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Round Table Discussion

The manufacturers' perspective: Regulation
of allergen products in European countries

Kroon, The Netherlands

Ladies and gentlemen, I want to open the morning session again. As you have seen in your programme, there is now planned a Round Table Discussion on "Manufacturers perspectives: Regulation of allergen products in European countries". There will be four invited discussants: Dr. Carmen Garcia, Spain, she is regulatory affairs manager from Leti, Dr. Oliver Cromwell, Germany, he is the head of research and development of Allergopharma, Dr. Louis Champion, France, is the general manager from Stallergenes, and Dr. Birgitte Kristensen, Denmark, she is the global regulatory manager of ALK. I hope that we will have a good discussion afterwards. I also hope that many regulatory experts from the various European countries are present, also those countries which have not regulated so much so far. And, that we can come to some conclusions that may lay a good basis for further cooperation between manufacturers and regulatory authorities. And I would like to ask Dr. Kristensen to start.

Birgitte Kristensen

Thank you very much and thank you to the organizers for inviting me to this seminar and the Round Table Discussion.

I would like to focus on the implementation of the current European regulation. The legal requirements we have in Europe are based on the codified directive which was adopted in 2001. It came back to the two directives which I have quoted here. In the directive 89/342/EEC we have the requirement that also the allergen products should obtain a marketing authorization and there are some arrangements for the existing products at that time. Furthermore, the directive 89/341/EEC indicated that there might be some national exemptions to this rule for products which were prepared based on individual prescriptions from the doctor and which were intended to be used by the prescriber's individual patients. This is the legal frame in this area.

The national implementations have been rather divergent throughout Europe. In several countries the authorities have actually implemented this request for marketing authorization to be a condition to market the products. The request for marketing authorizations has not been effectively implemented by the authorities in France, Italy, and Spain. And, when I say effectively, it means that they might have required applications but nothing has happened since.

We have the exemption rule also in the directive and here we have two groups of countries again. We have systems for named patient products which are valid in Germany, France, Italy, and Spain and maybe others as well, and there are divergent national systems which are also in accordance with the directive. In other countries, mainly the Scandinavian countries, systems implementing the same paragraph in the directive where you issue specific permissions for these exemptions. And what is interesting here is that these divergencies show different balances between the implementation of the request for marketing authorizations and the exemptions. And the problem that I see here is that we have some countries where the exemption has actually been the general rule. And, on top of that, the systems implemented for the named patient products in those countries are – to my best knowledge – based on handling to which the control of the authorities is rather limited. It is mainly in the hands of the manufacturers.

I have been asked also to focus on the situation in my own country, Denmark. Here I have tried to show you that marketing authorizations also for allergen products were required since the legislation in 1976; that means more than 25 years ago and the exemptions are handled by specific permissions to distribute the not authorized products. These permissions may be granted in special cases in limited amounts and they are granted by the authorities and there are lots of restrictions and justifications for obtaining such an authorization. The manufacturers are not in charge of the system, the authorities would be in control.

Another problem with the European countries and the lack of harmonization is the limited scientific consensus on the documentation which would be required for registration of allergen products. We have – of course – the codified directive, we have the European Pharmacopoeia and we have the guideline which is a rather brief and broad guideline which was last revised in 1996. I at least would welcome the initiative which we have now seen this summer from the efficacy working party of the CPMP/EMEA to issue a note for guidance related to the clinical development of the allergen products in order to obtain a consensus amongst the authorities on what they really would require from us, the manufacturers.

In conclusion, I would say that the divergent national implementation of the requirements is a problem, the divergent national systems for the exemptions are a problem and when you combine this with the limited scientific consensus related to the documentation to be presented by the manufacturers, we really have challenges for the mutual recognition and the centralized procedures which are also mandatory for our products. So, I would really encourage the authorities to harmonize their own rules.

Carmen Garcia

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Carmen Garcia

The following issues were addressed:

1. Adoption of EU legislation in Spain;
2. Current situation;
3. LETI's experience;
4. Issues for the future.

Adoption of EU legislation in Spain

Directive 89/342 was adopted by the Spanish legislation as Royal Decree 288/1991, entitled "Immunological Products for Human Use", that became mandatory for all allergen companies in Spain as of 31st December 1992 and includes the following specific points:

1. The Spanish Decree explicitly refers to individual allergen vaccines or NPPs.
2. Manufacturing, distribution and sale of NPPs can only be done under medical prescription.
3. NPPs always have to be produced with industrially manufactured allergens.
4. Immunological products are considered to be medicinal products only when they are industrially manufactured.

In 1993, in order to comply with the adoption of a series of the EU Directives concerning the "Marketing Authorization of Medicinal Products", another royal decree was issued: RD 767/1993. The principles applicable to allergens in this decree can be summarized as follows:

1. Allergens shall be evaluated and authorized according to the rules of this decree with the appropriate adjustments to be introduced.
2. Health authorities shall regulate the conditions required for applying for a marketing authorization.
3. The decree establishes some specific requirements for allergens, in terms of quality, pharmacology, toxicology, and clinical data, all of them in accordance with the directives.

The current status of allergen regulations in Spain

All allergen manufacturers in Spain have to be duly certified by the Ministry of Health, and have to comply GMP. Allergen products in the Spanish market include *in vivo* diagnostics and therapeutic vaccines as named patient products. Further development of the regulation of '93 decree is still pending.

Regarding to LETI's experience

The treatments are present in the market in European, American and African countries as NPPs. These allergen-specific therapeutic vaccines are an effective and safe treatment of allergies, as has been demonstrated over many years of clinical experience.

The quality of allergen products is assured by GMP compliance and, at least in LETI's case, by ISO 9001 certification as well. LETI has obtained marketing authorizations for *in vivo* diagnostics in Germany.

Issues for the future

The availability of a common regulation and approach to NPPs would be beneficial for both, the companies and the authorities. Health authorities of member states and allergen companies should agree on a common "regulation" for NPPs in Europe, otherwise, mutual recognition would be unacceptable.

I believe that the use of the "representative allergen" concept will be welcomed by both the allergen companies and by the different national authorities for bulk preparations used in NPPs. The European Guideline already introduces the use of this concept for industrially produced allergens.

The acceptance of a single "base dossier" for each pharmaceutical form with complementary dossiers for each specific allergen would facilitate the preparation and evaluation of the documentation submitted to the authorities.

Oliver Cromwell

The European Pharmacopoeia Monograph, published in 1997, and the CPMP/ICH Guideline on Allergen Products provide the framework within which European allergen producers and regulatory authorities work in order to ensure the quality of allergen-based diagnostic and therapeutic preparations.

Our experience with regulatory authorities is that some are more enlightened than others. In Germany we are very fortunate in that the responsible department at the Paul-Ehrlich-Institut has in-depth experience, expertise and understanding of allergen products which enables them to recognise realistic standards and to adopt pragmatic interpretations of the Monograph and Guidelines. Other authorities tend to follow more rigid interpretations of these documents with expectations more in line with those for pharmaceutical preparations incorporating defined chemical entities. In some cases this may stem from either a lack of experience of allergen preparations or the availability of only limited resources to appraise them.

In Germany, test preparations generally have to be registered, and in Allergopharma's case a significant number of therapeutic preparations are also registered. This is also the case for some other companies. A full listing is available on the Paul-Ehrlich-Institut homepage for those who might be interested to see it. Various of these products are also registered in other European countries.

The German marketing authorizations include 150 skin test preparations in various categories including pollens, mites, moulds etc. Other diagnostics include an extensive range of intracutaneous test preparations and a more select number for provocation

testing. The number of preparations is restricted to pollens, grass pollen, birch and the house dust mite *Dermatophagoides* and some carefully selected extracts of hazel pollen, grass pollen and mites. The register of allergen products for dust mite preparations is small. Companies have registrations for their products and acquire the data in the register. The registration has been kept up to date with allergens registered in the CPMP/ICH Institut. Some other countries follow this approach.

It goes without saying that there are standards, but in order to ensure the safety and necessary to ensure the quality of those concerning preparation and appraisal. Standards are adopted and administered to their own standards.

However, there are burdens on producers to ensure the first use which sets the standard for the market for the first time. Some find some mechanisms to ensure the requirements of the standards.

Although various countries implement the allergen standards. When seeking to ensure the quality of preparation may be the most difficult, to obtain impossible, to obtain when current guidelines are often difficult to judge. It is very difficult to reach a consensus. There have been on the one hand, which a pre-existing standard account in order to ensure the quality of possible, but in many cases the same. The different consistent policies to ensure standards for national standards from the market. Some are aware of, but not all products.

testing. The number of registered therapeutic preparations is much smaller and is restricted to pollens and mites. The list includes single allergens such as birch pollen and the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and some carefully selected, tried and tested mixtures such as birch together with alder and hazel pollen, grass with cultivated rye and a combination of the two house dust mites. The registered pollen preparations include a range of allergoids and three house dust mite preparations are also registered for oral applications. Other manufacturers have registrations for wasp and bee venom preparations. The workload necessary to acquire the data in respect of stability, safety and clinical efficacy to support these registrations has been kept in proportion through the use of the exemplar allergen concept, with allergens representative of particular taxonomic families. This principle was set down in the CPMP guideline on Allergen Products and accepted by the Paul-Ehrlich-Institut. Some other national authorities, however, seem less willing to accept this approach.

It goes without question that allergen products should be produced to high standards, but in order to achieve this consideration has to be given as to what is reasonable and necessary to ensure quality and safety. The implementation of guidelines such as those concerning pre-clinical safety testing and good clinical practice during the development and appraisal of products is an important step, and in the knowledge that such standards are adopted doctors should have more confidence in the products that they administer to their patients.

However, there are other guidelines that place additional and possibly unnecessary burdens on producers. For example, the guideline relating to product shelf-life after first use which sets an arbitrary 28 day period. In instances where a product has been on the market for many years without showing any problems it should be possible to find some mechanism whereby this can be taken into account when deciding whether the requirements of a particular guideline have to be enforced or not.

Although various new products for allergen-specific immunotherapy are in development the allergen manufacturers rely largely on a long established product range. When seeking to go into a new market with the existing products a new national registration may be the only route available. However, it can prove very difficult, if not impossible, to obtain such registrations on the basis of data generated years previously when current guidelines, particularly those related to GCP, were not in force. It is often difficult to justify new clinical trials to an ethics committee and furthermore, it is very difficult to recruit study centres and patients for clinical trials of preparations that have been on the market for many years. This is a good example of the situation in which a pre-existing registration in another European country could be taken into account in order to facilitate the approval process. In a few cases this has proved to be possible, but in most instances it is not the case. No two regulatory authorities are the same. The differences go even further. One national authority appears to adopt inconsistent policies towards different manufacturers, in particular by applying different standards for national and foreign companies and thus effectively excluding the latter from the market. Another European country has no registration requirements that we are aware of, but nevertheless we have no opportunity to go into that market with new products.

Allergopharma has as yet had no experience with the mutual recognition system whereby a European registration can be granted for a new product following successful appraisal of an application by a reference EU member state. It remains to be seen how willing some authorities will be to accept the opinions and decisions of another. To this end it is desirable that national registration authorities should enter into dialogue with one another sooner rather than later in order to pave the way for successful central and mutual recognition processes.

The subject of named patient preparations has already been addressed by Prof. Kroon, but it is perhaps appropriate to come back to one or two points. I personally have problems with the term "named patient preparations" and I would prefer "individual patient prescription" or something along these lines to indicate that it is for a specific individual. In Germany, non-registered named patient preparations can only be produced on an individual basis, that is to say they cannot be produced on a batch basis in the form of finished products. They are instead formulated to an individual prescription using bulk materials or intermediate products. In Allergopharma's case, and also in the case of some other companies, many of these bulk lots are likely to come from production charges that are in fact registered preparations and that have undergone the batch release procedure, whilst other preparations are characterised and subjected to quality control to the same standards as the registered preparations. In this regard, it is perhaps of interest to consider whether it would be possible to register such intermediate bulk products rather than the end products, a procedure that would simplify the registration process and make it possible for a wider range of allergens to be registered and controlled.

Responsibility for the quality of the named patient preparations lies with the manufacturer, and although the responsibility for the final prescription is that of the physician, the manufacturer has an opportunity to influence that decision. We at Allergopharma have a system in place to control all orders that are received. Orders for single allergens and registered mixtures are straight forward, but some of the allergen mixtures requested can pose problems. In the event that we receive a request for a mixture that is out of the ordinary, a medical consultant will contact the doctor to discuss the individual case and it is then usually possible to agree on a more appropriate prescription. Certain rules are applied, for example seasonal and perennial allergens are never mixed.

In conclusion I would say it is one of the declared aims of the Paul-Ehrlich-Seminar to harmonize the implementation of rules and regulations for allergen products. It is a fact that the majority of preparations that are sold for allergen specific immunotherapy in Europe are not registered, either because the requirements cannot be easily achieved or, as in the case with a few countries, the requirements do not exist. Regrettably very little progress has as yet been made to change this situation. It is very desirable that we find a pragmatic solution to this problem whilst taking into account the fact that many products are used in small volume, each representing only a very small part of the total turnover. I hope that the discussion in this forum will help us to make some progress towards solving these problems.

Louis Champion

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Louis Champion

Although allergens have been on the market for decades, their regulatory frame remains still quite confused.

In several instances, this regulation is lagging behind the European directives. Moreover, it varies dramatically from country to country in Europe; in some cases, the *de facto* situation is a "no regulation" one. In today's world, such a situation entails major drawbacks for immunotherapy (SIT):

- The European regulatory patchwork strongly affects the very credibility of SIT
- Competition is distorted between regulated market-based companies and not regulated market-based ones
- While SIT enters an era of major innovations after *status quo* decades, a clear and consensual European evaluation guideline turns out to be mandatory

Allergens are to be regulated and registered, taking into account their biological nature. An European mutual recognition process within the European health authorities should be set up.

Nonetheless, in our view, the debate on Named Patient Prescription (NPP) relates to the fact that allergen extracts are the only medicine which toxicity is linked to the patient and not to the compound itself: To check prescription consistency over time for a given patient is the only reliable way to provide with full safety. NPP is the only trustworthy way to check this consistency before the delivery of the product and this could be done only at the manufacturer level.

At a time where the risk zero is a public demand, the NPP system which has proven to be very efficient should still be considered for the distribution of allergen extracts.