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The International Pharmacopoeia

Even though the wish to establish an international pharmacopoeia dates back to the seventeenth century, it was only in 1902 that a first attempt was made by several countries to set up an international pharmacopoeia under the Brussels Protocol. In that year an Agreement for the Unification of Formulae of Potent Durgs was prepared, and this was ratified by 19 countries in 1906.

The Brussels Agreement was drawn up in 1925 and ratified in 1929, with a provision that the League of Nations should assume part of the task of preparing an international pharmacopoeia.

In 1937 the Health Organization of the League of Nations set up a Technical Commission of Pharmacopoeial Experts, which in 1948 was succeeded by the WHO Expert Committee on the International Pharmacopoeia, and in 1951 by the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

The first edition of the International Pharmacopoeia was published in three volumes: 1951, 1955 and 1959. A second edition was published in 1967.

Specifications for 162 newer drugs were introduced in the second edition, while 114 monographs of the first edition were omitted, to give a total of 555 monographs with 69 appendices. The text was prepared in co-operation with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a large number of other specialists from different countries. The analytical procedures given in the monographs and appendices have been tested in the laboratories of national pharmacopoeiae, in national laboratories for pharmaceutical quality control, in the laboratories of a number of manufacturing firms, and in pharmaceutical and other institutions.

Modern analytical methods used in pharmaceutical quality control are described in the appendices; for example, infra-red spectrophotometry, polarography, chromatography (column, paper and thin-layer), radioactivity, non-aqueous titration, and determination of melting-range and melting-point and identification of substances by the Kofler method.

Although some of the methods such as polarography have not been applied to the requirements of any particular mongraph, it was thought that the International Pharmacopoeia should be representative of the best current practice in drug quality control and that they were a desirable addition.

A provisional text of the second edition was sent on 9 March 1964 to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a number of other specialists interested in this work, with a covering letter asking for comments, which were later examined for possible integration in the provisional text.

In October 1964 the revised provisional text was forwarded to Member and Associate Member States, inviting them to submit comments within three months.

These and further comments were integrated in the text of the second edition in order to adapt it to latest requirements.

The present way of establishing the specifications of the International Pharmacopoeia can be criticized from viewpoints which also apply to many national pharmacopoeias:

(1) The time between new editions is too long in relation to the speed with which new drugs are introduced onto the market and the relatively short lifetime of most modern drugs;

(2) there is a tendency to conservatism in the sense that technically simple but not very selective methods are sometimes described.

Discussions are now taking place at WHO as to how the International Pharmacopoeia can best serve its purpose in the future. In 1967 the World Health Assembly requested the Director-General to "continue work on analytical control specifications for international acceptance to be published as they are completed". This phrasing expresses the urgency which the World Health Assembly attaches to the wide and rapid distribution of specifications for drug control.

The Expert Committee on Specifications for Pharmaceutical Preparations has discussed two ways to achieve this goal:

(a) To devise a scheme by which WHO, in co-operation with the producers of drugs, could issue analytical data on drugs very soon after they are introduced onto the market.

Such specifications, even if not complete, but made available early, might contribute to the achievement of more uniform specifications throughout the world. Comments from interested parties would be invited and form the basis for revision of the specifications for eventual inclusion in the International Pharmacopoeia.

In order to be successful, such a scheme would, of course, require free co-operation between WHO, producers, pharmacopoeia commissions and national control authorities.

The Expert Committee on Specifications for Pharmaceutical Preparations suggested proposals for such a scheme[1], but it must be realized that it must be a long-term project to put such a scheme into effect.

(b) To continuously amend and revise the International Pharmacopoeia and to issue Addenda reflecting the latest developments in quality control. The twenty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations, which met in Geneva in November 1969, recommended that this procedure should be followed at present, but at the same time attempts should be made to pursue the approach mentioned under (a). Even if it must be considered as a long-term project the Committee stressed its potential importance for the future work of WHO on specifications for newer drugs.

Specifications for Reagents

During the work on the first edition of the International Pharmacopoeia it was felt that more detailed specifications for reagents used in conjunction with the assays and tests included therein should be drawn up.

Work on specifications for reagents, based on existing specifications and on collaborative work of experts was later co-ordinated with the preparation of the second edition of the International Pharmacopoeia.

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[1] Wld Hlth Org. techn. Rep. Ser., 1969, No. 418

In 1958 draft specifications for reagents became available and were widely distributed for comments, which were taken into consideration in the preparation of the final text by the Secretariat assisted by specialists in the matter. The "Specifications for Reagents mentioned in the International Pharmacopoeia" were published in English (1963) and in French (1966).

The specifications included in this volume also apply to the reagents required for the tests and assays of drugs described in the second edition of the International Pharmacopoeia and are quoted in the list of reagents and test solutions in that volume.

Chemical Reference Substances

In 1952 the WHO Expert Committee on Specifications for Pharmaceutical Preparations noted a recommendation from the Expert Committee on Biological Standardization that a collection of authentic chemicals be established including a number of biological standards and chemicals required for some of the assays described in the International Pharmacopoeia or for biological research. One reason for this recommendation was that it had been decided not to replace the biological standard for Vitamin A but that a standard was still needed as reference for spectrophotometric determinations. Later the same year the proposal was discussed and it was agreed that there was a need for such a collection, which should include:

"(a) substances for which international biological standards have been provided in the past but which can now be characterized entirely by chemical methods and for which no biological standards will be provided in the future;

(b) chemicals required as working standards for the assays and tests described in the International Pharmacopoeia;

(c) other chemicals required as reference standards for reseach purposes."

During the next few years the subject was further discussed and in 1956 a centre was created at the Apotekens Kontrollaboratorium in accordance with an agreement between the Apotekarsocieteten, Stockholm, and the World Health Organization for the collection, storage and distribution of chemical reference preparations. The collection included, apart from Vitamin A, some discontinued biological standards such as estrone and progesterone and some new substances - for example digitoxin and ergometrine maleate.

At the meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1958 two suggestions were made to study the inclusion of substances:

(1) for checking melting points;
(2) for checking the absorption reading of spectrophotometres operating in the ultra-violet and visible part of the spectrum.

At a meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1964[1] the following guiding principles for the establishment of chemical reference substances were recommended.

For the second edition of the International Pharmacopoeia it was agreed that reference substances should be provided in the following cases:

(a) when infra-red identification is required;
(b) when chromatographic tests and assays are given in the monographs;
(c) when spectrophotometric or photometric methods are necessary for the determination of the substance.

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1 Wld Hlth Org. techn. Rep. Ser., 1965, No.307

If the substance itself can be analysed by a "classical" method but, for example, tablets or injections are analysed by spectrophotometric methods, it was considered permissible to use a substance which compiled with the monograph as reference substance.

As for the evaluation of substances for their suitability as reference material, it was urged that an estimate be given of the content of total impurities. Such a figure was considered valuable even if not of high accuracy.

For the tests and assays of the second edition of the International Pharmacopoeia about 40 International Chemical Reference Substances are available[1] - mostly steroids, cardiac glucosides and semisynthetic penicillins.

The appended table lists the reference substances of the second edition and also indicates for what purpose they are needed. The substances are available from the WHO Centre for Chemical Reference Substances, Apotekens Centrallaboratorium, Box 333, 171 03 Solna, Sweden.

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1 World Health Organization (1967) Specifications for the quality control of pharmaceutical preparations - second edition of the International Pharmacopoeia, Geneva - Appendix 22

APPENDIX

TABLE RELATING TO USE OF CHEMICAL REFERENCE SUBSTANCES IN THE SECOND EDITION OF THE INTERNATIONAL PHARMACOPOEIA

CHEMICAL REFERENCE SUBSTANCE	USE
(a) Steroids	
Cortisone acetate	IR identification; colorimetric assay (blue tetrazolium)
Desoxycortone acetate	IR identification; colorimetric assay (blue tetrazolium)
Dexamethasone	IR identification; colorimetric assay (blue tetrazolium)
Dexamethasone acetate	IR identification; colorimetric assay (blue tetrazolium)
Estradiol benzoate	IR identification; colorimetric assay (Kober reaction)
Ethinylestradiol	IR identification; spectrophotometric assay (280 nm)
Ethisterone	IR identification; spectrophotometric assay (240 nm)
Hydrocortisone	IR identification; colorimetric assay (blue tetrazolium)
Hydrocortisone acetate	IR identification; colorimetric assay (blue tetrazolium)
Methyltestosterone	IR identification; spectrophotometric assay (240 nm); colorimetric assay (dinitrophenyl hydrazone)
Prednisolone	IR identification; colorimetric assay (blue tetrazolium)
Prednisolone acetate	IR identification; colorimetric assay (blue tetrazolium)
Prednisone	IR identification; colorimetric assay (blue tetrazolium)

CHEMICAL REFERENCE SUBSTANCE	USE
(a) Steroids (cont'd)	
Prednisone acetate	IR identification; colorimetric assay (blue tetrazolium)
Progesterone	IR identification; spectrophotometric assay (240 nm)
Testosterone propionate	IR identification; spectrophotometric assay (240 nm)
(b) Cardiac glucosides	
Digitoxin	IR identification; colorimetric assay (Baljet)
Digoxin	IR identification; colorimetric assay (Baljet)
Lanatoside C	IR identification; colorimetric assay (Baljet)
Ouabain	IR identification; colorimetric assay (Baljet)
(c) Semisynthetic penicillins	
Ampicillin	IR identification; bio-assay
Ampicillin sodium	IR identification
Cloxacillin sodium	IR identification; bio-assay
Meticillin sodium	IR identification; spectrophotometric assay (280nm)
Nafcillin sodium	IR identification; spectrophotometric assay (280nm); bio-assay
Oxacillin sodium	IR identification; spectrophotometric assay (235 nm); bio-assay
Phenethicillin potassium	IR identification; spectrophotometric assay (268 nm)
Propicillin potassium	IR identification; iodimetric titration using the reference substance to determine the equivalent; spectrophotometric assay (268 nm)

GENERAL REFERENCE SUBSTANCE

(d) Others

Ergometrine maleate	Test for secondary alkaloids (paper chromatography); test for secondary alkaloids (Thin-layer chromatography); colorimetric assay (Van Urk)
Ergotamine tartrate	Test for secondary alkaloids including semi-quantitative determination of ergotaminine (paper chromatography); colorimetric assay (Van Urk)
Folic acid	Colorimetric assay
Riboflavine	Spectrophotometric assay (267 nm); fluorimetric assay
Tubocurarine chloride	Bio-assay
Warfarin	Spectrophotometric assay (308 nm).