

STANDARDISATION AND PHARMACEUTICAL DEVELOPMENT: CONTRIBUTION OF THE EUROPEAN PHARMACOPOEIA AND THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES

A. ARTIGES

The last ten years have seen profound changes in the organisation of the European people and the regulation of medicinal products. 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 twenty-seven States and by the Commission of the European Communities; moreover, sixteen European and non-European countries 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. To keep up with evolving needs related to international trade and the requirements of the public health authorities, the European Pharmacopoeia has redesigned its monographs and set up a procedure for the certification of suitability of these monographs.

Key words: Specifications — Standardisation — Certification — Harmonisation — Pharmacopoeia.

La dernière décennie a vu de profonds changements dans l'organisation des peuples européens et la réglementation des médicaments. Aujourd'hui, la Pharmacopée européenne, avec 1 500 monographies et près de 250 méthodes générales d'analyse, a remplacé la plupart des réglementations nationales : la Convention de la Pharmacopée européenne est maintenant adoptée par vingt-sept Etats et par la Commission des Communautés européennes ; de plus, soixante pays européens et non européens ainsi que l'OMS ont un statut d'observateur. D'étroites relations sont maintenues avec les autorités réglementaires de l'Espace économique européen, où l'intégration se développe grâce à l'adoption de directives communes et de recommandations sur les médicaments à usage humain et vétérinaire. Pour rester en contact avec l'évolution des besoins liés au commerce international et aux exigences de santé publique, la Pharmacopée européenne a redéfini ses monographies et mis au point une procédure de certification de leur pertinence.

Mots clefs : Spécifications — Standardisation — Certification — Harmonisation — Pharmacopée.

The last ten years have seen profound changes in the organisation of the European people and the regulation of medicinal products:

- the European Union has completed its harmonisation of national regulations in the field of human and veterinary vaccines and has created a European Agency for the Evaluation of Medicinal Products (EMA),
- there is growing international convergence as a result of the ICH (International Conference on Harmonisation) cycle attended by the licensing authorities of the three large regions that are the most innovative in the search for new medicines: the United States, the European Union and Japan.

Scientific and technological developments significantly affect the regulatory environment; it therefore becomes even more important for the industry, licensing and pharmacopoeial authorities to work in close partnership.

The success of the European system also depends on the partnership between national competent authorities and the European institutions (European Union/EMA, Council of Europe/EDQM). The European Pharmacopoeia, which brings together these partners, has tirelessly worked to ensure this success, first by expanding its circle of participants and correspondents, and second by regularly adapting the contents of its monographs and chapters to keep up with the expansion of world trade and the changing regulatory and technological environment. I will give some examples.

I. THE CIRCLE OF PARTICIPANTS

From the start, the European Pharmacopoeia has had the objective of making harmonised regulations on the quality of medicines available to the largest number of participants.

To be valid, the rules for elaborating common standards require a solid legal basis for the benefit of public health. This was why the European Pharmacopoeia convention [1] was drafted. It was signed in 1964, under the aegis of the Council of Europe, and it binds the signatory States to ensure that jointly adopted specifications become official and obligatory on their territories. This was the first decision to create a supranational organ in this area. Given the revolutionary and novel character of this commitment, the drafters of this convention ensured its solidity by opening it to partners other than the eight original signatory States (Belgium, France, Germany, Italy, Luxembourg, The Netherlands, Switzerland, United Kingdom) only after the parliaments of the original Member States had ratified it. The work needed for ratification was extensive, taking ten years and requiring substantial legislative amendments in several Member States. These ten years, however, were put to good use by developing from scratch an original European approach that was free from the conservatism of national structures and which, from the start, was focussed on the future and the integration of scientific advances on the one hand, and on international collaboration on the other hand.

Once a solid legal basis was established, the structure created in this way was free to develop fully, and progressively came to include all the European countries. This growth was accelerated by the work accomplished in parallel by the partners of the treaty of Rome. Indeed, in accordance with an agreement between the European Union and the Council of Europe, the European Pharmacopoeia was from the beginning intended to be integrated into the pharmaceutical legislation of the European Union. This happened as soon as the first directive was issued on standards and protocols (75/318/EEC) [2].

When a State becomes a party to the Convention, this means not only that it can participate in the elaboration or revision of common standards, but also that it undertakes to replace any pre-existing national texts by the specifications of the European Pharmacopoeia. The Pharmacopoeia now consists of nearly 1,600 monographs and a set of general methods of analysis that are commonly used for the testing of medicines.

This entails considerable adaptation by new candidates who must make sure that they can uphold their commitments before signing. This is why the European Pharmacopoeia Commission very soon set up a flexible procedure for this adaptation, with observer status preceding membership for prospective candidates.

Observer status allows them to send representatives to the sessions of the Commission, to follow the discussions and to take national initiatives for the adaptation of their standards to appropriate European standards. Most central and eastern European countries wished to obtain this observer status. According to their national needs, many of these countries have voluntarily undertaken national translation of certain parts of the European Pharmacopoeia (general chapters, dosage forms, monographs on biological products or preparations, vaccines) that they implement progressively as permitted by their regulations and as needed for public health.

Today, the Convention has been signed by twenty-eight parties (the European Union and twenty-seven Member States) and eight countries have observer status, thus covering, directly or indirectly, all of Europe except for Russia.

Observer status is not limited to Europe. Starting in the nineties, it was extended to traditional partners of the main founder States: Member States of the Commonwealth or former colonies, which initially referred to national pharmacopoeias and, as the national texts of these pharmacopoeias were progressively replaced by the European texts, wished to establish direct links with the European institution driving the system. Hence observer status has been granted to Canada, Australia, Syria, Malaysia, Morocco, Tunisia and Algeria, which directly or indirectly apply the standards of the European Pharmacopoeia. This procedure has also allowed the establishment of links with China, one of the major exporters of raw materials for the manufacture of medicines in Europe.

II. ADAPTATION TO THE EXPANSION OF INTERNATIONAL TRADE AND THE CHANGING REGULATORY AND TECHNOLOGICAL ENVIRONMENT

One of the main characteristics of the European Pharmacopoeia is its very close relationship with the regulatory authorities

of the European Union in charge of marketing authorisations of medicinal products, and its policies and content reflect this partnership.

The European Pharmacopoeia also participates in the work on the rapprochement of licensing dossiers within the framework of ICH (cycle of international conferences organised by the regulatory authorities and manufacturers associations of Europe, Japan and the United States). It has contributed to the elaboration of guidelines on analytical validation, impurities, residual solvents and specifications and, later on where relevant, has integrated their principles and content into its monographs and chapters. The following aspects will be highlighted.

1. GENERAL NOTICES

This introductory chapter summarises the characteristics of the legal environment of the European Pharmacopoeia and gives the principal definitions. It explains the legal significance of each part of the Pharmacopoeia and the role of each section of a monograph. This chapter is essential reading when reference has to be made to a monograph of the European Pharmacopoeia.

2. MONOGRAPHS ON CHEMICAL SUBSTANCES

All such monographs are elaborated according to the same format, which is described in the *Technical Guide for the Elaboration of Monographs of the European Pharmacopoeia* [3]. This guide contains the same concepts as those defined in Community guidelines, which themselves contain the guidelines adopted jointly at the international level (ICH). Hence, the two guidelines on analytical validation are integrated into this technical guide and are even supplemented by specific chapters on the principal methods of analysis (such as spectrophotometry, liquid chromatography, etc.).

The ICH guideline on impurities is also integrated into the technical guide and the guideline on residual solvents has been integrated into a general chapter of the European Pharmacopoeia. European Pharmacopoeia monographs on chemical substances have therefore been modified in connection with these changes for better control of the impurity profile of substances produced by numerous manufacturers using diverse methods of synthesis.

Each revised or new monograph now contains an impurities section at the end, which describes the list of impurities known to be detectable by the monograph. Whenever necessary, this impurities section consists of two parts: the list of qualified impurities and the list of impurities that can be detected analytically by the monograph but which are not qualified according to the ICH guideline. The list of impurities includes both the chemical nomenclature and the graphic formula, which makes the section easier to use.

In addition, the elaboration of monographs has now been supplemented by the establishment of a procedure for certification of suitability of monographs (see later) [4], thus fully satisfying the requirements of directives 75/318/EEC for medicines for human use and 82/852/EEC for medicines for veterinary use and the EU guideline on «General Requirements on Active Ingredients».

3. MONOGRAPHS ON BIOLOGICAL SUBSTANCES

Important conceptual changes have also been made to the establishment of this type of monograph to satisfy the needs of Community licensing and to keep up with progress in this field. The following changes merit special attention:

- the introduction of a «production» section,
- the replacement, whenever possible, of tests involving the use of laboratory animals,
- the elimination of the test for abnormal toxicity and its replacement by the test for endotoxins (LAL).

3.1. The «production» section

The role of the «production» section is described in the general notices. The requirement described in this section applies mainly to the manufacturers of the substance in question and to the body of inspectors responsible for checking compliance with the prescriptions of the European Pharmacopoeia or with the information given in the licensing dossier.

The tests described in this section cannot necessarily be carried out on the finished product by outside analysts, unlike the tests described in the sections on «identification», «tests» and «assay». They nevertheless play a major role in this area to guarantee the quality of the substances in question.

3.2. The replacement of laboratory animals

In recent years, the European Pharmacopoeia Commission has elaborated a policy of replacing the use of animals in quality control testing of medicines, in parallel with the application of the corresponding Convention of the Council of Europe. A sizeable programme of work has been set to apply the «three R» concept (refine, reduce, replace). To this end, the Council of Europe, represented by the European Directorate for the Quality of Medicines (EDQM), and the Commission of the European Communities are now working on an extensive standardisation programme [5] to set up collaborative studies to:

- evaluate, develop and improve the standardisation of test methods for biologicals,
- prepare European working standards,
- apply the 3 R concept to replace the use of laboratory animals,
- continue the harmonisation of test methods for biologicals in Europe, and if possible the world, in collaboration with the WHO.

These collaborative studies have led to the establishment of European working standards. Consequently, the titres and potencies of biological products will be expressed with respect to the same reference standard. The existence of reference standards recognised throughout Europe enables national control agencies and manufacturers to avoid costly duplications of work on secondary standards, which could otherwise lead to disagreements.

4. MONOGRAPHS ON DOSAGE FORMS

A new chapter has been introduced that brings together all

the monographs describing dosage forms and, whenever necessary, the monographs have been supplemented by technological tests and harmonised so that the chapter constitutes a coherent whole.

It should be noted that this chapter and the previous EEC guideline published in 1991 on «Authorised Terms for Dosage Forms, Routes of Administration and Containers» were revised together by the European Pharmacopoeia Commission at the request of the Commission of the European Communities.

Both tasks were therefore carried out in parallel and coherently: on the one hand, the revision of all the monographs of the European Pharmacopoeia and, on the other hand, the revision of the Community guideline on authorised terms.

This guideline has now been replaced by a revised version elaborated by the European Pharmacopoeia, which has been translated into all the languages of the Community. Indeed, not only does this document give the terms in the languages of the Community but it also includes terms in the national languages of several countries of the European Pharmacopoeia that are not members of the European Union but which also wished to provide a translation in their language. The revised document will therefore list terms in twenty-one European languages (Bulgarian, Croatian, Czech, Danish, Dutch, English, Finnish, French, German, Greek, Hungarian, Icelandic, Italian, Norwegian, Polish, Portuguese, Slovenian, Slovak, Spanish, Swedish and Turkish).

This relatively large document, which covers both human and veterinary medicines, is published as a special issue of *Pharmeuropa* [6]. The first version was published in November 1996, then revised yearly; the latest revised version has been published in February 2000. This will produce a harmonious and coherent whole that can be used throughout Europe. The terms are mandatory for applications and summaries of product characteristics for EU centrally authorised products. The list can be extended on request if justification is provided. A specific procedure has been set up. Forms are also available on the EDQM web site.

5. CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

The certification procedure is a complement and a bridge between the public standards described in the European Pharmacopoeia and the need to prepare a file for licensing. This procedure is a result of much common discussion and agreement between the partners concerned [7]. It was in fact made to measure, in collaboration not only with the European regulatory authorities, so that they could totally rely on it and unreservedly recognise its validity, but also with the industries, so that they could be absolutely sure of the protection of industrial property. So, in parallel with the work of the European Pharmacopoeia Commission, a new and specific administrative section has been created in the EDQM of the Council of Europe.

On the basis of the data collected during the elaboration of the monograph and the specific data provided by a specific manufacturer on a specific substance, the certificate of suitability certifies that both types of data make it possible to conclude that the quality of the substance corresponds to the quality defined

in the European Pharmacopoeia monograph. The data provided by manufacturers are assessed by independent assessors from national licensing authorities and kept strictly confidential.

In principle, a certificate can be granted for any substance for which there exists a monograph published in the European Pharmacopoeia; examples are organic or inorganic substances (active substances-excipients), substances produced by fermentation as indirect gene products, products with risk of TSE. However, biological substances such as proteins, products obtained from human tissues, vaccines, blood products and preparations are excluded for the time being.

6. INTERNATIONAL HARMONISATION

This review will not be completed without highlighting the close relationship which has developed since 1990 between the European, Japanese and American pharmacopoeias. They co-founded the Pharmacopoeial Discussion Group, which is working assiduously for harmonisation at the world level and which participates in the ICH programme. This group meets regularly (twice a year) in Europe, Japan and the United States. About fifty 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.

A special section of the European Pharmacopoeia quarterly journal, *Pharmeuropa*, is now dedicated to this activity. Joint open conferences organised by the three pharmacopoeias, in Verona, Italy (on biotechnology products in April 1993), in St Petersburg, Florida (on excipients in 1994), in Barcelona, Spain (on microbiological tests in 1996) [8], in Seville, Spain (on dosage form-pharmacotechnological tests in 1998) [9], and in Strasbourg, France (on new trends in biologicals in 1999) [10], brought together specialists from all over the world.

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