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Summary of the Regulators' Session

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During the 11th IPES, a closed session was held and regulators were asked to discuss issues related to marketing authorisation and *in vitro* testing of allergen extracts. Structure and extent of data required for filing an application for marketing authorisation for a product to be used for allergy treatment by specific immunotherapy (SIT) and the extent of testing therapeutic products were considered. These aspects were mainly related to quality, pre-clinical and clinical aspects. For the latter aspect, specific consideration was given to the structure of clinical studies and to differences between industrially prepared and Named Patient Products. Some consideration was also given to products for diagnosis and treatment of allergies in animals.

The first topic related to quality was the taxonomic family concept. It was generally recognised that the concept of taxonomic family is not anymore satisfactory. As the knowledge on the structures of allergenic molecules increases, it appears that a representative allergen source for a given taxonomic family does not always exist or may be difficult to identify. The concept of homologous groups was therefore proposed, and it seems promising, also for the assessment of clinical trials. The homologous group concept can be regarded as a proposal to create groups of homologous allergen sources according to their similar allergen content and cross-reactivity. From this point of view, these groups can be modified as the scientific knowledge increases, and dossiers on one representative allergen source per homologous group should be filed to the regulatory authorities. It was discussed slightly controversial whether the allergen sources belonging to a given homologous group should be officially identified or left to the companies' decisions to propose such a list according to their own policies and scientific arguments. A representative allergen source should similarly be chosen by the company and justified or it should be defined by the National Competent Authority (NCA). It was proposed to further discuss this issue at the EU level, together with other issues, during the revision of the Note for Guidance on Allergen Products [1].

An important point which was discussed was the degree of characterisation which should be accomplished for a given extract. Therefore, it was proposed that allergen sources could be grouped not only in terms of homology but also on the basis of the intended use, taking into account that according to the intended use the degree of characterisation might be different. As an example, the highest quality level could be required for therapeutics, i.e. having as many parameters tested as possible, whereas a lower level could be envisaged for diagnostics, i.e. protein content and protein profile for rare allergen sources.

In any case, an important aspect is linked to the availability of the in-house-reference (IHR). As a matter of consensus, the IHR should be fully characterised, but in some member states (MS) new batches of IHR have to be tested *in vivo* (they have to be biologically standardised) and some MS would make their own reference preparation to compare the various commercially available extracts. From the standardisation point of view, recombinant standards and mass units labelling are too premature but promising. Independently from the degree of characterisation of the IHR, analytical testing, such as post marketing surveillance and batch release, could contribute to increase the degree of knowledge of the quality of the products available on the market. There was a general agreement on the concept that Post Marketing Surveillance studies are important, and that at least some tests can be performed on the finished product (free allergen, aluminium content).

Some countries perform batch release procedures for allergen extracts, and in any case it was highly desirable to test the bulks and finished products during the registration phase when possible.

No further quality points were specifically addressed during the closed session, and similarly no specific non-clinical issues were brought to the attention of the audience by the regulators.

A large part of discussion focussed on clinical issues. One major issue was how to define the end point of a clinical trial. In the dossier, it was agreed that details on the clinical study protocol are needed. Analysis of data, performed on the basis of criteria defined after the completion of the trial, should be avoided. Moreover, it was clearly confirmed that no surrogate markers are actually available, and that only clinical primary efficacy points should be accepted. Combined symptom and medication scores can represent an acceptable primary efficacy end point, but the role of provocation tests has still to be defined. Safety data from clinical trials are obviously required. In some cases, a huge amount of published data is available. However, published data are, according to EU Directive 2001/83 [2], acceptable as amendments for well established, in-use products only, and therefore, data from published literature must refer either to the product which is seeking registration or to a product which is "identical" to it. In this context, it has to be stressed that for biological products the concept of "identical" does not exist and bio similarity can be very difficult to prove for such a complex category of products. Therefore, published data relating to other products can almost never be accepted. However, published data

could be accepted if supported by adequate clinical trials performed under conditions of good clinical practice (GCP) on a case-by-case basis.

The importance of a harmonised approach at the European level to the evaluation of the allergen extracts was underlined by the audience's discussion on Mutual Recognition Procedures (MRP). A few MRPs for allergen extracts have already begun, but the experience so far, strongly indicate that specific guidelines could be helpful to harmonise the approaches to MRPs of the assessors in different MS. From this point of view, the Mutual Recognition Facilitating Group (MRFG) could play a pivotal role in the harmonisation of evaluation of the various modules of the application dossier, also considering the possible role of training sessions.

All the concepts discussed above were limited to industrially manufactured allergen extracts, and exclude Named Patient Products (NPP). However, it was clear that NPPs represent a large percentage of products administered to humans, and therefore they would urgently deserve similar regulatory attention. Since they cannot be regarded as industrially manufactured products, they are not covered by current European legislation. However, the issue of regulating NPPs can be approached on the national level, even though divergent national laws might result in different approaches in different European states. In any case, a model which has been recently established in a MS was explored to seek for possible approaches to be exported/extended in other MSs. In the model, the dossier containing all the relevant information is structured in a specific and dedicated manner, taking into account that the ultimate goal is to "approve the bulk" from which NPPs are made and not a finished product. Specific attention to GMP evaluation of the producer and its Quality Assurance (QA) system in place is envisaged, to assure that correct processing from bulks down to the final NPP occurs. The quality criteria for "bulk" approval are identical to those in place for industrially manufactured products, but from the clinical point of view it has still to be clarified how efficacy of NNP that often represent mixtures of extracts from different origins can be demonstrated. Pharmacovigilance has to be applied to NPP as well, although it is not clear in which manner data can be analysed and then associated to the specific active ingredient(s) especially in those cases where complex mixtures are involved.

Finally, two issues were discussed. The first topic was linked to products for diagnosis and treatment of allergies in animals. These products are covered by the EU Directive 2001/82 as amended by Directive 2004/28 (article 1) [3] and therefore they are (biological) medicinal products. Guidelines on allergen products have been issued by the Committee for Medicinal Products for Veterinary Use (CVMP), and similarly to all medicinal products GMP requirements and inspections should be carried out also according to the process description approved in the marketing authorisation dossier. Controlled clinical trials in allergic animals to confirm diagnosis and efficacy of treatment should be carried out in a controlled way. It was concluded that, similarly to allergen extracts for human use, the products intended to be used in animals should be a regulatory concern and companies should be encouraged to seek for scientific advice from NCAs.

The second issue was the use of recombinant allergens to standardise natural allergen extracts. A number of candidate molecules have been identified, and further steps are required. The audience felt that participation of the European Directorate for the Quality of Medicines (EDQM) in the organisation of collaborative studies for the establishment of methods, reference preparations and subsequent proficiency studies to reach harmonisation of the analytical testing of these very complex medicinal products is of utmost importance.

References

1. Note for Guidance on Allergen Products CPMP/BWP/243/96.
2. 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 by Directive 2002/98/EC of 27 January 2003, and Directive 2004/24/EC of 31 March 2004.
3. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, as amended by Directive 2004/28/EC of the European Parliament and the Council of 31 March 2004.

Discussion

Vieths: I would like to add one comment. We did not discuss the regulation or the quality criteria of recombinant allergens for therapeutic use. This will be discussed during the revision of the “Note for Guidance on Allergens”. There is also time during the general discussion after this session for any questions coming up regarding this topic.