59. Ibid., p. xii.
60. SONNEDECKER G., *Kremers and Urdang's History of Pharmacy* [*supra* fn.3], p.258.
*repository* 3rd Hex., 1810, 1 p. 178.
62. COWEN D.L. and HELFAND W.H., *Pharmacy: an illustrated history*, New York, 1990, p. 137.
63. THACHER J., *American new dispensatory* 3rd ed., Boston, 1817, p. xviii .
64. *Medical repository* N.S., 1821, 6, p. 427.
65. Philadelphia *journal of medical and Physical sciences*, 1820, 1, p.38.
66. *Medical repository* 3rd Hex., 1811, 2, p.74.
67. *American medical and Philosophical register*, 1814, 4, p.416.
68. Massachusetts *Pharmacopoeia [supra* fn.2] p.x.
69. *Medical repository* N.S.3, 1817, 272-273; *Philadelphia journal of medical and Physical sciences*, 1820, 1: 35-36.
70. *Philadelphia medical museum*, 1806, 2 p.443.
71. *Massachusetts Pharmacopoeia [supra* fn.2] p. vi.
72. Pharmacopoeia of the New York Hospital [supra fn.2] pp.iv, Vlll .
73. Massachusetts *Pharmacopoeia [supra* fn.2] pp. v, vi.
74. *Medical repository* N.S., 1817, 3:268-274.
75. *Philadelphia journal of medical and Physical sciences*, 1820, 1: 35-36, 40.
76. THACHER J., *American medical biography* [supra fn.20] Vol 1, pp.41-42.
77. COWEN D.L., *The Edinburgh Pharmacopoeia, Medical history*, 1957, 1, p. 132.
78. COWEN D.L., *Edinburgh dispensatories [supra* fn.27] p. 92.
79. DUVEEN D. and KLICKSTEIN H., *The introduction of Lavoisier's chemical nomenclature into America. Isis*, 1954, 45 p. 278.
80. DARLINGTON W., *Memorials of John Bartram and Humphrey Marshall*, Philadelphia, 1849, p. 304.
81. *Memoirs of the American Academy of Arts and Sciences. 1783*, Boston, 1785, 1: 419, 420, 446, 451
82. *New England journal of medicine and surgery*, 1818, 7 p. 70.
83. Rafinesaue, op. cit. [supra fn. 15] pp.18-21.
84. CHAPMAN N., *Discourses on the elements of therapeutics and materia medica*, Philadelphia, 1817, vol. 1 pp. x, 116-117, 196; vol. 2 pp. 22, 221, 232, 489
85. COWEN D.L., *Edinburgh Pharmacopoeia* [*supra* fn. 77] p.l31.
86. COXE J.R., *American dispensatory* 2nd ed., Philadelphia, 1810, p. 111.
87. URDANG G., *Pharmacopoeias as witnesses of world history, Journal of the history of medicine and allied sciences* 1 (1946) 46-70; A. Tschirch, *Die Pharmakopöe ein Spiegel ihrer Zeit, Janus*, 1905, 10, p. 281 et seq.

*This study is an advanced research based on the author's *America's Pre-Pharmacopoeial Literature* (American Institute of the History of Pharmacy, Madison, 1961)

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Articoli/*Articles*

# THE EUROPEAN PHARMACOPOEIA

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SUMMARY

*In defining a pharmacopoeia as* an instrument for the quality control of medicines in the public health field, *the Author illustrates the origin, history and development of the European Pharmacopoeia since the Brussels Treaty in 1948. 20 countries are now applying the European Pharmacopoeia standards; they are based on an international Convention, which is a sort of law-making and institutional treaty.*

A pharmacopoeia is a set of standards for ensuring the proper quality of medicinal substances, auxiliary substances, pharmaceutical preparations and other articles, the specifications of which are mandatory in a defined political area. This applies also to the European Pharmacopoeia. A pharmacopoeia is therefore an instrument for the quality control of medicines in the public health field, aimed at ensuring the proper quality of medicines which reach the consumer and patient for the prevention and cure of illness.

Within the framework of 1948 Brussels Treaty the idea of the harmonization of pharmacopoeial standards was discussed by representatives of Belgium, France, Luxembourg, the Netherlands and the United Kingdom, who proposed to establish a common standard for medicinal substances that would be useful and needed in times of war or following catastrophes.

Parole chiave/Key words: Europe - Pharmacopoeia

Following the accession of Italy and the Federal Republic of Germany to the Brussels Treaty (Paris Treaty) and the creation of the Western European Union in 1954, a working party composed of representatives of national pharmacopoeia commissions was established with a view to standardizing as a first step 135 important medicinal substances.

All economic, social and cultural activities of the Western European Union were in 1960 transferred to the Council of Europe and the Sub-Committee on Pharmaceutical Questions continued its activities at the Council of Europe within the framework of a *Partial Agreement* and it suggested in 1962 the concept of a European Pharmacopoeia.

The collaboration in Europe in pharmacopoeial matters was supported by further developments in the economic field. Free circulation of goods, as envisaged in the Treaty of Rome, presupposes the unification of the various national rules and the free movement of medicinal substances and medicines - as a consequence of this Treaty - obviously implies the need to unify the standards of the different national pharmacopoeias. Accordingly, on 22 January 1963, the European Economic Community (EEC) expressed its intention to elaborate a Pharmacopoeia for the six countries of the Common Market.

France, which, as far back as 1951, had already made a proposal to this effect within the Brussel Treaty, now resubmitted this proposal to the Sub-Committee on Pharmaceutical Questions at the Council of Europe. This Committee took up the proposal and, with the agreement of the EEC, prepared a draft Convention on the elaboration of a European Pharmacopoeia. The Convention was signed in Strasbourg on 22 July 1964 by the six founder States of the Common Market plus the United Kingdom and Switzerland.

Once the Convention was signed, the Contracting Parties agreed to apply it already provisionally, in conformity with their respective constitutional systems and not to await its official entry into force three months after the date of deposit of the eighth instrument of ratification or acceptance. This provisional





application enabled work to begin immediately and intensively in 1964, long before the entry into force of the Convention in 1974 (8 May 1974).

Only from that date it was possible for the original eight Contracting Parties to be joined by other Council of Europe member states: Sweden, Denmark, Iceland, Norway in 1975 - and which had collaborated until then in the Nordic Pharmacopoeia Council - Cyprus in 1976, Austria in 1978, Ireland in 1979, Greece in 1984, Spain in 1987, Portugal in 1989 and Slovenia in 1993. On 8 May 1980 the Convention was also opened to European States outside the Council of Europe: Finland took advantage of this possibility in 1982.

There are now 20 countries which apply the standards of the European Pharmacopoeia within their boundaries. Thus the Pharmacopoeia has come a long way since its establishment over 25 years ago by its 8 founder members.

In reality, however, its field of application goes far beyond these European limits: many countries having historical links with Europe have recognised the utility and efficacity of the Ph. Eur. and they apply its standards through national pharmacopoeias of European member countries. Thus the Ph. Eur. is not only a guarantee of improved quality and safety through control testing in Europe, but may also be a reference for States which intend to adapt their regulatory system in order to provide optimal guarantees for the treatment of their patients.

Poland, Hungary, Bulgaria, the Czeck and Slovak Republics, Turkey, Australia and Canada have been given official Observer status at Sessions of the Commission.

It should be pointed out that the European Pharmacopoeia Commission has a productive relationship with the WHO, particularly in the area of standards and reference substances for biologicals such as vaccines and immunosera.

The elaboration of the European Pharmacopoeia is based on a Convention which is a Treaty in Public International Law, since the Governments as Contracting Parties are the subjects of

public international law and as sovereign states fully competent to conclude international treaties.

By its content, this Convention is both:

— a law-making treaty and a contract, its aim being, in accordance with Article 1, to harmonize the legislation of the Contracting Parties in Pharmacopoeial matters which undertake to take the necessary measures to ensure that the monographs which will constitute the European pharmacopoeia shall become the official standards applicable within their respective countries;
— an institutional treaty since it also determines the organs concerned with the elaboration of the Pharmacopoeia, namely the Public Health Committee and the European Pharmacopoeia Commission and it also defines that the Commission shall have a permanent Technical Secretariat.

The Public Health Committee is composed of national delegations appointed by the Contracting Parties. It exercises a general oversight over the activities of the Commission and it approves all decisions taken by the Commission, other than those of a technical or procedural character and finally it fixes the time limits within which the decision of the Commission on technical matters (in other words, the actual text of the European Pharmacopoeia) shall be implemented within the territories of the Contracting Parties.

The legal form of a decision of the Public Health Committee is that of a resolution which is immediately transmitted to the governments of the Contracting Parties for implementation, i.e. for transfer and incorporation of the standard of the Ph. Eur. into the national law within the time limit fixed. Thus a monograph of the European Pharmacopoeia supersedes any monograph on the same substance in a national pharmacopoeia.

What are the means of such a transfer? We can distinguish between several types:





— Direct transfer: use of one of the original versions of the Pharmacopoeia (The Netherlands; Nordic countries)

— Indirect transfer:

(i) integration of the original version into the national pharmacopoeia, the *European* origin being identified by means of a symbol such as a circle of stars (France),
(ii) adaptation to the style and format of the national pharmacopoeia (United Kingdom),
(iii) translation of the original version followed by publication (Portugal, Spain),
(iv) translation of the original version followed by integration into the national pharmacopoeia, the origin again being indicated by a symbol (Germany, Austria, Switzerland, Greece and Italy).

The European Pharmacopoeia Commission is a scientific and technical body consisting of delegations with a maximum of 3 delegates for each State and which are appointed by the Contracting Parties for their knowledge and competence in matters relating to the Pharmacopoeia.

In accordance with the Convention, the Commission decides all technical questions, including:
— the adoption of monographs and other texts,
— the choice of monographs to be included in the Pharmacopoeia,
— the order of priority to be given to their elaboration and
— the general methods of analysis and the quality of reagents to be used.

The Commission also recommends to the Public Health Committee the date of entry into force of the monographs or amendaments to them. (Fig. 1)

We can see from the above that the Public Health Committeee and European Pharmacopoeia Commission enjoy, in some

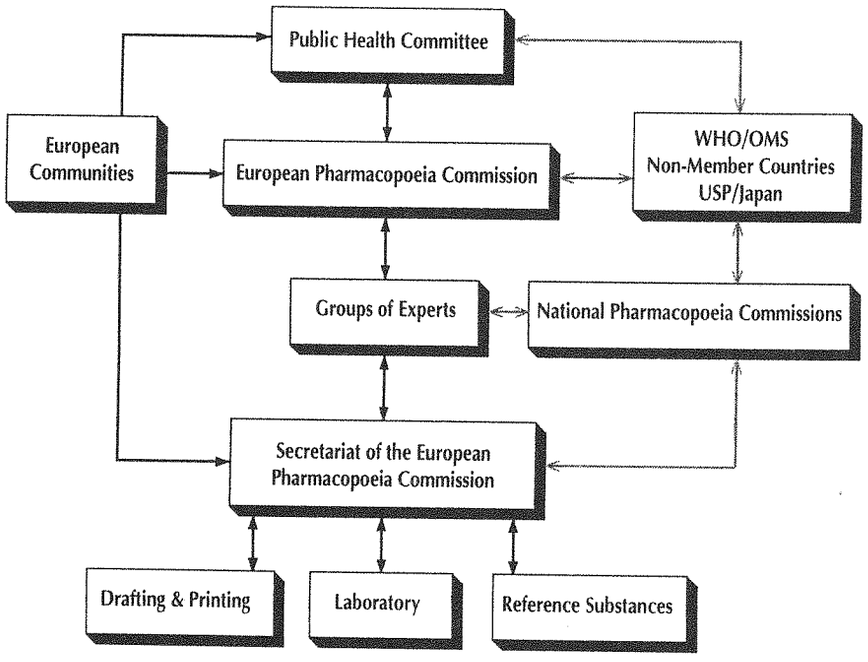


Fig. 1





respects, supranational powers since the decisions of the Commission on technical matters (in other words, the actual texts of the Ph. Eur.) are directly applicable in the member states on a date agreed upon by the Public Health Committee without having to be approved *a posteriori* by national authorities.

In the Preamble to the Convention - and here it should be noted that Preambles to international treaties contain no obligations additional to those in the texts of the agreement, but facilitate the interpretation of the treaty and, to this end, have legal significance - it is stipulated that the Contracting Parties:

— consider that the aim of the Council for Europe is the achievement of a greater unity between its members in order to promote, *inter alia*, economic and social progress including the field of public health;
— consider that such measures are now more than ever necessary in respect of the manufacturer, circulation and distribution of medicines in Europe;
— are convinced that it is desiderable and necessary to harmonize specifications for medicinal substances which, in their original state or in the form of pharmaceutical preparations, are of general interest and importance to the people of Europe;
— are convinced of the need to hasten the drawing up of specifications for the growing number of new medicinal substances appearing on the market and consider that this aim can be best achieved by the progressive establishment of a common pharmacopoeia for the European countries concerned.

These parts of the preamble define in broad terms the scope of the Pharmacopoeia and also indirectly refer to its dual function.

In the said Convention, it is also stated that the Commission shall draw up its own Rules of Procedure: they define and describe *inter alia* the role and functions of Experts and the procedures to be applied concerning:

— proposals for texts and monographs to be included in the European Pharmacopoeia;
— the routine revision of texts and monographs of the European Pharmacopoeia;
— the suppression of texts and monographs from the European Pharmacopoeia.

The detailed work of the elaboration of texts and monographs is entrusted to Groups of Experts. The Experts who serve in these groups are proposed by their national delegations in the Commission and are appointed by the latter. Each expert is appointed on a personal basis for this personal competence.

The existing plenary Groups of Experts can be divided into two classes:

— one class being responsible for the elaboration of methods and basic texts,
— the second class being responsible for the elaboration of monographs.

The Convention also defines that the Commissions shall have a permanent Secretariat, the head and the scientific staff of which are appointed by the Secretary General of the Council of Europe on the advice of the European Pharmacopoeia Commission.

The Secretariat arranges Session of the Commission and meetings of the Groups of Experts and any other meeting asked for by the Commission.

The Secretariat prepares the agendas, the reports of the meetings and edits all working documents. It is also responsible for the final editing and publication of the Ph. Eur. in English and French, the official languages of the Council of Europe as well as for *Pharmeuropa*, the Forum of the European Pharmacopoeia.

The Laboratory of the Technical Secretariat cooperates with the group in work on monographs, undertakes work necessary for establishing reference substances, carries out monitoring





of established reference substances and arranges for storage of reference substances and reference preparations and their distribution to users.

The Secretariat also establishes and maintains communication with national pharmacopoeia organizations whether from Contracting Parties of the Convention or not, with observers from member States and non-member States of the Council of Europe and with international governmental or non-governmental organizations. (Fig. 2)

The European Pharmacopoeia is now in its second edition: it consists of 18 Fascicules and includes about 900 monographs as well as the general methods of analysis etc. Studies are underway for approximately 400 further monographs.

It is important to remember the dual origin of the European Pharmacopoeia: it is elaborated by the Council of Europe, an organization concerned with improving living conditions, developing human values, human rights and democracy at the European level, but it could equally have been elaborated by the EC, an organization mainly concerned with economic problems.

The European Pharmacopoeia, undoubtedly, is of interest to the EC; the Pharmacopoeia is constantly striving to harmonize and standardize quality criteria for medical substances and, in this area, it is one of the keys to opening the Single Market of 1992; it fully intends to continue playing this role very actively.

Henceforth, the Directives of the EC on pharmaceutical activities require that substances in use comply with specifications of the European Pharmacopoeia whenever a corresponding monographs exists. In this way, the texts of the European Pharmacopoeia, once implemented, are part of EC legislation. In other words, all member States of the EC must apply the standards of the Pharmacopoeia also through the directives.

The rules for marketing authorization and control of medicines as published in the 5 volumes of EC Directives refer in several places to the Ph. Eur.

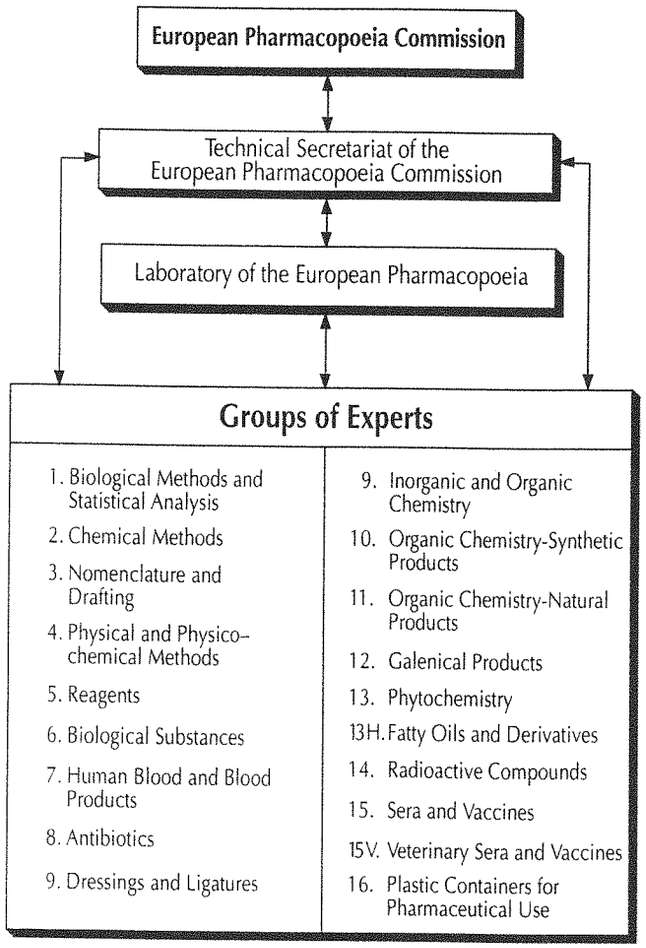


Fig. 2





As a result the EC puts an obligation onto the European Pharmacopoeia Commission.

On the other hand the EFTA countries and especially the Nordic Council of Medicines have discussed and are developing contracts of reciprocity in the field of medicines so that a development of the Ph. Eur. is *de facto* needed from the side of all the member countries having signed the Convention.

A Protocol to the Convention on the Elaboration of a European Pharmacopoeia allowing the EC to become a Party to this Convention was opened for signature.

Moreover, the European Pharmacopoeia Commission, by developing common standards for veterinary vaccines, provides valuable assistance to the Commission of the EC in its campaigns to eradicate animals' diseases, within the framework of directives on the protection of the health of animals used as food for human consumption.

On the initiative of the EC an even closer cooperation is going to be developed in the field of biological standardization for which that organization will be paying the greater part of the inherent costs. This common venture is going to ensure that:

— existing monographs of the Ph. Eur. are updated,
— tests on animals are replaced by new biological or physico-chemical methods,
— single biological reagents or standards are developed,
— a single methodology, validated both at the inter-laboratory level and with reference to the biological reagents or standards are developed.

The European Pharmacopoeia has set itself an ambitious goal, namely to become the reference Pharmacopoeia.

The expansion of the international trade, which is now worldwide has resulted in the appearance of a very wide variety of qualities of medicinal substances in the territory where the Convention applies. These various supply sources make it necessary to take additional measures to protect public health.

For the PH. Eur. to continue to play its role as a reference in the definition of the quality of medicines, it is essential to supplement its monographs with a number of mechanisms by increasing the transparency of monographs either by giving the names of specific impurities in the monographs, if possible, especially for toxic impurities or by elaborating monographs that are as exhaustive as possible taking into account all the different methods of synthesis and procedures of preparation.

The introduction of a certification scheme of conformity of the quality of substances with regards to the Pharmacopoeia monographs is also under consideration.

But the European Pharmacopoeia not only satisfies the needs of the EC and the EFTA countries, which are all parties of the Convention, since its geographical application directly and indirectly goes far beyond these boundaries.

The Convention is open to all European countries and it may be expected that the European Pharmacopoeia will become a real Pan-European Pharmacopoeia which already is and will continue to be the guarantee of European quality for medicines *Made in Europe*.

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Saggio/*Essay*

# THE ITALIAN PHARMACOPOEIA FROM 1800 TO 1892

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While in the rest of Europe national entities were already consolidated with the creation of independent states, the Italian peninsular, at the beginning of the nineteenth century, was still divided in numerous states, each with its own autonomy: the kingdom of Sardinia, the kingdom of Lombardy -Venetia (as part of the Austria- Hungarian Empire), the Dukedom of Parma, the Dukedom of Modena, the Dukedom of Lucca, the great Dukedom of Tuscany, the Pontifical state, and the kingdom of the two Sicilies.

The most important states among these had their own official Pharmacopoeia, compiled, that is, by order of the authorities and recognised by the rulers and governors, and valid throughout the territory.

It was precisely these official compilations that served as a basis for the formation of the first unitary pharmacopoeia of the Italian kingdom, which however only came to light in the thirtieth year of the Italian kingdom.

In other European countries, which had long since reached or conquered unification, the first national pharmacopoeia, which substituted regional ones, had already been formed by the beginning of the eighteenth century.

The Danish Pharmacopoeia is of 1772, the Rossica Pharmacopoeia is of 1782; in France, the *Codex medicamentorium* became national in 1818, substituting many local Pharmacopoeia.

In Switzerland, in 1855, the Swiss Pharmacists society published a Helvetic Pharmacopoeia, which was adopted in nearly all the cantons and was made obligatory in July 1894 and came in