

Arbeiten aus dem Paul-Ehrlich-Institut, Band 94
10th International Paul-Ehrlich-Seminar, Lübeck 2002
Druck- und Verlagshaus Sperlich

Overview: Biological Standardization in Europe and the USA

Henning Løwenstein

This paper is not a scientific one including any technicalities but a simple overview of the status where we are now. It will include state of the art within standardization in Europe and the USA.

Furthermore, it includes some reflections of where we are and how we managed ourselves into the present situation as well as a few predictions for future development.

The major tasks in allergen standardization have always been attempts to develop common standards, methods and reagents to be able to perform standardization all in order to obtain a common unit for potency of allergen extracts used for diagnosis and therapy of type I allergy. This is possible as long as it is clearly understood that a common unit for potency does not mean common potency.

At present the European situation is a mixed one: Although some common roles stated in the European Pharmacopoeia have to be followed, these are relatively vague and interpretation varies from nation to nation. The level of standardization is more dominated by the various companies' own selection of references, methods, reagents and units.

Common to all companies are measurement of biological activity (*in vivo* and/or *in vitro* potency) and for some companies furthermore measurement of concentration of major allergens is performed. This is now recommended by the WHO.

In the USA the regulation is more strict than in Europe. FDA selects references, methods and reagents for biological potency (*in vivo* and *in vitro*). For some allergen sources they also select allergen molecules, the concentration of which has to be measured. In all cases the FDA additionally supplies the companies with reference material, manuals for methods as well as reagents, which have to be used.

During the last 2 decades a number of standards or references have been developed: As mentioned above, the FDA currently selects and exchanges standards/references which allergen manufacturers producing for the US market have to refer to. The same is certainly the case for many European allergen manufacturers who currently select and exchange their in house reference. There has, however, been an attempt to develop a common international standard under the auspices of IUIS/WHO. Thus, eight such international reference preparations (selected, representative allergen extracts) were developed in a project where allergen manufacturers, academia and health authorities were participants. Most of these preparations were approved by WHO as international standards. Nevertheless, they never came into the intended use due to lacking consensus between the participants about their use. Today a new array of international reference preparations (selected, representative?, major allergen molecules) is being developed and intended to be used as standards for allergen products. The rationale for using major allergen molecules is practical and can be supported by empirical observations: Practical, because the concentration of an allergen molecule is much more accurately measured than the allergenic potency of a mixture of proteins. The empirical observations are that patients almost always express significant response to major allergens and that maintenance dose for successfully specific allergy vaccination can be related to mg major allergen content. To avoid our earlier mistakes it is extremely important to discuss, decide and have approved the future use of selected allergen molecules as standards. This approval shall if possible make the standards useful for present allergy vaccines including mixture of extracts, named patient products and authorized (registered) products. For potential, future allergy vaccines such as naturally occurring isoallergens, mutated isoallergens, and fragments or combined fragments of these, it might be expected that public control of allergy vaccines will be performed in other ways.

The aim of standardization and quality control of allergen products is to optimize accuracy, safety and efficacy of specific allergy diagnosis and vaccination. And specific diagnosis is only needed provided specific prevention or vaccination is performed. Undoubtedly, specific allergy vaccination will continue as an essential allergy treatment – often combined with other treatments. But in order to fulfil the increasing demands for efficacy/safety documentation for the treatment, the materials must be changed to enable use only as authorized allergy vaccines. Probably, authorized allergy vaccines only will be developed for a few essential allergen sources. In the future the authorized allergy vaccines might only be composed of one or a few recombinant allergen molecules which even through strategic mutations might be provided with optimized safety profiles. In that case “classical standardization” of allergens will be discontinued and in the future performed as for other authorized, medicinal pharmaceuticals.

Discussion

Kroon: To be clear, molecule?

Løwenstein: Well, we have 150 extracts of extracts which cover the step, you may pass if they will cover the dominating allergens.

Kroon: And how to have three or four?

Løwenstein: Well, allergens. For grass, for example. There are other allergens.

Chapman: Dr. Løwenstein, pharmaceuticals, or not?

Løwenstein: I think, naturally engineered, but I don't know if it will be in the future.