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History and Future of Allergen Standardization and of the Paul-Ehrlich-Seminar

Alain L. de Weck

When the organizers of this Paul-Ehrlich-Seminar kindly asked me to present a historical lecture at the end of three days full of new scientific presentations, I had some misgivings, fearing that this could become a rather boring exercise to the audience. With the dubious privilege of having been associated with international efforts to foster allergen standardization for over 30 years, I certainly felt informed enough to put the field in perspective. But hearing here all the young enthusiastic scientists of today and their interest in allergen standardization, my hesitations have vanished. Indeed, some historical perspective of the field may be quite useful since here too "those who do not know history are condemned to repeat it".

First attempts at international allergen standardization

Attempts to achieve allergen standardization may have started earlier but to my knowledge, the first focused initiative in the field was a meeting convened on August 7, 1971, by Harold Baer, at that time Chief of the Division of Bacterial Products, Division of Biologic Standards, National Institutes of Health, Bethesda. The meeting was convened on the occasion of the First International Congress of Immunology organized in Washington by the freshly born International Union of Immunological Societies (IUIS).

The aim of the meeting was to discuss how and through which mechanisms a better standardization of allergens could be achieved. Beyond skin tests, which were the sole basis for quantitative evaluation of allergens at that time, new serological methods, in particular the fresh discovery of IgE raised the hope that more reliable tests would soon become available. At this first meeting, the following were attending: Harold Baer, Bethesda; Lars Belin, Göteborg; Merrill W. Chase, New York; Alain L. de Weck, Bern; N. M. Franklin, Bethesda; S. Gunnar O. Johansson, Stockholm; T. P. King, New York; David G. Marsh, Baltimore and Philip S. Norman, Baltimore.

At the First International Congress of Immunology, it was decided to give to standardization of immunological reagents, not only to allergens, a top priority. Indeed, the leading immunologists at that time had recognized that progress in the young discipline, where new factors and biological reagents were discovered almost daily, very much depended upon thorough characterization and standardization of such reagents. Therefore, an IUIS Standardization Committee was set up, with a Subcommittee for Allergen Standardization, among several other Subcommittees. In the list of attendees at this first meeting (Figure 1), indeed many of the leading immunologists of that time may be recognized.

During the period of 1971-1979, many more meetings were convened to discuss the new approaches to allergen standardization but also new structures to foster such efforts, since various international groups and societies were interested in and concerned by the problem. They were, however, not linked and had hitherto approached the field in dispersed order.

COMMITTEE OF STANDARDIZATION OF THE INTERNATIONAL UNION OF IMMUNOLOGICAL SOCIETIES (IUIS)	
A meeting of the Committee of Standardization of the IUIS was held at 0900 hours on Saturday, 31 July 1971 in the Arlington Room of the Sheraton-Park Hotel, Washington D.C., U.S.A.	
The following were present:	
<u>Name</u>	<u>Place of Work</u>
Irene Betty	Wellcome Research Laboratories, London
John Bisnesstock	McMaster University, Hamilton, Ontario, Canada
David Catty	Experimental Pathology, Univ. of Birmingham, E
Bernhard Cinsader	Inst. of Immunology, Univ. of Toronto, Canada
Ruth Clayton	Dept. of Genetics, Edinburgh University, Eagle
Geoffrey Edsall	State Lab. Inst., Boston, Massachusetts
Hugh Fudenberg	University of California, San Francisco, Calif
Ira Green	NIH, Bethesda, Maryland
W. Frederick Hynes	Meloy Laboratories, Springfield, Virginia
Claude Lippesle	Institut Pasteur, Paris, France
Jean T. Papavassiliou	Dept. of Microbiology, Univ. of Athens, Greece
Franz Peetoom	Hyland Labs., Costa Mesa, California
Karel W. Pondsman	Central Lab of Blood Transfusion Service, Net
David Rowe	W.H.O. Immunoglobulin Lab., Geneva, Switzerland
Gerhard H. Schwick	Behringwerke, AG, Marburg/Lahn, Germany
Charles E.D. Taylor	Central Middlesex Hospital, London, England
Strathearn Wilson	Connaught Labs, Ontario, Canada

Fig. 1.
*Participants to the
first meeting of the
IUIS Standardization
Committee, 1971.*

A major step forward was therefore to unite all these efforts in a single International Joint Committee, sponsored by the International Union of Immunological Societies (IUIS), the International Association of Allergy and Clinical Immunology (IAACI) and the International Association of Biological Standardization (IABS). The Committee was established on October 26, 1976, at the Congress of the IAACI in Buenos Aires, with the aims to coordinate worldwide all activities in international allergen standardization and in cooperation with the World Health Organization (WHO), which had become in the health field the only organization legitimized to set up recognized international standards. Since IUIS was one of the few biological societies recognized directly by WHO as a Non Governmental Organization (NGO), the perspectives of the new Joint Committee appeared indeed rather bright.

But beyond the primary scientific goal to set up international standards for major allergens and to establish consensus criteria by which allergens could be standardized,

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a number of practical and organizational problems were also hampering progress. In many countries, allergens were more or less home-made products (literally dirt extracts!) which were not regulated and could be produced and sold on the market by (almost) anyone. This had led to many abuses, including the use of unsafe and/or ineffective products for diagnosis or therapy of allergic diseases. However, in a climate where consciousness of the responsibility of regulatory authorities for public health was rapidly increasing, this had become a situation which was no longer tolerable. However, it became also quickly obvious that efficient and affordable solutions to the problem were not easy and that regulatory authorities could not simply dictate inapplicable rules for allergen "customers" (patients and physicians) and manufacturers.

The situation was also unpleasant for manufacturers facing the perspective of increasing and possibly discrepant regulations from one country to another. It was therefore almost natural, but in no way self-understood that the projected Joint International Committee on Allergen Standardization would encompass not only the "customers", i.e. the scientists and physicians directly concerned by allergenic products, but also the regulatory authorities and the manufacturers. This consensus was well reflected in the first membership list of the Joint Committee, which was supposed to function as some kind of Executive Committee or Executive Board. In order to ensure broader representation, later a Steering Committee composed of 8 members and a Subcommittee composed of 16 members plus a third much larger Committee, to which anyone interested in the field could adhere, were created. This concept of a two- or three-tiered committee, one or two levels restricted to initiate projects and take decisions, the other one broader as a means to disseminate information has been found to be quite efficient in other areas.

The Joint Committee, later named IUIS/IAACI Allergen Standardization Subcommittee, has subsisted until today, but with more or less intense activity and representation of its three constituent groups. The list of the chairmen and officers of the Committee is shown in Table 1.

Fig. 1.
Participants to the
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Table 1. IUIS Allergen Standardization Subcommittee 1979-2002.

Chairmen	William Brighton, Harold Baer (1979-1981)
	Henning Løwenstein (1981-1986)
	Philip Norman (1986-1992)
	Jean Bousquet (1992-1997)
	Martin Chapman (1997-)
Secretary	Alain de Weck (1979-1981)
	Robert Goldstein (1981-1992)
Treasurer	Alain de Weck (1981-1997)
	Wolf-Meinhard Becker (1997-)

The Paul-Ehrlich-Seminars

Around the end of the 1970ies, the general climate had therefore become ripe for organizing a meeting entirely devoted to allergen standardization and which would gather the three main clienteles: scientists, regulators and manufacturers. In that perspective, the concept of the Paul-Ehrlich-Seminar was unique and has remained so until today. The first Seminar was convened by Prof. Dr. H. Göing and Prof. Brede, Director of the Paul-Ehrlich-Institut, at that time in Frankfurt. It took place at the Hotel Arabella from May 19-21, 1979.

This first meeting was then followed at three year intervals by 9 others on the same format, the 10th Paul Ehrlich Seminar being held now in Lübeck. Already by the time of the 3rd meeting in 1983, the venue had become international since we were the guests of the University of Leuven (Belgium). At the time of the 4th Symposium in 1985 (Figure 2), we crossed the Atlantic for the first time and were the guests of the National Institutes of Health and of the FDA.



DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Food and Drug Administration
Center for Drugs and Biologics
Rockville, MD 20857 USA



PAUL-EHRlich-INSTITUT
Bundesamt für Sera und Impfstoffe
6000 Frankfurt am Main 70
Federal Republic of Germany



Fourth International Paul Ehrlich Seminar
on
Regulatory Control and Standardization of
Allergenic Extracts

October 15 - 18, 1985
PRELIMINARY PROGRAM

Fig. 2. Announcement of the 4th PEI Seminar in Bethesda, USA, 1985.

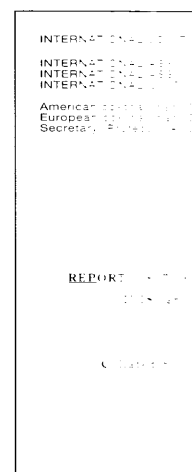
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This is not the place to remind in detail about the programs, the presentations and the participants to the various Paul-Ehrlich-Seminars over two decades. A very useful record is available in the Proceedings series of these meetings (Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf a M).

Since this presentation is also supposed to discuss the future, I can only express a wish, namely that these Seminars should continue, about in the same format, since they practically still represent the only forum at which regulators, allergen manufacturers and scientists come into common discussion at the international level. This endeavor is and remains the major justification for this Seminar. An additional bonus is also the rather complete review of scientific progress in allergen research and the unique gathering of all researchers active in the field.

Technological and educational achievements of the Allergen Standardization Subcommittee

The Committee soon realized that it was not enough to talk about things; there was also an urgent need to do something about the problem of allergen standards.

One of the first needs was to develop and harmonize the methodologies by which allergens can be evaluated and quantified. At that time, the most promising and relevant method appeared to be based on the *in vitro* interaction between allergens and the

INTERNATIONAL JOINT STEERING COMMITTEE FOR ALLERGEN STANDARDIZATION	
INTERNATIONAL ASSOCIATION OF ALLERGOLOGY INTERNATIONAL ASSOCIATION OF BIOLOGICAL STANDARDIZATION INTERNATIONAL UNION OF IMMUNOLOGICAL SOCIETIES	
American co-chairman: Dr. H. Baer European co-chairman: Dr. W. D. Brighton Secretary: Professor A. L. de Weck	Please reply to:
REPORT OF THE INTERNATIONAL COLLABORATIVE ASSAY OF THE IUIS anti human IgE Reagent.	
Collated by Dr. W. D. Brighton	
June 1979	

Fig. 3.
Anti-IgE Antibody Standard.

PROPOSED RAST INHIBITION PROCEDURE
Bureau of Biologics
January 1979

Fig. 4.
RAST Inhibition technique.

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standards. This study, unfortunately, never materialized, for a variety of reasons but to some extent due to disagreements between American and European scientists on the optimal way to evaluate an allergen by skin test.

The final result was that the International Standards were never used by regulators and manufacturers as the benchmark by which commercial allergen products would be evaluated and registered. The ambitious original goal was therefore not achieved, despite a considerable amount of time and money invested by the international community. This experience left to many a somewhat bitter taste and certainly hampered further efforts at allergen standardization in the following decade.

1 <u>INTERNATIONAL STANDARDS</u> (5)		
DERMATOPHAGOIDES PTERONYSSINUS	82/518	1984
PHLEUM PRATENSE	82/520	1984
AMBROSIA ELATIOR	84/581	1984
BETULA PENDULA	84/522	1986
CANIS DOMESTICUS	84/685	1986
2 <u>INTERNATIONAL REF. REAGENT</u> (1)		
CYNODON DACTYLON	-	1989
3 <u>INCOMPLETE</u> (3)		
ALTERNARIA	: WITHDRAWN	
CAT	: NO REPORT; NO STABILITY	
PERENNIAL RYE	: IN PROGRESS	
4 <u>OTHERS ORIGINALLY PROPOSED</u> (7)		
D.FARINAE	OLIVE	CLADOSPORIUM
PLANE	MUGWORT	PARIETARIA
OAK		

PE13a

Fig. 5. International Allergen Standards and further allergen references – Further impact of the IUIS Allergen Standardization Subcommittee.

The failure to achieve recognition of the International Standards as the standard bench tool for allergen evaluation, manufacture and registration should not be looked at as a complete flop. Indeed, in the 1990ies, a multitude of In House Reference reagents were developed and made comparisons between results of various allergen manufacturers more difficult. In addition, most manufacturers, and even the US regulatory agency, developed their own unitage system, so that at the present time, the field of allergen standards has become some kind of Tower of Babel, precisely the worst scenario in respect to what was hoped for 20 years ago.

But the impact of the International Allergen Standards Program was not entirely negative. The multicenter evaluation studies based for the first time on common and standardized technologies taught scientists, manufacturers' laboratories and regulatory

agencies how to work together and speak the same language. It also demonstrated how various modern technologies could improve allergen manufacture and reduce variations from lot to lot. With this, even allergen manufacturers who were not directly involved in the standardization effort were obliged to improve their practice. This resulted indirectly over the years in marked improvements in the quality and consistency of commercialized allergen products and in the elimination of lesser quality conscious manufacturers or of dubious procedures, such as homemade allergen extracts. In 1981, more than 5000 allergen products were available on the US market alone, among which the majority had neither documented safety nor efficacy. The situation has considerably improved since.

The Subcommittee was also involved in the propagation of new technologies and their development for allergen standardization. In 1987 already, the group of Thomas Platts-Mills approached the FDA suggesting the use of allergen-specific monoclonal antibodies in order to quantify major allergens in mass units. The whole field of recombinant allergens experienced a spectacular development in the 1990ies and holds great promises for future allergen standardization, although many of this promises are not yet reality at the regulatory level.

A very successful activity in this respect has been the organization of courses attended not only by scientists working at universities but also in manufacturers' laboratories. A first course was organized in 1980 by Henning Løwenstein in Copenhagen. A second course on recombinant allergen technologies was organized by Dietrich Kraft and Rudolf Valenta in Vienna in 1995 and had a visible impact on the dissemination of molecular biology technology in the allergen industry.

Guidelines for allergen evaluation and registration

One direct effect of the increased consciousness about allergen quality and safety in the early 1980ies has been the development of legislation and of registration guidelines, at the national and international levels.

In the US, under the impulse of the FDA Bureau of Biologics (later CBER) a whole set of uniform assays and requirements, including FDA reference reagents, were developed and to some extent imposed on manufacturers. Although this system included a dialogue between manufacturers and the regulatory agency, it is to some extent rigid and one-sided, eventually leading to undue delay in adopting new approaches and to administrative obstacles in the testing of new products, such as recombinant allergens. It has the advantage, on the other hand, to provide single transparent rules for one big market.

In Europe, the development has been quite different. In 1981, the regulatory agencies of Scandinavian countries provided a set of so-called Nordic Guidelines, which were the first to spell out requirements and regulations for allergen registration. The originality of these Nordic Guidelines was to propose a biological reference system based on the skin reaction to histamine (Histamine Equivalent in Prick testing: HEP). This system, despite its apparent theoretical attraction, however, never really took off,

since the pathophysiologic basis of skin reactions and the lack of registration were not covered by or specific legislation in Germany and the rest of the allergen field.

The matter was discussed, decreed, and that registration was for a long time in the case of allergen. The problem was therefore the Pharmacopoeia of manufacturers and of the products produced by this way ("Allergen Products") interpretations, with harmonization of the European Union.

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since the pathophysiology and time course of histamine-induced and allergen-induced skin reactions are quite different. At that time, the national requirements for allergen registration were variable among the various European countries. Many had no basic or specific legislation in this respect; most regulatory agencies, with the exception of Germany and the UK had no particular expertise and laboratories working in the allergen field.

The matter was then tackled by the European Community which, after much discussion, decreed in 1992 a "Note of Guidance" essentially establishing for the first time that registration of allergens should follow the same rules as those already established for a long time for pharmaceutical drugs. It was obvious, however, that such rules, in the case of allergens, were neither applicable nor meaningful in all details. The problem was therefore pursued for two years by a working group of the European Pharmacopoeia including representatives of the scientific community, of the manufacturers and of the regulatory agencies. For various reasons, the ultimate document produced by this working group, and published by the European Pharmacopoeia in 1995 ("Allergen Products") was a poor compromise. It was too vague and led to various interpretations, with the result that its implementation has not resulted in the desired harmonization of allergen registration procedures among the various members of the European Union up to now.

This basic general document was not followed, as originally intended, by specific recommendations for single allergens or allergen groups. It was also not sufficiently opening the door to new technologies, such as monoclonal antibodies, standardization in mass units and the use of recombinant allergens as standards. Finally, ten years after publication of the first EU guidelines, there is still no harmonization among European national regulatory authorities about allergen registration procedures. For most such agencies, allergens have remained a minor problem for which they have no in house experts, no competent laboratories and consequently no priority and interest.

The future of allergen standardization in view of the past

A critical analysis of the history of allergen standardization in the past 20 years yields positive and negative aspects (Table 2). In view of the greatly increased prevalence of allergic diseases during the same time and of the increased recognition of allergy by health authorities as a major problem, I personally find the overall picture rather frustrating and depressing, particularly in the field of regulation. There is no doubt that availability of high-quality and reproducibly manufactured allergens is a condition "*sine qua non*" for optimal diagnosis and therapy in allergy. But it is also increasingly difficult to achieve this, in view of the current inefficiency, or rather non-existence, of a common European allergen registration process. This state of affairs is not only costly but downright discouraging for the steadily decreasing group of allergen manufacturers. Since allergen manufacture is by far not the most lucrative of pharmaceutical endeavors, the risk that allergic patients may not count in the future on sufficient, optimal and cost-effective products is not to be taken lightly. Therefore, the current state of "benign neglect" by most of the European regulatory agencies represents, in terms of public health, a neglect of their basic duty. The most efficient proper remedy

from the fact that the main professional allergology associations (IAACI, EAACI, AAAAI) have pretty much neglected the field of allergen standardization in the past ten years. It is not unfair to state that for most of the allergology leaders operating during the 1990ies, allergen research and standardization were a lesser priority than epidemiology, public health and public relations aspects of allergy. But allergen standardization and registration have also a major impact on the practice of allergology!

So, at this point, looking backwards and forwards, I feel a number of serious concerns about the future (Table 3). These are not scientific but health policy problems and the only way to tackle them is by professional associations to renew their old commitments, and for regulatory agencies to set up the proper organization and procedures to fulfill their public health duties in the field. The quality of allergy practice and the benefits and safety for the patients should be a sufficient basic motivation to pursue our efforts in this respect.

Table 3. *Current concerns.*

Incompatibility between various guidelines and regulations (US, EU)
Costs of registration: duplicate procedures, unnecessary requirements
Legitimate future of patient-named allergen products
Lack of continuing real and constructive dialogue between regulatory authorities, allergen manufacturers and "consumers"
Low priority of allergen standardization in allergology/immunology organizations
Undue emanation of useful products due to administrative and/or market procedures
Lack of common reference preparations: extracts, sera, reagents – However, recombinant allergens and monoclonal antibodies increasingly available
Increasing gap between scientific knowledge on allergens and its practical use for standardization and registration