

The role of pharmacopoeias in international harmonisation

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Abstract

The last 30 years have seen profound changes in the organisation of the European people and the regulation of medicinal products. Thirty years ago, each country had its own regulations, with all the possible variations between the various national pharmacopoeias. Today, the European Pharmacopoeia, with its 1500 monographs and nearly 250 general methods of analysis, has replaced the major part of these national regulations: the European Pharmacopoeia Convention has now been signed by 27 states¹ and by the Commission of the European Communities; moreover 16 European and non-European countries² and the WHO have observer status. Close relations are maintained with the licensing authorities of the European Economic Area, where integration is developing via the implementation of common directives and guidelines on medicines for human and veterinary use. In addition, in 1990, the European Pharmacopoeia co-founded, with the Japanese Pharmacopoeia and the US Pharmacopoeia, the Pharmacopoeial Discussion Group (PDG); this group is working assiduously for harmonisation at world level. © 2001 Elsevier Science B.V. All rights reserved.

1. European international harmonisation and the European Pharmacopoeia

The growth of trade and closer relations between countries has made the international harmonisation of laws and regulations indispensable. The area of medicines, which is one of the most heavily regulated areas for reasons of public health, is specifically affected and harmonisation here is particularly delicate and laborious. Indeed, to be effective it must be sufficiently developed or even taken to its extreme — uniformization.

Europe, with its historical heritage of fragmentation into numerous states, is the ideal proving ground for harmonising regulations. In 1964, a Convention was signed for the elaboration of a

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¹ Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Grand Duchy of Luxembourg, Norway, Netherlands, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, 'The Former Yugoslav Republic of Macedonia', Turkey, UK and the EU.

² Albania, Algeria, Australia, Bulgaria, Canada, China, Estonia, Latvia, Lithuania, Malaysia, Morocco, Poland, Romania, Syria, Tunisia, Ukraine and WHO (World Health Organization).

European Pharmacopoeia between eight countries. Today, the convention has been extended to 28 parties.

In the 1990s, the people in charge of the public and private sectors in Europe, Japan and North America, faced with the growth of world-wide trade and the increasing costs of scientific research, decided to approach each other to identify potential areas for harmonisation [1–3]. The Pharmacopoeial Discussion Group (PDG) was founded.

The Convention on the Elaboration of a European Pharmacopoeia is based on a dual commitment by its signatory states [4]:

- a commitment to elaborate a common pharmacopoeia, by contributing financially to its budget and by sending experts;
- a commitment to make official on their territories, the specifications of the European Pharmacopoeia, if necessary replacing the existing national requirements.

This commitment has been made official and integrated into the regulations for the registration of medicines manufactured industrially since the adoption in 1975 of the first directive (75/318/EEC) on the standards and protocols for analytical, pharmacotoxicological and clinical studies on medicines; this principle has also been applied in the area of drugs for veterinary use, according to directive 81/852/EEC and also when these requirements were extended to immunological products: vaccines, immunosera and allergens (directive 89/342/EEC), to veterinary vaccines (directive 90/677/EEC), to homeopathic medicines for human use (directives 92/73/EEC) and for veterinary use (92/74/EEC).

The legal links created between the states are clearly specified and binding. In addition, appropriate means for this endeavour have been provided, as the 1964 convention created a permanent ad hoc Secretariat, which was integrated into the administrative system of the Council of Europe as a partial agreement. Monographs are adopted by a unanimous decision of the member states.

The harmonisation envisaged involves real integration and the creation of supranational European specifications. This has been the decision taken by the European Pharmacopoeia Commis-

sion since its first meetings. To this end, it created groups of experts in the various pharmaceutical areas.

Hence, since 1964, European groups of experts, consisting of the best national experts, have been elaborating a pharmacopoeia de novo, which benefits from national experience and contributions, but with a view to the construction of a single European specification. Chapters on general physico-chemical, biological, pharmacotechnological methods were elaborated first, followed by the first monographs. The monographs and general methods were soon integrated into the national pharmacopoeias, replacing the national texts. Hence, while new European monographs are being elaborated, a necessarily long and laborious process since it concerns more than a thousand texts, European harmonisation through the general notices also makes its way into national monographs, which continue to exist pending a European text.

1.1. Achievements and European harmonisation procedures

After 30 years of the European Pharmacopoeia convention, the following has been achieved.

1.1.1. Number of member states

The desire for harmonisation in Europe, manifested by the eight founder states (six EEC states in 1964, UK and Switzerland), has continued to spread and it now covers the whole of Western Europe and part of Central and Eastern Europe. This desire for harmonisation has also spread to non-European countries that historically have had close cultural ties with Europe and the status of observer to the European Pharmacopoeia has been granted to these countries.

1.1.2. Relations between the Pharmacopoeia and the licensing authorities

The roles played by the licensing authorities and the Pharmacopoeia to guarantee the quality of medicines are completely integrated and complementary, whether they act through the directives of the EU, as mentioned above, or through the work carried out by the various groups of experts. The finishing touches have been put to this co-operation by the accession of the EEC to

the Convention on the Elaboration of a European Pharmacopoeia on 21 June, 1994. The Commission of the European Communities then becomes a full member of the European Pharmacopoeia Commission and will represent the EU jointly with the new European Medicines Evaluation Agency. It will be able to vote on non-technical matters (procedures etc.) with a voting strength equal to the number of EU member states; the member states will retain their responsibilities in the scientific and technical fields.

1.1.3. Relations with the users

The European Pharmacopoeia Commission has developed a policy of openness, consultation, information, explanation, mainly through the quarterly newsletter *Pharmeuropa* or through professional associations.

The procedure for the elaboration of monographs was made public through the publication of the Guide for the Technical Content of Monographs [5]. This document is regularly updated to keep pace with technical advances and with the requirements for public health expressed by the European registration authorities.

The third edition was published in December 1999 and has integrated the concept on ICH guidelines for analytical validation.

1.1.4. Number of monographs

The production of new harmonised monographs has accelerated with the concomitant harmonisation of European registration legislation. It has reached 1500 and every year ≈ 100 additional monographs are produced.

Thus, the European harmonisation work of the European Pharmacopoeia in the area of specifications of medicines is well under way and now world-wide harmonisation is being initiated.

2. The role of the European Pharmacopoeia in world-wide international harmonisation

The European Pharmacopoeia, whose original aim was to harmonise European regulations, has not grown in isolation, but instead it has sought international exchanges whenever possible.

Hence, the European Pharmacopoeia Commission has invited the WHO to attend its sessions from the beginning of its work. The European Pharmacopoeia uses the international non-proprietary names recommended by the WHO whenever they exist and it invites an expert from the WHO to participate in the biological groups of experts (vaccines and, recently, blood products). Similarly, when European biological reference preparations have been elaborated, the work has been co-ordinated with the establishment of WHO international standards.

In 1989, on the 25th anniversary of the European Pharmacopoeia convention in Strasbourg and at the congress on the perspectives of international harmonisation in Tokyo, multinational pharmaceutical companies expressed their need for the harmonisation of the pharmacopoeias of Japan, Europe and the US [6].

The heads of these pharmacopoeias immediately decided to organise regular contacts among themselves and a procedure for rapprochement. In this way, the Pharmacopoeial Discussion Group was founded and meets twice a year.

About 50 monographs on excipients and general methods of analysis proposed by national associations of manufacturers of pharmaceutical products have been selected for convergence and harmonisation among the three pharmacopoeias. Proposals for harmonised texts are regularly published in the forum of the three pharmacopoeias for public enquiry (*Pharmeuropa*, US Pharmacopoeial Forum and the Japanese Pharmacopoeial Forum).

As commented by J.A. Halperin [6], harmonisation at the world level rarely means identical standards (unlike the results obtained in Europe), but rather the elimination of elements of disharmony whenever possible and whenever useful to international trade. Indeed, many parameters are involved and there are many conflicts between monographs, methods of analysis and reagents. Furthermore, attaining identical standards is complicated by expanding markets. Hence, the first stage of harmonisation involves the elimination of standards that are not scientifically justified, the revision of obsolete specifications and the search for compatibility between the chosen standards.

To be effective, it requires much explanation and public relations between all the partners concerned so that the constraints and limits of each are known.

Colloquia and open conferences are organised, with the location rotating among the three continents. The USP organised two open conferences on the harmonisation of excipients in 1991 in Orlando and in 1994 in St. Petersburg (Florida); in 1993, the European Pharmacopoeia organised an open conference in Verona on biotechnological products in which its Japanese, American and European partners actively participated.

More recently, an international conference was organised in conjunction with the programme of work of ICH on Sterility (Barcelona, 1996), Dosage forms (Sevilla, 1998), Biologicals beyond 2000 — Challenges for the quality standards in an evolving field (Strasbourg, 1999).

The pharmacopoeias also participate in the work on the rapprochement of licensing dossiers within the framework of ICH. The pharmacopoeias have observer status in the Quality Working Party and Biotech Working Party and notably have participated in the elaboration of guidelines on analytical validation, impurities, residual solvents and specifications. Where appropriate, they integrate the general principles of these guidelines into their specifications.

Following the adoption of the last quality guidelines by ICH Steering Committee in October 1989 on 'specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances', it is intended that the regulators of the three regions (FDA–USA–EU/Europe and MHW Japan) will recognise as interchangeable procedure and acceptance criteria of any of the three Pharmacopoeias where harmonisation of this procedure and criteria have been successfully completed. To signify the harmonised status of these procedures, the three pharmacopoeias have agreed to include a statement in their respective texts which indicates that the procedures and acceptance criteria from all

three pharmacopoeias are considered equivalent and are, therefore, interchangeable.

At this time, a 'sign-off document' is available for SDS polyacrylamide gel electrophoresis and bacterial endotoxins tests.

This agreement takes effect as soon as the three pharmacopoeias publish the common text that was agreed on.

In conclusion, the following points can be emphasized:

- The great commitment of all partners over the last few years has led to the elimination of distortions due to ignorance, lack of partnership or disguised protectionism which are to the detriment of all.
- It is difficult to obtain tangible results within very short deadlines due to the complexity and interactions of the various parameters to be harmonised. Indeed, while the technological and commercial constraints are becoming more uniform from one continent to another, the legal and regulatory environments in Japan, the US and Europe are far from being harmonised and this acts as a brake on the rapprochement of pharmacopoeias.

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