EUROPEAN PHARMACOPOEIA

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VOLUME I

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NOTICE

The official texts of the European Pharmacopoeia are in French and English and are published in the present volume and ts French language counterpart.

No translation to other languages may be considered as official other than those appearing in the national pharmacopoeias of the signatory countries of the European Pharmacopoeia Convention or those which may from time to time be authorised by the European Pharmacopoeia Commission and published by authority of the Council of Europe.

All communications concerning the European Pharmacopoeia should be addressed to the Secretary to the European Pharmacopoeia Commission, *Council of Europe - Strasbourg - France.*

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PREFACE

« ... *hinc tanto studio summaque sollicitudine omnes Europae Medici, utiliores prestantioresque formulas medicamentorum in unicum corpus colligere semper consueverunt.* »

Preface of the " Formulae Medicamentorum " of Simoni, Naples 1773.

Political developments in Europe during the course of the last century which have brought about a certain degree of unification of several European states, together with scientific developments and the growth of new disciplines such as chemistry, have contributed to give a new perspective to pharmacopoeias. These changes are shown not only in the structure and aims of pharmacopoeias but also in their scope.

In the countries already unified, the first national pharmacopoeias began to appear at the end of the 18th and the beginning of the 19th centuries, notably in Switzerland (1775), the Netherlands (Pharmacopoeia Batavia 1805), France (1818). From the second half of the 19th century up to 1900 in many countries regional pharmacopoeias were replaced by national ones.

This development was seen particularly in Italy between 1840 and 1882. During this period local pharmacopoeias such as those of Turin, Sardinia, Siena, Parma, Austria, the Florentine codex, and the Roman pharmaceutical codex, to quote only those

which had an official character and without mentioning other non-official works, which were nevertheless widely used such as the pharmacopoeia of Ferrara, gave way to a single national pharmacopoeia, The Official Pharmacopoeia of the Kingdom of Italy.

The first British Pharmacopoeia was published in 1864. In Germany developments similar to those in Italy also took place. These developments demonstrate the influence of historical, political and social events on pharmacopoeias which, since the 13th century, have reflected the importance attached by the state to the control and safeguarding of the production of medicaments.

Another notable development during the 18th century was the appearance of works by individual authors, working in private, and representing an enormous effort of compilation in attempts to bring about unification in the matter of drugs. Of these the most noteworthy are the Pharmacopoeia Internationalis of LEMERY (1690) and the pharmacopoeias of JAMES (1745), DE QUINCY (1747), TRILLER (1764) and especially the work of JOURDAN who, in his Universal Pharmacopoeia, combined the details of about fifty different pharmacopoeias and formularies.

The rapid growth of scientific knowledge and the developments during the 20th century of new forms of political association designed to increase commercial activities and facilitate the greater mobility of goods and populations, have had a large influence on the nature of pharmacopoeias and have shown the need for new works capable of satisfying the new situation.

During this period we have seen, parallel with the development of national pharmacopoeias, a movement towards unification at supra-national level. The International Congress of Pharmacy of 1865 and those which followed had as their aim the establishment of a pharmacopoeia which would have the same legal value for all the associated countries. However, it was only in 1902, on the initiative of the Belgian government, that an international conference was held in Brussels which decided to unify the standards for potent drugs, and reached an agreement known as the "Arrangements" of Brussels. Continuing its initiative in this field the Belgian government, with a view to establishing an International Pharmacopoeia, proposed a protocol of 38 articles which became known as the International Convention of Brussels, where it was signed in 1925.

The countries which adhered to this agreement decided to proceed under Article 24 of the Pact of the League of Nations

and to create a permanent secretariat, intended to be the motivating organ, with its headquarters at the seat of the Belgian Pharmacopoeia Commission.

A precise mandate was given, as provided for in the Convention. In the first place, it was to work with experts representing the various member states on 80 important drugs which were to form the first part of a common pharmacopoeia.

The result hoped for was not realised. Other sporadic attempts were made in the years up to 1939, but these also were doomed to failure and only served to accentuate the difficulties. It is quite a different matter for a single author to prepare a compilation, such as those mentioned above, than for an official body to prepare the kind of standards envisaged by the Convention, which would have the force of law throughout signatory countries. Such an achievement is only possible if the traditional ways of thinking can be changed in the light of scientific knowledge and of the industrial needs of the different member countries during the course of calm and frank exchanges of view and with mutual goodwill to reach reasonable agreements.

In 1946, under the provisions of Article 57 of the United Nations Charter, the World Health Organisation decided to prepare what was to become The International Pharmacopoeia. However, contrary to the provisions of the Brussels Convention, the World Health Organisation created its own system, composed of experts chosen on a personal basis. These experts did not represent their national authority and consequently could only establish recommended standards without any obligatory legal force.

The International Pharmacopoeia was first published at Geneva in 1952, in English and French, and was approved by the Third World Health Assembly. Although this is an important document in the field of drug control, it consists only of recommendations to the member countries and contains no obligatory standards. It is, nevertheless, a work of great value and takes its place among the political achievements of the World Health Organisation in the field of public health, and is of importance particularly in the developing countries, where it forms a useful basis for the control of drugs and for the establishment of a national pharmacopoeia.

In the same year the Brussels Convention was abandoned, since it was considered that with the realisation of the International Pharmacopoeia further work was unnecessary, the major part, if not the final objectives, having been achieved.

However, on the initiative of the French delegation (the Vaille proposal, July 1951) the idea of a European pharmacopeia was advanced, which this time would be developed on a realistic European basis. The idea was put forward within the framework of the Brussels Treaty Organisation, which was founded on the 17th March 1948 by the five countries of Western Europe (Belgium, France, Luxembourg, the Netherlands and the United Kingdom) to promote collaboration between these countries in the economic, social and cultural fields. So far as drugs are concerned the Brussels Treaty Organisation had not only to bring about the harmonisation of the legislation concerning the production and sale of pharmaceutical specialities, but also the standardisation of a certain number of drugs essential for the protection of the population in time of war.

The French memorandum was re-examined in 1952 at a meeting in Luxembourg. It proposed the creation of a Commission to establish a pharmacopoeia common to the member countries, and set out in general terms the structure of the organisation which would be needed to achieve this object. It proposed to give priority to the study of " potent " drugs and those required for civil defence. The Sub-Committee on Pharmaceutical Questions supported the French initiative and underlined the need for the active co-operation of national pharmacopoeia commissions in achieving a genuine unification. The Public Health Committee (April 1953) was not able to accept this proposal but asked that a study be undertaken of the specifications for essential substances for civil defence without necessarily requiring the member countries to undertake to adopt the standards set up.

Following the establishment of the Western European Union in 1954, Italy and the Federal Republic of Germany joined the other five countries and took part in the work of the various committees, including those dealing with drugs. In August of the same year and in accordance with the decision of the Public Health Committee, the Working Party on Essential Drugs was created, on which served the representatives of the national pharmacopoeia commissions of the various member states. The task of this group was to define the characters of 135 drugs required as " first-aid " in civil defence. The specifications were drawn up in such a manner as to cover all the specifications of the member countries, and without requiring that the analytical methods were shown.

In 1960 certain activities were transferred from the Western European Union to the Council of Europe (Partial Agreement), which consisted of the seven countries, Belgium, France, Federal

Republic of Germany, Italy, Luxembourg, The Netherlands and the United Kingdom. The Working Party on essential drugs continued its work throughout these changes and completed its task in 1963.

Before it was dissolved the Working Party drew attention to the importance of authorising a study of the possibility of creating a permanent body composed of the national pharmacopoeia commissions to start work on the unification of pharmacopoeias. It also recommended to the Sub-Committee on Pharmaceutical Questions that the governments should take the necessary steps to include the minimum standards for the essential drugs in their national pharmacopoeias.

This brought to an end after 10 years the plan originally proposed by the French representatives. The rules which were established had no obligatory force, but the meetings of the experts from the various national pharmacopoeia authorities had enabled them to establish good relations and to agree on common aims for future work.

As the study of " essential drugs " was nearing its completion, the French delegation raised again at Strasbourg the idea of preparing a European Pharmacopoeia.

The delegates of the member states of the European Economic Community had met in January 1963 in Brussels to study, within the framework of directives for the control of drugs, the creation of a European Pharmacopoeia. The proposals provided for the creation of a pharmacopoeia common to the six member states, its structure and its limitations, a programme for its achievement, the conditions under which it could be realised, and a financial budget for carrying out the work. The results of this discussion appeared in 1964 in Article 13 of the Draft Directive:

> " From the announcement of the present Directive the Commission, in collaboration with the competent authorities of the member states, undertakes to establish common rules and the preparation of protocols for the testing of drugs as provided for in Article 4, line 2.8 of the Directive of (date) ".

This Article was clarified by certain explanatory notes attached to the Directive:

> " The need for establishing general standards for the quality of drugs (standards of purity, stability, etc.) has been underlined in different instances. Thus, parallel with work undertaken by certain international organisations such for example as the World Health Organisation or the Council of Europe, the Commission has undertaken work with a view to establishing a European Pharmacopoeia. It seems opportune,

on the other hand, that the Commission should take the initiative, in collaboration with the competent authorities of the member states and with the help of scientific bodies in the community, to seek standardised methods for carrying out the various tests on drugs (physico-chemical, biological, microbiological, pharmacological, toxicological and clinical tests) and for their evaluation. Consequently two closely connected programmes of work are involved, the results of which should have a favourable influence not only in health matters but also in the economic field. In the public health field, both the work on the pharmacopoeia and that on the protocols for drug testing have undoubted importance, on the one hand because of the advantages and guarantees which standardisation brings to the scientific bodies, and on the other hand, from the fact that it will enable drug manufacturers in the community to profit from the most advanced scientific knowledge.

In the economic field, the establishment of a pharmacopoeia would bring advantages in the rationalisation of production: through its protocols it would enable those responsible for the testing of drugs to know the standards they must respect and the methods and interpretation of results.

The work would increase the efficiency of the control of drugs by the appropriate authorities and would avoid, to a very large extent, divergent results in tests made in connection with requests for the marketing of pharmaceutical specialities.

The setting up of the standards and the protocols envisaged in this document will require complicated and long-term work. Moreover, it will have to be kept up to date. In now setting a period for the first part of this work it is important to underline that it is progressive in character, and it is important to the interests of public health as well as of production, to put the results of the study into operation as soon as they are available."

The delegates of the member countries had thus recognised that in order to permit the free circulation of drugs in a common market it was necessary to create a common European Pharmacopoeia. In fact according to the time limits fixed by the European Economic Community it was necessary to achieve free exchange of drugs and unification of legislation concerning them in 1968. For this reason it was decided to set up a commission to carry out the unification of the pharmacopoeias of the six countries.

However, before any executive decision was taken by the European Economic Community, and as a result of an intervention by the Secretary General of the Council of Europe, the Sub-Committee on Pharmaceutical Questions, meeting in Rome in February 1963, recognised the need to recommend to the Public Health Committee (Partial Agreement) of the Council of Europe the establishment of a European Pharmacopoeia and it laid down the main guiding lines in a memorandum. These guiding lines may be summarised as the need for the progressive establishment of a

European Pharmacopoeia, starting with the general methods, the preparation of monographs, the adoption of common names, the continuous revision of the monographs, the adoption of reference substances, and the progressive publication of the texts.

For this purpose the Sub-Committee advised that a Commission be set up, consisting of representatives of national pharmacopoeia commissions, which would have a permanent Technical Secretariat. The Commission was given the responsibility for " establishing the said monographs, which, afterwards, would be adopted as the official monographs for each of the participating bodies ". It would have groups of experts to help with the work and would be provided with a laboratory for checking that the analytical methods worked smoothly and that the editing of the texts was satisfactory from the technical point of view.

The sixth meeting of the Sub-Committee on Pharmaceutical Questions, held in Paris 25th-27th June 1963, proceeded to deal with the remaining details. In particular the meeting laid down the responsibilities of the Commission and its relations with other organs of the Council of Europe, on which it directly depends, and in particular the Public Health Committee. A plan for the technical organisation of the Commission was drawn up, as well as a plan for the technical secretariat and the laboratory. The seat of the Commission was fixed at Strasbourg at the Council of Europe. The administrative arrangements, the choice of methods and of monographs, and finally, the time-table to be observed were also agreed. Further a draft convention was approved which was later to be signed by the seven participating countries of the Partial Agreement. The Consultative Assembly of the Council of Europe took note of these developments on 8th August 1963. The documents were finally approved at the meeting of the Sub-Committee on Pharmaceutical Questions on the 15th-17th October 1963, with the legal and administrative help of the Administrative, Economic and Social, and Legal Directorates of the Council of Europe. The proposals were adopted by the Public Health Committee, on the proposition of the Italian delegation, on the 17th November 1963, and became the European Pharmacopoeia Convention.

On the 17th March 1964 the Council of Ministers of the countries of the Partial Agreement adopted a resolution setting up a European Pharmacopoeia and asked the governments concerned to sign the Convention.

Since by the terms of the agreement it was possible to start work before the Convention came into force, the Commission was constituted immediately, consisting of delegates of the seven countries, and it met for the first time at Strasbourg on the 28th April 1964. This purely formal meeting was for the purpose of accepting the adherence of Switzerland as the eighth adherent of the Partial Agreement and consequently of its participation in the work of the European Pharmacopoeia, in which it began its participation on the 1st and 2nd July 1964.

In June 1964 in an exchange of information between M. REY of the European Economic Community and M. MODINOS, Deputy Secretary General, Council of Europe, the latter outlined the stage reached in the preparation of the European Pharmacopoeia by the Council of Europe, which body, since 1960, had taken the initiative in the field of social activities among the six countries of the Community together with the United Kingdom in the framework of the Partial Agreement. M. MODINOS outlined the arrangements whereby the work of the Commission could begin without waiting for the coming into force of the Convention, all the legal measures adopted for its realisation and the financial implications of the expenses of the Commission. The Council of Europe also stated that in conformity with the provisions made in 1964, the Commission was now ready to start its work. It was precisely for this reason that the European Economic Community did not itself embark on the preparation of the pharmacopoeia envisaged by the Treaty of Rome and referred to in Article 13 of Directive No. 2 concerning medicaments. On the basis of this understanding the Council of Europe agreed to keep the European Economic Community informed of the progress of work on the pharmacopoeia.

Thus the European Pharmacopoeia can be prepared by the Council of Europe without overlapping or duplication of effort with other bodies and will profit from their common interest and full, active co-operation.

At the meeting of the European Pharmacopoeia Commission on the 1st and 2nd July 1964, the first Chairman was elected, who, by the terms of the Convention, was to remain in office for three years. He not only presides at meetings but is also responsible for ensuring the continuity of the work of the Commission, and it is to him that members look for advice, provisional decisions, directions, and authority in the interval between meetings. During his period of office the Chairman is not a member of his national delegation.