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## ***Regulatory Aspects of Allergen Products for Immunotherapy – Considerations from the viewpoint of manufacturers***

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### ***Summary***

The present publication describes the actual situation *anno* 2005 with respect to registration of allergen products for specific immunotherapy (SIT) in Europe. It is concluded that the lack of the implementation of regulations and directives in force, is due to underestimation of the specific demands and aspects of the pathogenicity of allergic diseases at the one hand and of allergen products as a unique set of biological medicinal products at the other.

The issues of regulatory nature that need careful attention and consideration in the opinion of the manufacturers are given in a number of statements.

The main conclusion is that an EU-guideline for allergen products is urgently needed. A dialogue between regulatory authorities and representatives of the manufacturers, prior to the formulation of a new guideline seems of the utmost importance, as to prevent a similar stalemate as after the introduction of the foreseen regulatory measures of the past.

The new guideline should include:

- An allergen product monograph
- Recommendations for clinical development of allergen products like:  
Number of patients for efficacy and safety  
Acceptability of different efficacy parameters
- Recommendations for toxicology

### ***Introduction***

IgE-mediated allergic diseases are developed mostly towards naturally occurring allergens and have a high incidence and prevalence. Allergen products have a long history of use in both diagnosis and treatment. Patients show a remarkable diversity

of symptoms, especially of the respiratory tract. It is now well established, that the signs and symptoms associated with rhino-conjunctivitis and asthma are the expression of a single underlying immunological lesion. Hay-fever and asthma should therefore be considered as different parts of a single disease, having a major impact on quality of life, both socially and economically, and can, if not properly treated, become life-threatening.

Already some time ago it was realised that the difference between immunotherapy and pharmacological treatment of allergic disease is not restricted to efficacy and safety [14]. Specific immunotherapy (SIT)<sup>1</sup> is widely recognised as the only treatment that may alter the natural course of the disease. It is, furthermore, well realised that SIT makes sense especially if the respiratory tract is not yet irreversibly damaged. Nonetheless, SIT features at the bottom of all treatment scenarios of ARIA, IPAG and GLORIA.

Most allergen sources cannot be avoided and may contain several different proteins with allergenic potential. The range of allergen products for SIT used in clinical practice extends to several hundreds, if not thousands of allergenic determinants, of which individual patients may be sensitized to different combinations of. Thus, allergic patients represent an extremely heterogeneous group in spite of the fact that they all present with similar symptoms, albeit at variable degree of severity.

There exist at least 200 inhalant allergen molecules, many of which have only regional significance. The multiplicity of allergens of a single source is well known; 89 allergenic molecules were already detected 20 years ago in just 7 common allergen sources [18]. Epitope mapping has shown that many of these allergenic molecules carry several allergenic determinants (see e.g. [1,4]). In the paragraphs below these issues will be dealt with in more detail and attempts will be made to formulate the key-points in definitive statements, mentioning the merits and disadvantages under consideration, as the basis for an open discussion.

### ***Placing Allergen Products for SIT in the spectrum of Medicinal Products***

Allergen products for SIT are very special biological products, quite different from medicines containing chemical drug substances and from other biologics such as antibacterial or antiviral vaccines. It seems necessary to raise the awareness for the specific characteristics of allergen products for SIT that differentiate them from these other drugs. This is particularly important with respect to the development of new pharmaceutical forms (tablets or other solid forms), isolation procedures, new active substances (peptides, recombinant proteins), routes of administration (sublingual, transmucosal) and adjuvants.

<sup>1</sup> Abbreviations used: ARIA: Allergic Rhinitis and its Impact on Asthma; GLORIA: Global Resources in Allergy; IPAG: International Primary care Airways Group; PTAP: patient tailored allergen products; SIT: specific immunotherapy.

The manufacturers will be in a position to make progress once unified consensus has been reached with regulators on, at least, the following issues:

- Placing allergen products for SIT in the spectrum of medicinal products
- Acceptable endpoints for clinical efficacy
- Awareness for the specific characteristics of allergen products with respect to their inherent allergic reactivity
- Acceptance of the allergic reactions as effects, albeit undesired and “adverse” if strong or threatening
- A proper definition of side-effects and demands for safety measurements with respect to number of persons/patients to test

In this paper the viewpoints of the manufacturers are formulated as statements accompanied by the considered arguments.

### **STATEMENT 1**

Allergen products for SIT shall be classified as special and unique group of biological medicinal products in the group of biologics.

#### **Arguments in favour of statement 1:**

1. Allergic disease is highly variable with respect to the pathogenetic parameters although relatively uniform qua symptomatology.
2. The degree of pathogenetic heterogeneity differentiates allergic disease essentially from auto-immune diseases and even more from infectious diseases.
3. Allergen products for SIT are treating the cause of a manifested disease by redressing an existing aberrant immune reaction rather than inducing an immune reaction to relieve symptoms (auto-immunity) or to prevent disease (infection).
4. Allergen products for SIT represent a large family of medicinal products directed against a large number of different allergenic determinants.

### ***The present stage of regulation***

Allergen products for SIT are legally considered as medicines requiring registration. The implementation of foreseen regulatory measures does, however, meet with problems and delays. The present regulatory framework is based on the Pharmacopoeia Monograph Producta Allergenica and on the Note for Guidance, CPMP/BWP/243/96, and its extension directives 89/341/EC and 89/342/EC, now codified into 2001/83/EC and amended by 2003/63/EC and 2004/27/EC. The latter directive will come into force 1 November 2005. Within these directives the definition of a medicinal product to be registered changed from ready prepared medicinal product (65/65/EC) to medicinal products for human use intended to be placed on the market in member states and either be prepared industrially or manufactured by a method involving an industrial process (2001/83/EC).

Implementation of the EU-legislation has been very divergent in the EU member states and the regulatory authorities have so far not succeeded to harmonise the sci-

entific requirements for allergen products. It can be foreseen that mandatory EU-application procedures leading to harmonisation of the conditions for marketing authorisations will present problems also in the future if the regulatory methodology is not adjusted.

At present, in 7 out of 29 European countries in which allergen products are sold, no allergen products for SIT are registered at all. In some other countries the spectrum of registered allergen products for SIT as compared with the available variety of allergens and product forms is rather limited. All registrations are based on the national procedures for marketing authorization. Mutual recognition of these authorizations is scanty. European Community procedures for the authorization and supervision of medicinal products have not been applied so far.

### ***What hampers harmonisation?***

The background for the current situation is that, apparently, implementation of the legislation is more difficult than foreseen by the authorities some 12 years ago. This, in turn, is most likely due to the fact that allergic disease represents a diverse group of diseases and further by the underestimation of allergen products for SIT as a special class of medicines. The pathogenetic diversity predicts the necessity of the coexistence of allergen products for SIT as specialties and as patient tailored preparations. The incidence of sensitization may of course vary between the various allergen sources [2,6].

The presently available allergen products for SIT are safe and efficacious, but in fact all of them are mixtures containing multiple allergenic determinants and allergenic molecules.

### ***What to expect of Regulation EU 726/2004, potentially operational for allergen products for SIT from 20 May 2008 on?***

On the 31<sup>st</sup> of March 2004 the Regulation EC 726/2004 of the European Parliament and of the Council was issued. This regulation covers, as the previous Regulation 2309/93, all products developed by means of biotechnological processes, e.g. recombinant DNA technology. Consequently these products have since 1995 to be applied for by means of the centralised procedure. The regulation will with effect from 20 May 2008 cover medicinal products for auto-immune diseases and other immune dysfunctions. It is currently not published whether allergen products belong in the latter category. The definitions still are to be defined at a later stage. However, no statements, presentations etc. from the authorities prior to the adoption of Regulation 726/2004 indicate that allergen products would be covered by this requirement.

The regulation is judged by the non-specified experience that national measures have shown the necessity for a centralised procedure for high-tech medicinal products.

Arguments raised are:

- Maintenance of high level of scientific evaluation.
- Confidence of patients and medical profession.
- Emergence of new therapies (gene-, cell-, xenogenic somatic therapy).
- Effective operation EU-market.

The main points are:

- New substances
- Scientific innovation
- Technical innovation
- Interest of patients
- Significant clinical benefit in comparison with existing therapies

One may strongly doubt whether these arguments and main points really apply to the new allergen products presently in development or under clinical investigation.

The said regulation frequently refers to the directives 2001/83/EC, 2001/82/EC, 2001/20/EC and 2001/18/EC that presently have little impact on the regulatory procedures for allergen products.

## **STATEMENT 2**

**2A:** It is not advisable to subject a new allergen product for SIT, manufactured without the aid of rDNA techniques, to the European centralised authorisation procedure that is compulsory for high-technology medicinal products.

**2B:** It is not advisable to subject a new allergen product for SIT, manufactured with the aid of rDNA techniques, to the European centralised authorisation procedure that is compulsory for high-technology medicinal products.

### **Arguments in favour of statements 2A&2B**

1. Isolated allergens or recombinant allergens do not give rise to emergence of a new therapy (2A & 2B).
2. It will inhibit the development of new allergen products for non-ubiquitous allergens, beneficial only for patients in a limited number of countries (2A & 2B).
3. It will unnecessarily increase the cost of treatment (2A & 2B).
4. A large number of potential recombinant allergens, if high efficacy can be shown, will have highly restricted areas for application (2B).
5. Production of recombinant proteins is common practice anno 2005, certainly those produced in a prokaryotic host-system (2B).

### ***Efficacy parameters: how to raise objectivity?***

To demonstrate clinical efficacy of allergen products for SIT one needs a homogeneous patient population with a well-defined sensitization-pattern. This limiting condition holds as long as the only accepted indicators for the clinical efficacy are based only on the subjective parameters of symptom-scores and the need for rescue-

medication during a defined period of allergen exposure. Ideally clinical efficacy should be tested in a population of mono-sensitized patients.

If one defines mono-sensitization as the sensitivity to a single pathogenic determinant, three levels of poly-sensitization can be distinguished: towards different determinants of a single pathogenic molecule, towards different pathogenic molecules from a single source of pathogens and towards pathogenic molecules from different sources of pathogens.

By far the most patients are sensitized against more than one non-cross-reactive allergen source and patients sensitized to a single allergen molecule from a certain source are rare.

Recruiting a sufficient number of patients within an acceptable area of investigation to demonstrate clinical efficacy is difficult. This problem will even more strongly arise if single allergens or peptides containing only one pathogenic determinant have to be tested for clinical efficacy. The more specific the allergen product, the more difficult it is to find a suitable patient population.

### **STATEMENT 3**

The magnitude of the clinical improvement together with the statistical power of the results of a clinical study with allergen products for SIT shall be the basis for judging the efficacy.

#### **Arguments in favour of statement 3**

1. In view of the high efficacy of IT as compared to symptomatic treatment, low numbers will suffice for statistically relevant conclusions.
2. The smaller the number, the higher the chance to obtain a precisely defined patient population.
3. The smaller the number, the easier to find comparable exposure conditions.

The quality of data derived from the commonly used diaries is not satisfactory if symptom-scores and rescue medication-scores are judged separately, since these represent two facets of the same endpoint. For, medication masks the symptoms. This determines the need to combine these two parameters into a single, validated formula.

It seems essential to consider further parameters to evaluate clinical efficacy as endpoints in studies on SIT. It seems logical to concentrate first on those signs and phenomena that are considered essential for the indication to start SIT (see e.g. [3]). But also other possibilities can be envisaged. A prerequisite will remain that the methods are validated (see e.g. [10]).

A choice can be made from the following parameters.

- **Quality of Life (QoL) Parameters:**  
Rhinoconjunctivitis QoL Questionnaire (see e.g. [8,9]).  
Other Questionnaires (see e.g. [5]).

- **Provocation Tests:**
  - Experimental Exposure Chambers (see e.g. [7])
  - Conjunctival Provocation Test
  - Nasal Provocation Test
  - Bronchial Provocation Test
  - Skin Provocation Test
- **Laboratory Tests:**
  - Allergen-specific serum IgE changes
  - Allergen-specific serum IgG increase
  - T-cell parameters
  - Levels of Interleukins and other mediators

#### **STATEMENT 4**

Change in the diagnostic tests on which the indications for immunotherapy are based and other efficacy parameters shall also be accepted as a primary endpoint for efficacy.

#### **Arguments in favour of statement 4**

1. The changes of standard parameters of symptom scores and rescue medication are subjective and not always reliable and strongly influenced by the environment.
2. Other parameters could be more objective measurements.

#### **Safety parameters: how to define adverse?**

Adverse reactions of allergen products for SIT are extremely rare, practically absent (see e.g. [12]). Since the whole population, allergics and non-allergics, is exposed to the inhalant allergens, it does not make too much sense to demand toxicity studies for the allergenic molecules in preclinical development. Moreover, allergen products for SIT of various compositions and from many different sources have been used in humans for many decennia. Most, if not all of the fatalities recorded, were based on injudicious application and/or failing medical action (see e.g. [15]). Allergenicity of allergen products for SIT is neither adverse nor unexpected as bleeding is not an adverse effect of surgery.

A major question is how one should define adverse. The following considerations seem of paramount importance:

- Safety is depending on the skill and knowledge of the physician.
- Initial treatments are based on the inherent allergenic properties (phase-II approach).
- Allergic reactions of allergen products for SIT are neither adverse nor unexpected. Strong reactions are rare (see e.g. [13]).
- Side-effects of allergen products for SIT are extremely rare, practically absent.

**STATEMENT 5**

Allergic reactions related to the administration of allergen products during immunotherapy shall not be declared side-effects.

**Arguments in favour of statement 5**

1. Allergic reactions are inherent to allergen products for SIT.
2. Allergic reactions are not unexpected. Treatment-scenarios are based on its possible occurrence.

**STATEMENT 6**

The demands for safety control concerning the allergenic properties of allergen products for SIT shall be based on the judgement of the allergic reactions obtained during the clinical investigations for efficacy and on the results of prolonged post-marketing surveillance.

**Arguments in favour of statement 6**

1. Allergic reactions represent an effect, not a side-effect.
2. On the basis of reactions in the up-dosing phase of the initial treatment physicians will become aware of patients tendency towards strong allergic reactions.
3. Reducing the maintenance dose in strongly reacting patients is standard practice.
4. Physicians record allergenic reactions in the period of 30 min. after injection and of late-phase reactions reported by the patients
5. Large-scale allergenicity studies will not prevent mistakes of practitioners.

**Batch release**

Related to the regulatory aspects of allergen products for SIT is the question of batch release. The current European legislation is not asking for batch release of allergen products. The procedure, that is obligatory in Germany at the present time, is time-consuming and delays the actual introduction of the batches on the market.

**Statement 7**

Release of standard registered allergen products for SIT and for diagnostic procedures or other allergen products shall not require individual batch release by the regulatory authorities.

**Arguments in favour of statement 7**

1. Such an approach reduces the administrative and laboratory burden on the responsible institutes and reduces the cost and administrative burden on the manufacturer.
2. Such an approach reduces the length of any out of stock problems and therefore ensures better continuity of care for patients.
3. Modern cGMP requirements and inspections ensure that the manufacturing and release processes are extremely tightly controlled by the manufacturer and that

there are frequent, rigorous independent inspections to ensure compliance with this.

4. The current requirements for individual batch release in Germany are out of line with all other countries within the EU and out of line with the release of other registered products.
5. Batch release of allergen products is not compulsory according to article 114 of Directive 2001/83/EC.

### ***The future scenario***

It will be necessary to develop a scenario that contributes to the design and implementation of significant and practical regulatory measures that benefit the patients and warrant optimal treatment for them. The scientific and medical knowledge recently acquired underlines the importance of allergen products for SIT as a first-choice treatment for allergic diseases rather than as an ultimatum refugium if other treatments have failed. A concerted approach of regulators and manufacturers seems the best scenario to reach this goal.

### ***Statement 8***

The manufacturers of allergen products, gathered on the occasion of the 11th Paul Ehrlich Seminar, propose to establish a Working Group consisting of 5 representatives of the European regulators and 5 representatives of the European allergen manufacturers.

The task of the Working Group will be to formulate a consensus proposal towards the legislators for future regulation in Europe of allergen products for SIT based on the outcome of the discussions at the said seminar.

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## Discussion

**Malling:** I have several comments. I think that the first and most important is maybe related to the definition of clinical efficacy. I think that we have to accept that we are dealing with a treatment that should reduce the burden of the disease, meaning clinical symptoms and the use of drugs. To me it is not important whether it is a combined score or individual scores. I think that all in all the other parameters are secondary endpoints because neither quality of life nor exposure tests, provocation tests, or immunological tests have any clear-cut relation to the reduction in clinical symptoms and the use of drugs. The second point is that one of your statements, related to side-effects versus adverse effects, was that unexperienced users might overlook the problems. However, I think that this treatment should not be used by unexperienced physicians. I think, it is very important to see that this treatment is extremely difficult to perform in a high-quality manner. The third point is that I think this working group is extremely interesting, but I would really recommend to include some clinicians in this group because to have only the statements related to manufacturers and regulators might miss very important points of the clinicians' view.

**Löwer:** I would like to ask two questions with respect to your statement not to use the centralized procedure when you deal with a recombinant allergen. It is my understanding of the legislation that there is no room for flexibility. It is a clear statement: if you have a recombinant product you have to go centrally. So, my question is what is the consequence from the statement for the industry? Do you try to ask the commission whether they are willing to change the legislation or is this statement just an excuse not to use recombinant products in the future? Is it simply that the industry has no experience with the centralized procedure and for this reason there is some hesitation? Did you discuss the concept of orphan drugs, for example, which gives some relief with respect to rare allergens?

**Kroon:** The point is that we see that in the present situation the laws do not allow to follow the statement. That is also an argument against the statement. The idea is that in the regulations the emphasis is that the production of recombinant proteins is a highly technological procedure. I think that anno 2005 you cannot say that producing recombinant DNA-derived proteins in a procaryotic system is high-tech. It is done in practical courses at many universities. The idea is that perhaps there is a reason to change the law; we will not do that ourselves. But if you keep the idea that a recombinant DNA-derived allergen, which is a genetic factor in a small population, should be registered all over Europe and all over the world, this is not a nice idea of development. That is actually one of the reasonings.

**Löwer:** May I comment on this. I believe it is unrealistic to expect that the legislation will be changed in moving tasks from the EMEA back to national authorities. I think that it is the wish of the Commission to move as many products as possible to the EMEA. To reverse this is politically very unlikely. On the other hand, it is well known to the Commission that the centralized procedure has disadvantages for products that are only used in some regions and not all over Europe. As far as I know – however, I am not too familiar with this area – there are some efforts to make provisions for this situation also in the centralized procedure. So you do not have to translate every package leaflet into all European languages. I think the Commission understands this problem, but I think it is unrealistic to expect that legislation will be changed to address this issue.

**Kroon:** I may answer something to Dr Malling. I agree that the symptomatology is the main point for judging efficacy of treatment with allergen products. However, and that was also the feeling in the discussion yesterday, rescue medication and symptomatology are related with each other. If you want a significant difference in both, the symptom score and the rescue medication, you can get impossible situations. It can also be seen in those studies in which the symptomatology was reduced very strongly that the effects on the rescue medication were even much larger. So I think, the fact that these two variables influence each other makes it clear that we need to combine both in a validated parameter. The other point is that we cannot introduce skin prick tests and look at increasing IgG levels as suitable endpoints. But I expect that for instance a validated system of exposure – in exposure rooms during a clinical study – may help quite a lot because then you can overcome the problems with many clinical studies which last long periods. This could overcome the problems of failing exposure, but it is not yet ready for introducing. However, I think that it must be possible to change a certain provocation test towards a methodology that is indeed giving information about the symptomatology of the patients.