Italian Medicines Agency, manufactures had to submit afterwards a comprehensive set of dossier dealing with quality aspects but limited to the Drug Substance part. In summary, more than 250 dossiers were scrutinized and the assessment process confirmed a general overall improvement of the information provided at the end of the questions and answers steps that were part of the assessment process. Further steps of the process moving onwards from the evaluation of the drug substance aspects of the dossiers are currently in progress. For this, decisions on the timeline and the procedure for handling the assessment of the drug product aspects of the dossiers will be taken by the Italian Medicines Agency after the conclusion of the assessment step involving the respective drug substances.

There is no batch release requirement for allergen products on the Italian market.

The Netherlands

Brief history

Before 1993, allergen diagnostics and therapeutics in the Netherlands were not regulated as medicinal products. The adoption of Directive 89/342/EEC (4) in 1992 implied that any allergen product was now subject to the requirements of European pharmaceutical legislation. From 31 December 1992 this was also applied to allergen products already existing on the market in The Netherlands. As a result, all industrially produced immunotherapeutic and diagnostic allergen products needed to be registered as medicinal products based on a full dossier, including quality, non-clinical and clinical information. For the existing products a transitional period was allowed, provided an application had been received by December 1993. In this period the marketing authorisation holder could provide the complete dossier, develop all required analytical methods and especially obtain the required clinical efficacy evidence. The product could be marketed until authorities had irrevocably decided about the MAA (Marketing Authorization Application).

For the majority of the existing products a MAA was received. MAA was generally only sought for the main indications (grass and tree pollens, house dust mite, bee/wasp venom and cat epithelia). By 2003, 10 allergen products had been approved, several rejected and for three products the applications were still pending. Of the latter, one product was eventually approved while the other two were rejected.

Current regulatory situation

Currently, the following allergen therapeutics (SCIT) are available as registered medicinal products in the Netherlands: Grass pollen extracts, Tree pollen extracts (*Alnus*, *Betula*, *Corylus*), House dust mite extract, Cat epithelia, Hymenoptera Venom (*Vespula* and *Apis*). All of these were registered following a national MAA procedure of products that were already on the market before 1993. In addition two SLIT grass allergen products have been registered, as new applications received after 2003 (via Mutual Recognition Procedure). For many other indications (e.g. weed pollen, fungi or horse/dog epithelia allergies) allergen therapeutics are available as Named-Patient Products.

There is no batch release requirement for allergen products on the Dutch market.

Named-Patient Products (NPP)

Directive 89/341/EEC (6) also lays down exemptions from the general requirements of the EEC pharmaceutical legislation. It is under these exemptions (Article 1, par. 4) that the so-called NPP are regulated. These are medicinal products supplied: “in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility ('named patient exemption')”.

The current legislation in the Netherlands allows dispensing of non-licensed medicinal products (so-called Named Patient products) only under strict regulation (article 3.17 of the Dutch Regulation medicinal product act.; (7)) meeting several conditions:

- 1) The doctor has to consider it necessary to treat the patient with that preparation,
- 2) There is no registered adequate alternative available
- 3) The doctor should apply in writing to the manufacturer/pharmacist separately for each patient
- 4) The manufacturer must provide each application to the Dutch Health Care Inspectorate
- 5) The Inspectorate determines the amount and period it can be given for
- 6) The manufacturer/pharmacist has to record the number of patients, amount of medicine supplied and adverse events.

The regulation of NPP is under the responsibility of the Dutch Health Care Inspectorate. The Inspectorate has clear instructions concerning all conditions for use of non-registered (allergen) products on its website (8). These include that for each patient a doctor's declaration is required and that these are only valid for one year to allow regular evaluation. Furthermore, the manufacturers, wholesalers and pharmacists that have a permission for NPP need to provide an annual overview of the number of patients treated with these. If this number is too large a registration with the MEB or EMA is expected, as the article 3.17 (NPP) regulation is not intended to evade the obligatory Marketing Authorization. In 2009 the inspectorate decided that non-registered allergen therapeutics could only be used in exceptional cases (9). From

2014 the regulation with respect to the dispensing of non-registered allergen products is further enforced (10).

It is noted that the Dutch market for allergen extracts decreased about 30% between 2009 and 2013 (from 50 Million Euro to around 32 million Euro with a similar development in prescriptions) (11). At the same time, the market share of NPP dropped from around 80% to around 52% in 2013. Based on condition 2 of article 3.17 the use of NPP would be limited to allergens for which no registered adequate alternative is available (around 1-2% of total use of allergen therapeutics). Considering this, it is expected that the use of NPP will further decrease and be limited to small categories of patients. Just as for registered allergen products, there is no batch release requirement for NPP allergen products on the Dutch market.

Spain

In Spain, allergen products for both in vivo diagnostics and immunotherapy have been traditionally placed on the market as NPP. Thus, apart from the few products registered by the Decentralized or the Mutual Recognition Procedures, the majority are in use today without any previous marketing authorization and as such, without any regulatory assessment of their quality, safety and efficacy, irrespective of whether they are manufactured by an industrial process or not. Manufacturers are required to hold a manufacturing license and to comply with the GMP guidelines. However, given that a very important aspect of GMP inspections is to make sure that the products are manufactured according to the approved specifications, assurance of full GMP compliance is difficult in the absence of previous quality assessment.

Consequently, a proposal to regulate allergen products already on the market has been drafted in Spain, which is still pending publication. The proposal has established specific regulatory routes for the different types of products, summarized as follows:

- 1) Allergens for in vivo diagnostic: in general, most of these products are industrially-manufactured and as such, submission of a full dossier will be expected. After assessment, successful products will receive a full marketing authorization.
- 2) For specific immunotherapy products, several scenarios are envisaged:

- *bona fide* named-patient products will not need to present a Marketing Authorization Application (MAA), but a communication to the national Competent Authority (AEMPS) before manufacturing may be required. For these products, information on manufacturing history, number of units, etc. should be kept ready for inspection for a specified time;
- specific mixtures for individual patients, prepared from industrially manufactured bulks. In this case, mixtures will only be possible from previously authorized bulks. Authorization of bulks will only be possible after assessment of the relevant quality information. It is intended that the authorization includes those mixtures in which the bulk can be used, hence restricting the mixtures to those previously authorized. Final mixtures prepared on a named-patient basis will be subject to similar requirements than those on the previous point;
- industrially-manufactured finished products will require submission of a full dossier for assessment. The amount of clinical data required for authorization will be determined on a case by case basis.

Finally, a very important aspect of this proposal is that both bulks and allergens for *in vivo* diagnostics will benefit from a highly reduced tax. This was prompted by the restricted market for many of the *in vivo* diagnostic products, which would not make feasible their registration at full tax. Implementation of official batch release is not planned initially, but it cannot be ruled out for the future.

Once the regulation comes into force, no product others than the real NPPs will be expected to be on the market without previous authorization.

Additional approaches in the EU

There are numerous additional approaches by the EU member states. For example, in France, NPPs are supplied as allergènes préparés spécialement pour un individu (APSI) according to a national decree (12) implemented in 2004. Manufacturers were required to provide a list of allergen extracts (mother preparations) intended to be placed on the market in France. For each allergen extract to be distributed, quality documentation was mandatory and the application as diagnostic and/or treatment

had to be justified, respectively, taking into account bibliographical clinical data. In line with this, confirmatory clinical trials were not required. An expert group (APSI group) defined a list of clinically relevant allergens based on these submissions considering published evidence in relation to data available on efficacy for these allergen sources. Only products that contained allergen from these sources were allowed to be placed on the market based on the exemptions allowed by Art. 5 of Directive 2001/83/EC. According to this decree and the decisions of the APSI group, manufacturing and distribution of NPPs was authorized based on authorisations granted covering several products being bulk preparations. It is mandatory for manufacturers to report any serious adverse event in relation to the allergen products distributed under this decree. For further information on the regulatory system applied in France, reference to de Blay et al. (13) is made.

In Austria, a simplified registration can be applied according to the Austrian Medicinal Products Act (Article 7a) (14). As a basis for such a registration, the quality documentation, including the manufacturing procedure, are assessed and subsequently authorized by the Austrian Federal Office for Safety in Health Care. Furthermore, most provisions typically applicable for medicinal products do not apply for registrations according to this procedure, for example, the requirement for renewal of a marketing authorisation, sunset clause or the applicability of the variation regulation.

References

1. Bonertz A, Kaul S, Ruoff C, Vieths S. Die Umsetzung der Therapieallergene-Verordnung bei der spezifischen Immuntherapie. *Eine Bestandsaufnahme. AL* 2014;37:395-402.
2. Englert L, May S, Kaul S, Vieths S. The therapy allergens ordinance ("Therapieallergene-Verordnung"). Background and effects. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 2012;55: 351-357.
3. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology

- (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int* 2014;23:282-319.
4. The Council of the European Communities. Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens. *Official Journal of the European Communities* 1989.
 5. D.M. 13 dicembre 1991 - Disposizioni sui radiofarmaci e sugli allergeni. *Gazz Uff* 1991;297.
 6. The Council of the European Communities. COUNCIL DIRECTIVE of 3 May 1989 amending Directives 65 /65 / EEC, 75 / 318 / EEC and 75 / 319/ EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. *Official Journal of the European Communities* .
 7. Minister van Volksgezondheid, Welzijn en Sport. Regeling Geneesmiddelenwet. http://wetten.overheid.nl/BWBRO022160/geldigheidsdatum_03-09-2014#Hoofdstuk3 (Dec 14, 2016).
 8. Inspectie voor de Gezondheidszorg. Vragen over afleveren ongeregistreerde geneesmiddelen. http://www.igz.nl/onderwerpen/geneesmiddelen/productie_en_distributie_geneesmiddelen/aanvragen_toestemming/vragen_over_afleveren_ongeregistreerde_geneesmiddelen.aspx (Dec 14, 2016).
 9. Nederlandse Vereniging voor Kindergeneeskunde. IGZ beperkt gebruik allergeenpreparaten. <http://www.nvk.nl/Nieuws/tabid/606/articleType/ArticleView/articleId/51/IGZ-beperkt-gebruik-allergeenpreparaten.aspx> (Dec 14, 2016).
 10. VGZ. Machtigingen Farmaceutische zorg. <https://www.cooperatievgz.nl/zorgaanbieders/zorgsoorten/farmaceutische-zorg/machtigingen> (Dec 14, 2016).
 11. Zorginstituut Nederland. Genees- en hulpmiddelen Informatie Project (GIP-)databank. <https://www.gipdatabank.nl> (Dec 14, 2016).
 12. Décret n8 2004-188 du 23 février 2004 relatif auch allergènes préparés spécialement pour un seul individu et modifiant le code de la santé publique.
 13. Blay F de, Doyen V, Bloch-Morot E, Caillot D, Gayraud J, Laval A de et al. French application of the European guidelines for regulation of allergenic extracts. *J Allergy Clin Immunol* 2013;131:1435-1437.e7.
 14. Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln.

