

Regulation, Role and Future of Named Patient Products in Germany

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Allergens were subjected to European pharmaceutical legislation in 1989 by the Directive 89/342/EEC [1] reviewed in Lorenz et al. [2]. Directive 2001/83/EC [3] defines an allergen product as “any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent”. Article 2 of this Directive as amended by Directive 2004/27/EC [4] states that it “shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process”. Almost all allergen products that are prepared on the basis of an individual prescription are prepared by methods involving an industrial process because they are manufactured by allergen manufacturers. Although in general the named patient products (NPPs) can be categorized into the following types [5]:

- Allergen extracts manufactured from source material originating from the environment of an individual patient (the “true” NPPs),
- Allergen extracts and mixtures thereof prepared from commercial source material or intermediate products (bulks) on the basis of a prescription for an individual patient (the common situation in Germany).

All are “prepared industrially or manufactured by a method involving an industrial process”. For this reason NPPs as currently marketed in the EU are generally subjected to the regulations of Directive 2001/83/EC as amended.

Article 6 of Directive 2001/83/EC as amended [6] states that “No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No. 726/2004...”.

So the clear message is:

1. Allergens are medicinal products and
2. Medicinal products require marketing authorizations.

In the German Medicinal Products Act's section 21 (2) No. 1b [7] a specific exception is made that a marketing authorization is not required for medicinal products other than those referred to in No. 1a which are manufactured for individual patients on prescription. This exception was made in the 14th version of the German Medicinal Products Act in response to above mentioned EU Directive 2004/27/EC which changed the scope of Directive 2001/83/EC and included those medicinal products "manufactured by a method involving an industrial process". Without this exception in the German Medicinal Products Act, the corresponding change of the definition of finished medicinal products would have led – for virtually all allergen preparations – to the obligation to have a marketing authorization.

Products with a marketing authorization have to be produced in batches. For a relatively large number of therapy allergens and many allergen mixtures this rule causes problems as there are not enough patients with exactly the same requirements. Therefore the treatment of allergies with low prevalence and certain combinations of concomitant allergies is the intended domain of NPPs.

In other words, the rationale of NPPs is to offer specific immunotherapy as a therapeutic option to patients whose allergies cannot be treated with authorized products because they suffer from rare allergies or the patients are polysensitized to certain combinations of allergens.

What are the regulatory requirements for NPPs?

NPPs must have a manufacturing license. In Germany, this is granted by the authorities of the Federal States in consultation with the Paul-Ehrlich-Institut (PEI) and the production according to Good Manufacturing Practice (GMP) has to be certified.

What are the differences to authorized products?

For NPPs there is no independent evaluation of quality, safety and efficacy. Stability testing can only be done for model preparations but not for the finished product that is prepared for a patient according to a prescription. There is also no demand for the manufacturers to notify adverse events. Even if many of them do so – there is no official demand. No independent risk-benefit analysis is possible for NPPs. For many years these differences to authorized products were tempted to bypass the rules for marketing authorization. For example, 26 single allergen extracts from birch pollen were marketed in Germany in 2008 according to product lists of manufacturers. However, marketing authorizations have been granted for six products only. Keeping in mind that birch pollen allergy is a disease with a prevalence estimated at 10 percent, the possibility to perform clinical trials is clearly given. Thus, from a regulatory point of view and for the benefit of the birch pollen allergic patients there is no reason to sell products on a named patient basis without any independent approval of quality, safety and efficacy.

To resolve this unsatisfactory situation, the PEI together with the German Federal Ministry of Health took the initiative to prepare a regulation, entitled “Verordnung über die Ausdehnung der Vorschriften über die Zulassung der Arzneimittel auf Therapieallergene, die für einzelne Personen auf Grund einer Rezeptur hergestellt werden, sowie über Verfahrensregelungen der staatlichen Chargenprüfung (Therapieallergene-Verordnung)“, in short called „Regulation for Therapy Allergens“ [8]. It applies to NPPs prepared from industrially manufactured bulks, so true NPPs that are not prepared from pre-manufactured bulks are exempted. Moreover, only allergen sources with a high prevalence to induce clinical relevant allergies are concerned by the regulation. In the appendix to the regulation a list of these allergen sources is given and 100% preparations as well as mixtures containing one or more allergens from this list are subjected to marketing authorization. The allergens concerned are:

- Grass species of the *Poaceae* family except *Poa* may
- *Betula* sp. (birch)
- *Alnus* sp. (alder)
- *Corylus* sp. (hazel)
- *Dermatophagoides* sp. (house dust mites)
- Bee venom
- Wasp venom

Mugwort that was on the list initially but was deleted as actually there are not enough prescriptions in Germany to allow the performance of appropriate clinical trials.

The bulks prepared from allergens concerned will be subject to official batch release by PEI from 1 October 2008.

The regulation includes the possibility for relatively long transition periods:

- Within 6 months after coming into force notifications have to be made of products for licensing as well as of those that are not intended to be applied for marketing authorization to the PEI (deadline: 14.05.2009).
- The application for marketing authorization is supposed to be submitted within 24 months (deadline: 01.12.2010). A deficiency report will be send by PEI afterwards because many of these application dossiers can be expected to be more or less incomplete.
- Response by the applicant is required within 12 months (instead of usually 6 months). In case of deficiencies concerning clinical issues there is the possibility for PEI to grant a prolongation of the transition period for up to seven years if justified.

As there should be a certain control of the market soon after the enforcement of the regulation, quality control of bulks will take place approximately 5 months after the notification of the respective preparation. So independent access to quality data of the products is given within a relatively short period of time.

The main criticisms to this approach raised by the manufacturers are:

- The legal basis is doubted. The justification for this regulation is to prevent health risks and in fact there are direct health risks like anaphylactic reactions to products whose compositions are unknown to the regulators. There is also an indirect health risk as progression of rhinitis to asthma can occur in patients treated with a product lacking efficacy.
- It might not be possible to generate appropriate clinical data within 10 years.
- The regulation will have a strong impact on the availability of mixtures. Indeed it is possible that there will be problems for patients currently treated with NPPs whose availability will be discontinued. To defuse this problem, a transition period was integrated in the regulation for allowing completion of treatment of patients already under therapy when the regulation comes into force.
- PEI might not be able to review and process all marketing authorization dossiers in due time.

So the future of NPPs in Germany after implementation of the regulation will be characterized by the following key points:

- “True” NPPs will still be available,
- Independent evaluation of quality through batch release will take place after a short transition period,
- There will be a proof of efficacy and safety according to the state-of-the-art for allergen sources of high prevalence, so that a
- Risk-benefit evaluation will be possible and
- The use of mixtures of doubtful relevance will be reduced.

NB: Besides the enforcement of the German Regulation for Therapy Allergens [8] after the IPES 2008, some other important changes regarding quality requirements came into force referred to in the reference list [9–11]. Moreover, the exception from the requirement of marketing authorization for NPPs in the German Medicinal Products Act was moved from section 21 (2) No. 1b to section 21 (2) No. 1g with a new amendment of the law [12].

References

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Discussion

Lopes: Thank you very much for this presentation. I am very pleased to see that Germany will implement a new regulation for NPPs, France will not feel too alone anymore. I can confirm that it is a very difficult task to perform and I have a comment and a question. Why do you not also use the article 5 of the directive 2001/83/EC, because in France we were able to use that article? The other question is: How many marketing authorizations do you feel will possibly be given to false NPPs in the future?

Vieths: So, you mean how many new marketing authorizations we would expect in the future? We have calculated something around 200 to 250. The legal basis I cannot tell you, because the decision was made by our legal department. We discussed with them the tools that we have and they thought that the ones that I described were the best. So I cannot respond to this properly.

de Beaumont: I would like to ask you what you mean by “state of the art” regarding safety and efficacy. The point is, e.g., we have a couple of products such as tablets to be registered, especially in the phase 1, 2, and 3 clinical trials, and you can imagine the burden of investment and the process of registration. In parallel, for NPPs we have a couple of allergens and we are talking about proof of efficacy. These allergens are now let us say in clinical trials with the state of the art from 10 or 15 years ago, in terms of proving efficacy and regarding sample size. Do you consider we will have to implement new phase 3 clinical studies to demonstrate the efficacy for instance, which means a big number of patients, competition to have the patient in studies of two pharmaceutical companies. And for SCIT, e.g., with regard to

anaphylactic shock do you consider that we have to perform new clinical studies in subcutaneous IT from an ethical point of view, given the risk of anaphylactic shock that is predicted as a risk factor. What is your opinion on that?

Vieths: I am not sure if I got your point correctly. The “state of the art” is defined in the current guideline. So I think that it is relatively clear what you have to provide. The products you are referring to are products that are used as named patient products in Germany and in other countries. If you have not performed clinical trials so far you have to perform them. The answer is very clear.

Barber: If I understand correctly, under the current regulatory framework, when you will be granting new marketing authorizations for some existing products in Germany, Germany will automatically be the reference member state for any future registration in Europe of those products. Is that right?

Vieths: Yes. I mean you can turn it around. We have some problems with products that have a marketing authorization in the Netherlands or Spain and are sold as named-patient products in Germany. For those products, which are identical to products that have a marketing authorization, the MR procedure applies. This means that the transition period that I have shown here does not apply to those products. But that is a problem that is very difficult to solve for us at the national level.

Rüttgers: I have two questions to you. You spoke about mixtures with doubtful relevance. Can you give us an example for that and the second question is: What will happen to the approved products which come from a time when clinical evidence was not required?

Vieths: So first of all, I strongly disagree with your last statement, because clinical evidence was always required. I mean, the state of the art was different and the allowance for extrapolation was much broader than it is now, but we are still allowing extrapolations between different products. So, clinical evidence was always necessary to get a marketing authorization. We had this discussion before and some of you may know we also sent a letter to all the board members of the German allergy societies to correct some statements that were passed around. Mixtures of doubtful relevance: I think if somebody tries to treat grass pollen allergy and you have a strong reaction in prick test to timothy pollen and you have a small wheal to wheat extract and then you prescribe a mixture of 95% timothy grass and 5% wheat that is something that in my opinion is of doubtful clinical relevance. And we would ask for a justification of such a mixture.

Keyzers: First of all, I would like to thank you for the guidance so far because how you have processed it in the last couple of months gave us the impression that you really were looking for collaboration and to integrate the pharmaceutical industry. That I think is a comment which I think is fair to the PEI. One question I have is regarding the mixtures between homologous groups. For example, you mentioned trees and grass. What is your perspective on products which have been granted marketing authorizations in the 1990s and which have mixtures of 75% of one homolo-

gous group and 25% of the other homologous group? Marketing authorization has been granted for those, but from today's perspective we would not grant a marketing authorization any more.

Vieths: That is something we are trying to re-evaluate and discuss with manufacturers. We probably will have some activities in this field in the future. We have to look at the data that we have. Generally speaking, I think if somebody puts together a mixture of components which are not members of the homologous group it is not totally excluded. The homologous groups concept says if you do this with members of homologous groups, you can do this without additional clinical data. For allergens that are not cross-reactive – if you are able to show in a clinical trial that the product is effective and safe in the target population I would see, in general, no reason not to register such a product.

de Blay: I am not sure whether I understood this correctly, but is a German allergologist allowed to perform a desensitization for rare allergens, e.g. horse dander, without any clinical benefit or without any clinical efficacy?

Vieths: It would be permitted. It has always been permitted to prescribe horse extract on a named-patient basis, and it will be permitted in the future as well.

de Blay: And you did not think about any control of efficacy within 7 years or 10 years?

Vieths: The problem is how you can control efficacy of the product if the patient number is very low.

de Blay: Yes, we tried to figure that out in the French regulation. And we think about working with all the allergologists and try to perform something like a record. I know it is not very good, but it is better than nothing just to have an idea within 5 years whether it is worth to carry on or not.

Vieths: So the idea is to generate some data even if it is not double-blind placebo-controlled, but to get some evidence for clinical efficacy.

de Blay: Yes, coming from real life, I think in France it is the same that there are very few allergic patients desensitized to horse.

Vieths: Well, at the moment we are not having such an approach in Germany. Maybe it is a good idea, but of course it is also a lot of work and especially a lot of coordination work and thinking about criteria. So I think it is probably a good idea, but for us, at the moment, it is impossible to just organize such an approach.

Narkus: Could you speculate about when this new regulation really comes into force?

Vieths: Well, we have a member of the German Ministry of Health here and she thinks that probably by the end of this year it will be passed to the Bundesrat, the Chamber of the Federal States, either in October or November.

