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The EAMG Position on the Regulation of Existing Products for Treatment with Special Reference to Named Patient Products (NPPs)

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"Immunotherapy is the only treatment that may affect the natural course of allergic diseases, and it also may prevent the development of asthma in patients with allergic rhinitis." (1)

Introduction

The above citation from the WHO Position Paper indisputably emphasizes the importance of specific immunotherapy. It is the only causal treatment available for IgE-mediated allergies, if avoidance fails. Symptomatic treatments can only provide temporary relief, may not halt the progression of the disease (the allergic march), and over long periods are pharmaco-economically less attractive. The notion is based on a long history of treatment with allergen products, often designated allergen extracts or, as in the said Position Paper, therapeutic vaccines for allergic diseases. The principle of treatment by repeated administration of increasing doses up to a maintenance dose of extracts from the natural allergen sources does exist already for about 100 years.

The major sources of allergens inducing respiratory allergy comprise pollens, mites, animal epithelia, and moulds. The risk of sensitization is always present, but is highest in early childhood. New substances with previously unknown allergenic properties are regularly detected.

In the early days the products were prepared by pharmacists or by the physicians themselves, but the preparation as magistral recipes according to physicians' prescriptions has gradually been replaced by specialized companies, eleven of which are now associated in the European Allergen Manufacturers Group, the EAMG. The products are industrially prepared under Good Manufacturing Practice (GMP) conditions in

Problem Statement and Definition of a NPP for Allergy

The large number of different allergens and the variability in patient sensitivity towards these allergens, place allergen products in a specific position as compared to other medicinal products. In many cases there is need for an individual approach to the treatment of allergic diseases with therapeutic vaccines containing allergens.

The note for guidance (CPMP/BWP 243/96) divides allergen products into two categories:

- a. industrially produced allergen products for the purposes of *in vivo* diagnosis and for treatment of allergic disease;
- b. allergen products prepared on the basis of an individual prescription and intended to be used on a named patient basis.

This division is not practicable because on the one hand the products of the category b. are mostly industrially prepared and since on the other hand also prescription of products of the category a. often occurs on a named patient basis. The latter custom seems wise because the prescription can then take advantage of the inherent control system (see below). At present, in Europe at least 70-80% of the products for SIT, registered or not, are delivered as named patient products (5).

In view of the common misunderstanding that a named patient product stands for an allergen mixture by definition, it seems worth to define the NPP at the onset of this Position Paper.

A named patient product or NPP is an allergen product (6), prepared with a specific reference number in accordance with a prescription for an individual patient, identified by the name of this patient and the reference number, and delivered after control of consistency with previous treatments.

This definition describes the ideal situation. In view of the different legal and regulatory approach of allergen products in the European countries, the incomplete availability of the necessary data may -in some cases- hamper the adherence to the definition in practice.

Safety Aspects of NPPs: A Secured Delivery Control

In terms of controlled delivery of medicinal products, the safety aspects of NPPs present a further rationale for their existence. Current immunotherapy administration recommends a total treatment period of 3 to 5 years, with the administration of successive treatment sets along this period. NPP use should be best based on a computerized record of patient history, including prescription validation. This includes control of allergen composition and potency of the prescribed/delivered products, administration schedules for initial and subsequent maintenance treatments, and of time intervals between deliveries. The factual restriction for preparing specialties for less common

allergens and the possibilities of coping with oligo- and polysensitisations with a single preparation are further advantages¹.

The manufacturer of NPPs can be in direct contact with the prescriber and is thus able to advise him/her to correct certain prescriptions if they are not consistent with well defined formulation rules which have been devised to maximize safety and efficacy.

The link is also used to follow up patients, since all prescriptions are registered and filed for drug safety purposes. Only the manufacturer of NPPs is in a position to identify all the users (physicians and patients) of a defective batch, a more difficult task for products delivered unnamed. This results in safer use and better monitoring of the allergenic activity. It further enables products to be recalled very quickly. Allergen extracts are as safe as other medicinal products when used according to the recommended procedures.

The NPP-concept for allergen products represents a unique position in the pharmaceutical environment as it is used so more often than in other therapeutic areas. It offers additional tools to increase product safety and remains crucial for allergen-based immunotherapy products. The system can be easily linked to the pharmacovigilance service for tracing untoward reactions.

Industrially Prepared Allergens and Mixtures

There is a tendency to equate NPPs with allergen mixtures. For the practice of allergology in the Western European Countries this can detract from the efforts of allergen manufacturers to arrive at safe and controlled, industrially prepared named patient products containing relevant allergens. The NPP-concept covers not only non-registered products (single allergens and mixtures) but can be profitably applied also to allergen products, which have been submitted for marketing authorization and batch release procedures according to the Health Authorities. Presently, registered products are also often delivered on individual prescription and after a careful follow-up of the historical data as outlined above.

It seems important to stress that the term "single allergens" does not refer to a product consisting of identical macromolecules only, but rather of the extractable components from a single allergen source, e.g. pollens of one species. Further, in this context, combined extracts from different sources or extracts from different combined sources of fully cross-reactive allergens are considered "single allergens" as well, e.g. pollen of different grasses.

The EAMG recommends the use of industrially batch-produced allergen extracts, if available, leaving the use of individually prepared extracts for all other conditions,

¹See the French circular dated 23-07-1965. Quotation: "It is necessary, in certain cases and in view of possible advancements in the biological sciences, to permit the implementation of methods which are seen to be likely to be of use to prescribers in the future without necessarily leading to the production of specialised products". Not relevant in other countries.

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especially also for those patients sensitive to non-common allergens or with a special sensitization degree, which requires products not covered by the industrially prepared product ranges. The prescription of non-related allergenic components in a mixture is not encouraged. Preferably, materials that are considered not indicated for SIT should be excluded from individual preparations and mixtures. Mixtures should not contain compounds from more than 4 different, non-cross-reactive allergen sources. Material from non-related allergen sources should not be mixed, certainly not if incompatibility of the materials, such as mutual proteolytic digestion, is documented. If possible, mixtures of seasonal and perennial allergens should be avoided or discouraged.

In any case, the applicability of the NPP scenario for allergens should control all these aspects, driving the use of industrially produced extracts or individually prepared extracts, where appropriate. The limiting conditions given in the above paragraph can only be a guideline or direction for the prescribing physician. Manufacturers of NPPs are, however, in the position to maximally discourage the physicians to deviate from these conditions.

The Manufacture of NPPs

NPPs may be manufactured

1. as immunotherapy sets in fixed **final** product configurations (usually registered products).
2. as batch produced vials containing different allergen extract concentrations and finally configured as immunotherapy sets **on request** (industrially prepared but non-registered products). This procedure is not legally applicable in some countries.
3. from bulk solutions of allergenic extracts prepared in standard concentrations and diluted/mixed in vials according to **individual formulation**.

As outlined above, NPPs may be made up of a single extract or of a mixture of extracts and be prepared as one or more dilutions of the latter. These characteristics are related to the individual sensitivity of the patient and the nature of allergens.

For these reasons a wide assortment of products, including extracts from rare allergens for which regulatory demands cannot be fulfilled due to polysensitisation or low incidence, needs to be available in order to fit the patients' characteristics. The exceptionally wide product range cannot present the same level of documentation/quality for all the products, ranging from registered extracts with similar characteristics to those of other biological drugs to individually prepared extracts based on experience and on the extrapolation of the results obtained with other allergen products.

The quality of all NPPs is guaranteed by controlling source materials, controlling the extracts at appropriate stages (intermediate and/or finished products) and as bulks before and after physical and/or chemical modification and, further, by definition and implementation of and strict compliance with pharmaceutical codes (European Pharmacopoeia, etc.).

NPPs for immunotherapy include allergen extracts either unmodified or modified chemically and/or by adsorption onto different carriers for subcutaneous injection (solutions or suspensions), or by inclusion in specific formulations for sublingual or oral administration (solutions or solid-dose forms) or for nasal application (solutions or powders).

The preparation of mixtures and dilutions is considered one of the key steps in the preparation of NPPs. To secure consistency of the requested product with previous treatments, the IT systems should ideally include a validation step against historical data base, comprising precise data for the different products delivered to each patient, if available (delivery date, product type, composition, dosage, etc.). Databases containing patient data must be declared to the authorities, according to the current applicable EU Directives. All elements of the Data Protection legislation must be complied with.

Regulatory Aspects

NPPs have often been identified with poorly quality-controlled products (too diluted; too many components), instead of being considered as a unique concept of product manufacture / distribution, perfectly adapted to the special treatment characteristics of the allergic disease. For this reason NPPs deserve the full attention of the regulatory authorities from the health policy point of view.

The system of NPPs as described in more detail in the Position Paper of the EAMG is specifically designed to cope with these problems. Firstly, the preparation of the NPPs follows and has to follow strict procedures; the manufacturers are ready to commit themselves to the necessary inspections and auditing procedures. Secondly, the system prevents or at least minimizes errors and thereby safeguards the patients. One may argue whether it would be preferable that the legal and regulatory environment be adjusted all over Europe to enable the production and distribution of allergen products according to the conditions described. The legal possibilities for obtaining the necessary patient data are not similar in all European countries. Regulation in some countries makes it difficult, if at all possible to achieve this.

The European Regulatory Authorities should standardize their interpretation of the regulatory status of NPPs. By a change of an article of law in 1998, the French authorities already have officially confirmed and maintained the NPPs for allergens for French manufacturers². Also a Royal Decree in Spain³ and a Belgian "Arrêté Royal"⁴ proposed a similar approach whereas most other countries have interpreted the rules differently.

² In July 1998, the law on "Sanitary security" confirmed the official status of NPPs in France. NPPs were maintained in the new version as described in the initial Article L513 of the Public Health Code of 1959. The system used is known as A.P.S.I. (Allergènes Préparés Spécialement pour un Individu). An update of the decree is pending; new applications are presently not accepted.

³ Real Decreto 288/1991 por el que se regulan los medicamentos inmunológicos de uso humano. Issued March 8, 1991 by the Spanish Ministry of Health.

⁴ Arrêté Royal. Mon.B. 10-07-1969.

Some European countries have gone above for NPPs. In some countries, Doctors, patients and the regulatory authorities are involved in the prescription to the patient about the procedure. In a number of countries, the specific dose and the responsible person are not also to be determined.

Product registration is possible with the NPPs. However, errors that have occurred with allergen extracts. However, a sufficient number of patients have accepted on the basis of the materials, together with the safer use of the products.

Conclusion

For reasons of safety, the preparation shall be prepared in a controlled environment.

It is recommended that:

1. takes into account the specific characteristics of the product.
2. is not in conflict with the regulatory requirements.
3. EAMG-member countries should be informed.

The foundation of the system is maintained.

Summary

Allergen products for immunotherapy are used in the treatment of allergic disease. It is essential that the products are of high quality and indisputable and indisputable. The products are derived from IgE-mediated allergic reactions to these products.

Within the framework of the NPP system, a named patient is identified by a reference number.

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Some European allergen manufacturers already apply the procedures described above for NPPs in the production/distribution of allergen products for therapy. Doctors, patients and pharmacists rely on this strict follow-up of the product, from the prescription to the administration activities. Local Health Authorities are informed about the procedures. The system can only exploit its benefits fully if the legislation and regulatory measures allow the manufacturers to dispose of the necessary patient data. In a number of European countries this condition is not met. The data are considered the specific domain of the pharmacists. However, it seems not self-evident to restrict the responsibility of the allergen manufacturer to the production of the prescription and not also to include the terms for control.

Product registration procedures for the most common allergens are not incompatible with the NPP concept. On the contrary, NPP adds flexibility to protect patients from errors that have caused undesired reactions during the administration of allergen extracts. However, there are only a small number of allergens for which there are a sufficient number of monosensitised patients to perform proper clinical studies. For this reason the allergens, for which prevalence and incidence are less high, should be accepted on the basis of extrapolation and comparison of the nature of the source materials, together with a strict application of the NPP rules, which again contribute to safer use of these products.

Conclusion

For reasons of principle allergen manufacturers, which are members of the EAMG, shall be prepared to register all the allergen products, specialties and others.

It is recommended to work out a special format for a NPP dossier that

1. takes into account the above considerations;
2. is not in contradiction with the European directives;
3. EAMG-members are prepared to submit to regulatory authorities.

The founding of an interdisciplinary working group at the EU-level may be entertained.

Summary

Allergen products have a long history in both diagnosis and management of allergic disease. It is emphasized that the availability of named patient products presents a valuable and indispensable option for the effective and safe treatment of patients suffering from IgE-mediated allergic diseases. A regulatory climate should be achieved in which these products can survive until a safe and effective alternative is borne out.

Within the context of the paper the following definition is used:

A named patient product or NPP is an allergen product, prepared with a specific reference number in accordance with a prescription for an individual patient, identified by

the name of this patient and the reference number, and delivered after control of consistency with previous treatments.

It is stressed that the standards of quality that hold for registered products are also applicable for named patient preparations which, for various reasons, can not be filed for registration. The paper frequently refers to a Position Paper that has recently been adopted by the European Allergen Manufacturers Group, the EAMG. The presentation breaks a lance for a concerted approach of the NPP-concept by striving at harmonization of legal, regulatory, manufacturing, and distribution conditions.

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6. Definition of Allergen product from Ph.Eur. 1997: "Allergen products are pharmaceutical preparations derived from extracts of naturally occurring source materials containing allergens, which are substances that cause or provoke allergic disease".

Discussion

Vieths: First of all, I would like to thank you for your interesting presentation. The Paul-Ehrlich-Institut also advocates the efforts of the European Allergen Manufacturers Group to specify quality criteria for named patient products. I think this is important. On the other hand, it is obvious that your definition, as you also stated in your presentation, is not in accordance with the European guidelines, neither with the EU directive 2001/83 nor with the Note for Guidance. First, we would be interested to know why you would prefer not to stick to the European regulations. Second, I would also like to comment from the point of view of the patient. Prof. Cichutek already mentioned that, from our point of view, the patient is most important. I think the Allergen Manufacturers Group has to be aware that if you prefer to sell named patient products, then you recommend the use of products for which efficacy has never been demonstrated in patients. I would like to know if this is indeed the opinion of all the European manufacturers.

Kroon: Well, the main point is that the patients are also the central part in the considerations of the manufacturers. There is a large number of patients who have shown sensitization to allergens which are impossible to study clinically according to the present demands. The idea is that for all allergens where it is possible to fulfill the criteria of

the Note for Guidance. But in the meantime, should not be lost sight of the fact that named patient products are not their treatment products according to the regulations. Patients should be studied in controlled allergic trials with similar extracts. The regulations are not sufficiently protective. Hopefully, in the future, we will be able to explain to the manufacturers why they

Malling: I think it is important to have 10 years. We already had a Symposium. I would clearly stated that the discussion is not for Patients do not know they might be sensitive to them with different that based on science and that was not immunotherapy mixtures, you are Academy position. Fine treatment of clinical efficacy in clinical trials. In the position

Kroon: The point is that there is no sense in the clinical efficacy enough population scores and need effect of a single

Malling: As a consequence of those few allergic symptoms. And we have to accept that we have to accept that products is clinically