

New Regulatory Documents and Procedures I: Guideline on Clinical Trials of SIT Products, European Pharmacopoeia, and Note for Guidance on Allergen Products

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Introduction

Allergen products have been recognised as medicinal products when Directive 89/342/EEC, extending the scope of Directive 65/65/EEC and Directive 75/319/EEC was put into force. It was immediately considered that due to the peculiarity of the products involved, a specific guidance was required to help manufactures and National Regulatory Authorities (NRA) in the implementation of the various concepts introduced by the new legislation. Therefore, at the European level, the *ad hoc* Biotechnology Working Party (BWP) was appointed by the Committee for Proprietary Medicinal Products (CPMP) in Brussels to set a guideline for these products. The first edition of the Note for Guidance on Allergenic Products was issued in 1992 and as a revised version in 1996 within the European Medicines Agency (EMA – London) framework. Similarly, within the EDQM framework, a General Monograph on Allergen Products was published by the European Pharmacopoeia, to give the manufacturers and NRA further guidance in setting down testing requirements for allergens. More recently, the medicinal product status of allergen preparations was confirmed by Directive 2001/83/EC, as amended.

These two documents (guideline and monograph) are still in force. However, due to a number of reasons linked to new products and processes development, it was recently recognised that these texts, although still applicable in some areas, require to be updated in other sections, and therefore at the EMA and EDQM level the process to revise both texts was set. Briefly, this revision process has now generated three documents. At the EMA level, the original guideline, dealing with quality, safety and efficacy (being safety and efficacy very marginally treated and without real specific guidance) was split into two guidelines, one dealing with quality and the other dealing with safety and efficacy guidance for immunotherapy studies. At the EDQM level, the monograph was revised taking into account the parallel evolution of the guideline and introducing some new concepts to allow a broader application of the text.

EMEA Guidelines

The need for a revised European guideline was due to several factors linked to quality as well as safety and efficacy aspects. From the quality side, it was recognised that the concept of taxonomic families was too vague and not scientifically based due to the present level of knowledge available on structure and properties of allergenic molecules present in the various extracts. It was therefore proposed during the last PEI Seminar (2005) to move towards a new system introducing the “homologous group” concept. Second, it was felt as not being state of the art the fact that recombinant allergens were excluded in the current guideline, due to the number of clinical trials and published results currently available in the immunotherapy area involving such molecules. Third, the structure of the guideline was not in line with the current CTD distinction between drug substance and drug product, and an update, not only editorial, was regarded as appropriate. Finally, a fourth aspect was underlined, linked to the necessity to better define cases where IgE potency is not measurable due to the nature of the product itself, such as in those cases where the IgE binding activity is reduced/eliminated on purpose and the IgE-binding test itself would produce a result of limited value from the batch to batch consistency point of view. The revision was carried out by experts in a specific Drafting Group within the Biologics Working Party at EMEA. From the safety and efficacy point of view, the current guideline is giving almost no advice, and it makes a general reference to the fact that safety and efficacy data, collected according to the general indication of the relevant guidelines, can be extrapolated according to the taxonomic family concept. In the revised draft, a completely new guideline was prepared, addressing all the relevant points concerning safety and efficacy of allergen products. The guideline, however, deals with products for immunotherapy only, as this was felt as the area where most of the problems, due to lack of guidance, are present. Therefore, issues linked to the demonstration of safety and efficacy of products for *in vivo* diagnosis were left out on purpose. This guideline was prepared by experts in a specific Drafting Group within the Efficacy Working Party at EMEA.

Very briefly, the points which have been changed/introduced in the draft of the new guidelines under finalisation dealing with quality, efficacy and safety are the following:

Quality Guideline

The concept of taxonomic families was replaced by the introduction of the homologous group concept. This concept is well described in the Quality Guideline, together with the definition of what a “representative allergen extract” means, and conditions that have to be fulfilled by the applicant to go along this “homologous group” approach are clearly given. Briefly, allergen extracts are not grouped any more according to the taxonomic family of origin of the source material but according to four conditions which have all to be fulfilled. The conditions are:

- Comparable physicochemical and biological properties of the source material
- Cross-reactivity/structural homology of the allergens
- Identical formulation of the finished product
- Identical production process of the allergen extract and of the finished product.

However, the advantages of the introduction of the homologous approach essentially applies to efficacy and safety studies where extrapolation of efficacy and safety data within a homologous group is allowed. In fact the only aspect at the quality level which may take some advantage from the homologous group concept can be found at the level of stability data, where some extrapolation within a given homologous group can be accepted for ongoing stability data, being full data for the representative allergen required since the very beginning of the evaluation process. A section on recombinant products has been also introduced. The guideline structure has been harmonised with Common Technical Document structure. More details on IHRP establishment and sera pool preparation, and manufacturing process steps for both drug substance (DS) and drug product (DP) have been introduced, as well as for allergen mixtures. To avoid problems linked to changes introduced during product development and after process validation, the comparability exercise issue has been underlined. Moreover, the concept that the principles of the Guideline on Good Agricultural and Collection Practice (GAPC) for Starting Material of Herbal Origin and other relevant guidelines for the source material of plant origin should be followed where applicable has been underlined. Finally, more details for potency assay and stability evaluation both at the active substance and finished product level have been introduced.

Efficacy and safety Guideline

As already said, currently no real specific guidance for immunotherapy is available. A very short reference to the existing general safety and efficacy guidelines is made in the currently available document. In the draft which has been completed, a number of aspects has been specifically treated. Patient characteristics and selection criteria of patients have been inserted. Aspects such as diagnosis and selection of patients, co-morbidity and co-medication are considered in the new text. Moreover the strategy and designs of clinical trials are clearly discussed in the document. In particular concepts like early studies planning, dose-finding studies, pharmacokinetic/pharmacodynamic studies, confirmatory studies, food allergy, trials with purified allergens (native/recombinant/synthetic peptides), issue of cross-reacting allergens, necessity of comparability studies at the clinical level in case of product changes, different routes of application, etc. have now specific and detailed guidance to help manufacturers in setting clinical trials protocols. Finally, two important chapters, such as efficacy in children and safety concerns of the product, have been inserted in the text. Both guidelines are now updated and may provide state of the art guidance in the field.

European Pharmacopoeia Monograph

A number of points requiring updating of the monograph have been similarly identified. In particular, the current version of the monograph does not cover named patient products. This is mainly due to the fact that it was issued in relation to the current European legislation and EU guideline, which do not cover named-patient products as well. However, despite the fact that the revised draft EMEA guidelines still do not cover named-patient products, it was decided to revise the monograph also to include them, in order to provide regulatory authorities and manufacturers

with some guidance also for the named-patient products. Moreover, other issues were covered in the revision process, such as the deletion of abnormal toxicity test and the deletion of the antigen profile test; finally, limits of some tests (such as water content of freeze dried products, total allergenic activity and individual allergens content) have been extensively re-discussed and, where applicable, modified.

To briefly summarise, the following changes have been introduced in the draft which requires now the final approval by the European Pharmacopoeia Commission. As already said, the scope of the monograph was extended to cover named-patient products. At the level of source materials, a more detailed description has been included and paragraphs for hymenoptera venoms and food source materials have been added. Moreover, the issue of the content of relevant residual solvents, heavy metals and pesticides has been clarified and the concept that these residues have to be measured on a number of batches according to an appropriate sampling plan has been inserted. At the level of the manufacturing process, a more detailed description of information to be provided has been included. The stages for the manufacturing process have been defined as source material, active substance and finished product; all other stages of the manufacturing process are considered as intermediates. As regards the In-house reference preparation (IHRP), the possibility to use *in vitro* methods for the establishment of the IHRP has been added. In agreement with some recent regulatory decisions, the water content for oral lyophilisates may be higher than 5 per cent, if approved by the competent authority. Another important issue which has been addressed by the revision is linked to the fact that the skin-prick test preparations are not covered by the general monograph on "Parenteral preparations" (0520). Nevertheless sterility is a reasonable requirement for these products and is now requested. Similarly a reference to chapter 5.1.4. "Microbial quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use" has been added for non-sterile allergen products, the range for protein content has been redefined and to reduce the number of animal tests and in the light of large historical data, abnormal toxicity test was deleted. Moreover, the test to evaluate the antigen profile has been deleted due to its lack of clear meaning, whilst on the basis of data provided by regulatory authority and manufacturers the range for total allergenic activity and individual allergen content has been narrowed down to 50–150 per cent. Finally the text has been aligned with the EMEA draft guideline on allergen products: production and quality issues (see above EMEA/CHMP/BWP/304831/2007).

Conclusions

The available Note for Guidance and the Pharmacopoeia Monograph have been revised by various experts. The revised documents (two Guidelines and one Monograph) will be finalised very soon, and the new concepts which have been introduced will help regulatory authorities and manufactures in keeping the dossiers and products evaluation processes updated. It remains still controversial the impact of such documents at the national level for those products which are prescribed on a named-patient basis. In this specific context, harmonisation of views and approaches may remain an important issue to be achieved in Europe.

Discussion

Mari: Thank you, Carlo, for updating us on all these novelties. I guess we have to go through this document when it will be published to know more about all of these innovations. I would like to ask you to clarify some points that you reported. You reported some criteria to define homologous groups, but not how to apply these criteria. Because when you look at cross-reactivity, e.g., in grasses, it is different whether you consider group 1 or group 7.

Pini: I guess we had a long discussion about that and maybe Stefan can summarize a little bit the issue, because it is not a simple answer.

Vieths: You are right, Adriano. There is a couple of open questions and we had an informal meeting between members of the group, who wrote the guideline and the paper, with industry before the Paul-Ehrlich-Seminar to resolve those issues. There still is a number of open questions, but I think the important message for manufacturers is that the group concept has been kept. And that is very important. So there is still the possibility of grouping allergens and you can change the composition of the group on the basis of a justification which is also very important. So it is not something that is written there and everybody has to follow exactly what is written. You can change the members of the group, you can form additional groups, if you provide regulators with a justification. So it is a kind of flexible concept and the general principle of grouping has been kept, which is, I think, important because otherwise many products would simply disappear from the market. So that was the basic idea of it and that was also not simple to keep it – I can tell you!

Mari: You said the mixtures of homologous groups will be discouraged, right?

Pini: No, maybe I was not clear. What we would like to discourage are mixtures between two homologous groups, but not within the same homologous group. And anyway, it is just an approach because there is always the possibility for the applicant to show that there is a rationale behind it and they have stability data. In my opinion, it is something which has to be considered just as it was done for the taxonomic families 20 years ago. Here we are moving towards something which is a little bit more state-of-the-art, but the issues and the possibilities to change things are still quite a lot. It depends on the position of the applicant and on the reasons the applicant gives us on what he did and the choices he made.

Hahnstadt: Could you please clarify the concepts of curing allergy?

Mari: Well it is in the definition itself, I think. When you are free from symptoms after the immunotherapy treatment, given for a certain number of years, this is curing of an allergy: when you can prove for another number of years that you do not need any treatment.

Cromwell: Many of us here are very pleased that the recombinant allergens are now included in the guidelines. But, going to the clinical efficacy guideline, there is one sentence which disturbs me. It is the fact that it states categorically that the concept

of homologous groups is not applied to pure allergens, including recombinants. Now, that clearly implies to me that we will no longer be able to extrapolate, e.g., between *Der p 1* and *Der f 1*. And this seems to somewhat contradictory to what is allowed for allergen extracts.

Mari: I give you my answer and then Stefan or somebody else may also comment. I think that the main reason why we have no freedom with the recombinant allergens is because they are recombinant molecules and they belong to a different regulatory context. Unless we are able to break this wall between the two systems I guess that we have no choice to extrapolate the homologous groups' concept to recombinant molecules. This is my view.

Cromwell: Yes, I accept that. But this would clearly restrict the possibilities for developing an extensive panel of recombinant molecules, without question.