

SEVENTEENTH REPORT

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## INTRODUCTION

The Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 9-14 November 1959.

### Participants

#### Members

Professor A. Calo, Inspector-General (Chemistry), Istituto Superiore di Sanità, Rome; Member of the Italian Pharmacopoeia Commission

Dr T. Canbäck, Director of Chemical Research, Pharmaceutical Control Laboratory, Stockholm; Vice-Chairman of the Swedish Pharmacopoeia Commission; Member of the Scandinavian Pharmacopoeia Council (Chairman)

Mr T. C. Denston, Secretary, British Pharmacopoeia Commission, London (Rapporteur)

\* Professor J. A. Gautier, Professor of Organic Chemistry, Faculty of Pharmacy, University of Paris; Member of the French Pharmacopoeia Commission

Dr T. Itai, Chief of the Division of Non-Official Drugs, National Institute of Hygiene, Tokyo; Member of the Japanese Pharmacopoeia Commission

Mr F. A. Maurina, Director, Analytical Laboratories, Messrs Parke, Davis & Co., Detroit; Member of the Committee of Revision of the Pharmacopoeia of the United States of America

Dr L. C. Miller, Director of Revision of the Pharmacopoeia of the United States of America, New York (Rapporteur)

Dr J. L. Powers, Chairman of the Committee on National Formulary, American Pharmaceutical Association, Washington, D.C.; Member of the Committee of Revision of the Pharmacopoeia of the United States of America (Vice-Chairman)

Professor P. Senov, Professor of Pharmaceutical Chemistry, Pharmaceutical Faculty, First Medical Institute, Moscow; Chairman of the Soviet Union Pharmacopoeia Commission

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\* Unable to attend

Secretariat

Mr P. Blanc (Secretary), Chief Pharmaceutical Officer, Pharmaceuticals, WHO

Mr G. R. Brown, Department of Pharmaceutical Sciences, Pharmaceutical Society of Great Britain, London (Consultant)

Professor R. Hazard, Honorary Professor of Pharmacology and Materia Medica, Faculty of Medicine of Paris University; Member of the French Pharmacopoeia Commission (Consultant)

Mr O. Wallén, Pharmaceutical Officer, Pharmaceuticals, WHO

The members of the Expert Committee were welcomed by the Deputy Director-General who referred to the large amount of useful work which had been accomplished by collaboration between members of the Expert Advisory Panel and other specialists, in preparing recommended specifications which may be used for controlling the quality of pharmaceutical preparations in any of the 87 Member States and 3 Associate Member States of WHO. Following the publication of the Supplement to the First Edition of the International Pharmacopoeia, containing recommended specifications for 94 pharmaceutical substances and preparations, the main work of this session would be the revision of some of the specifications and other matter contained in volumes I, II and the supplement, with a view to establishing draft texts for the Second Edition.

The former title of the Expert Committee has been amended, following suggestions received at previous sessions, to indicate more clearly that the scope of the work now extends to providing draft specifications in forms other than the printed text of the International Pharmacopoeia but such as may be used in many countries for the quality control of the numerous new drugs produced locally or imported.

Specifications for reagents suitable for use in carrying out the tests and assays of the First Edition of the International Pharmacopoeia have now been prepared, and it is hoped that following discussion of these specifications at the session they can be completed and published. The WHO collection of authentic chemical substances is serving a useful purpose, and expansion of the collection to include substances needed in connexion with melting-point determinations and spectrophotometric procedures

is to be considered. The possibility of obtaining information on new pharmaceutical preparations, so that draft specifications can be sent out at an early date, preferably annually, to national authorities throughout the world, is another subject to be studied.

## 1. Revision of the International Pharmacopoeia Specifications

The Expert Committee reviewed the progress that had been made in the revision of the First Edition and prepared suggested texts for some of the monographs, appendices and general notices.

### General Notices

The text of the General Notices was examined in detail in the light of recommendations made at previous sessions and reports by members and a draft text was prepared which is annexed to this report.<sup>1</sup> The section on nomenclature was revised to indicate that international non-proprietary names are used generally, and it was agreed that some of the notices concerning galenicals should be transferred to General Monographs describing various pharmaceutical forms. It was noted that the statement concerning the standard dropper applies to droppers used for measuring medicines and is not intended to be used for analytical purposes. It was agreed that the section on errors in biological assays should be revised and might more properly appear in the form of an appendix. It was further agreed that in revising the preface, statements should be included of the rules followed in adopting systematic names for animals and micro-organisms, as well as those for plants and chemical substances mentioned in the First Edition.

Storage and containers. The Committee discussed the revision of the paragraph "Storage" in the General Notices of the First Edition of the International Pharmacopoeia, and agreed that information should be given separately on containers and on storage conditions.

In the First Edition no definitions are given for storage temperatures although certain monographs cite such conditions as "a cool place". It was recommended

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<sup>1</sup> Annex No. 1

that such information be given in the Second Edition but that descriptive terms be defined for use in the temperature ranges between 0°-15°C (for example "refrigerator", "cool place").

Because of the great variation in ordinary room temperature in different parts of the world, the use of this term should be avoided as far as possible.

The necessary restrictions for protection against excessive temperatures should be provided by specific mention in the monographs concerned. This should take the form of a statement of the maximum temperature to which the article may be exposed during shipment and storage.

A brief review of provisions in national pharmacopoeias concerning containers indicates that these either provide information on the materials of the containers or the functions that containers perform. Because of variations in the nature of available materials it would seem best for the International Pharmacopoeia to confine its provisions to statements on function. Thus, the first paragraph of the present section on Storage should be retained but under the heading "Containers". Consideration should be given, however, to the special case of containers for injectable solutions inasmuch as the question of the closure gives rise to special difficulties. It would appear that the most that can be done in the General Notices is to emphasize the fact that the closure is a part of the container.

Status of the specifications in the International Pharmacopoeia. It was recommended that this important statement should be separated from the other General Notices, preferably on a separate page, which might, however, contain also the notice on Patents and Trademarks. The following wording was suggested:

"NOTICE

The proposed specifications contained in this volume are intended to serve as recommendations for use in establishing specifications on a national basis. They are not intended to have legal status in any country unless adopted by a competent authority in that country."

In addition, the position should be explained in the preface.

Identification tests. The identification tests proposed by a working group at the previous session were accepted with minor modifications.

Determination of a melting-range and melting-temperature. A report<sup>1</sup> was examined and the proposed text for the future work was prepared. It was agreed to specify that melting-range is the range between the corrected temperature at which the substance begins to collapse or form droplets on the wall of the capillary tube and the corrected temperature at which it is completely melted as shown by the disappearance of the solid phase. The term "melting-temperature" was retained for use as a means of identification and it was suggested that it should be the temperature at which the substance is completely melted when determined in the same way as for "melting-range". It was agreed to recommend the use of liquid silicones in the heating vessel. The method of determining the melting-temperature of fats and waxes was also revised. Members agreed to report on the Kofler hot-bar method and the use of eutectic mixtures as an aid to identification. A revised method of determining boiling-point was accepted and consideration of the method for boiling-range was deferred for information as to whether the International Organization for Standardization has carried out work towards standardization of the apparatus. The limit test for sulfates was amended to include the use of a suspension of barium sulfate as a seeding reagent to induce prompt precipitation, thus making the test more sensitive and more reproducible than the one included in the First Edition. The proposed method of determining sulfated ash<sup>2</sup> was modified by specifying the addition of ammonium carbonate before the final ignition.

Monographs. The Expert Committee noted that a working group has reviewed the monographs on drugs and preparations in the groups of barbiturates, sulfonamides, antihistaminics, adrenaline and related compounds, with a view to correlating the specifications. The Expert Committee examined the revised texts and expressed its appreciation of the work done by the working group. A list of the revised monographs is annexed to the report.<sup>3</sup>

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<sup>1</sup> See item 10, unpublished working documents No. 8.

<sup>2</sup> See item 10, unpublished working documents No. 7.

<sup>3</sup> Annex 6

List of contents. Further suggestions were received and the Expert Committee proposed a number of further additions to and deletions from the list of substances for which the preparation of monographs will be undertaken for possible inclusion in the Second Edition, including some vegetable drugs and some synthetic medicinal substances.

Statements of dose. The Expert Committee confirmed the proposal made at the previous session that for the convenience of users of the Second Edition doses should be stated at the end of each monograph and also summarized in a table included in the appendix. Both the table of doses for adults and the table of doses for children should include a column with observations, as in the table of doses for children which appears in the Supplement. The tables including the revised doses for the drugs taken over from the First Edition and the doses proposed for the new drugs would be submitted to specialists and afterwards for comments to the World Medical Association. Consideration was given to the method of expressing doses - having in mind the risk of errors in reading them. It was agreed that the present system of expressing doses in either grams or micrograms should be retained in the International Pharmacopoeia.

Metric terminology. The Expert Committee noted that in drafting the First Edition the abbreviations for weights and measures were adopted on the advice of the International Office of Weights and Measures, and that this had encouraged the use of these symbols and abbreviations in some national pharmacopoeias and other works of reference, thus aiding unification to this extent.

Attention was drawn to the confusion and dangers arising from the diversity of the metric unit abbreviations still existing not only in national pharmacopoeias, but in regulations and laws relating to public health. The Committee recognized that the problem of attaining uniformity in metric terminology in public health matters extends beyond the scope of specifications for the quality control of pharmaceutical preparations. Because of this, the Committee warranted attention on as broad a scale as can be arranged within WHO.

The Committee therefore suggested that the Secretariat should study what steps could be taken to achieve uniformity in the abbreviations and symbols used for metric units in the specifications and regulations dealing with public health.

**Pharmacological Classification.** The Expert Committee recalled that at the previous session the view was expressed that it would be of value to include at the end of the monograph an indication of the pharmacological class to which the preparations of the International Pharmacopoeia belong. Documents<sup>1</sup> were examined in which the monographs of the First Edition were classified pharmacologically, and it was agreed that these would be revised and used as a basis for future work.

**Pharmaceutical Radioactive Isotopes.** The Committee was assured that the basic information for draft monographs was available as national pharmacopoeia monographs for therapeutic forms of radioactive isotopes of gold, sodium chromate, sodium iodide and sodium phosphate. Similar monographs were available for radioactive cyanocobalamin and radioactive human serum albumin.

The Expert Committee noted a resolution on radioisotopes of the International Organization for Standardization<sup>2</sup> and it was agreed that the specifications should be sent to them for possible comments.

**Checking of monographs.** The Committee felt that there was a need for a final check on certain monographs, particularly the newer ones, and recommended that a survey be made of those specifications which need to be verified by laboratory testing. It was agreed that complete examination of all proposed specifications under the collaborative scheme of testing between laboratories would be too great a task to be arranged in a reasonable time. However, careful selecting of the topics to be studied should make it possible to obtain much of the needed information.

## 2. Specifications for Reagents

The Expert Committee noted that considerable progress had been made by a working group in preparing specifications for reagents required to carry out the tests described in volumes I and II and the supplement to the First Edition of the International Pharmacopoeia. Specifications had been prepared describing materials suitable for general laboratory use with particular reference to the tests for which they are used in the International Pharmacopoeia. Comments on the specifications had been received as the result of circulating draft copies. The working group

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<sup>1</sup> See item 10, unpublished working documents No. 14.

<sup>2</sup> Annex No. 3

had reviewed the comments and had agreed on the general lines of revision. Many of the tests would be carried out by the general methods of the International Pharmacopoeia. A simplified method of determining boiling-range would be recommended. Instrumental methods such as flame photometry were approved as an alternative to conventional methods for the determination of traces of potassium and sodium ions; details of the method would be described in an appendix. It was agreed not to introduce polarographic methods for the determination of traces of lead, nickel, zinc and copper, since many laboratories do not have the necessary apparatus and experience with the method.

The Expert Committee thanked the members of the working group and in particular Mr W. C. Johnson and Dr J. L. Powers, for carrying out the work, and agreed that the specifications should be completed and issued as a volume. Provided that a notice is inserted in an early issue of the WHO Chronicle inviting those interested to apply for copies of the revised drafts, it would seem unnecessary to submit them to all Member countries of WHO for further checking before publication. Arrangements were approved, however, for their review after revision. Comments thus received from national authorities and manufacturers would be considered before final revision. An index has been prepared indicating the monographs of the International Pharmacopoeia for which these reagents are required, and it was agreed that this should be brought up to date and copies offered to any users of the specifications who might require it. Revised drafts were examined and three specimen drafts are annexed to this report.<sup>1</sup>

### 3. Classification of pharmaceutical preparations

The Committee noted that reports had been received from members of the Expert Advisory Panel and other specialists, suggesting some principles to be applied in classifying certain potent substances used both in therapeutics or for technical purposes so that in the interest of public health, appropriate safeguards could be applied to their sale and distribution. It was recognized that the problem is

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<sup>1</sup> Annex No. 4

complex because in some countries there is a scarcity of medical and pharmaceutical practitioners and the methods of distributing pharmaceutical preparations vary widely in different countries. However, it was agreed that general principles might be laid down, and it was recommended that the further study of the problem should be made, as requested in a resolution of the International Pharmaceutical Federation.<sup>1</sup>

#### 4. Future Action on the Preparation of Specifications for Pharmaceutical Preparations

Consideration was given to ways of preparing and issuing specifications which would be of value to the national authorities requiring them for quality control of pharmaceutical preparations, as a protection of public health. It was agreed that the dissemination of data at an early stage in the distribution of a drug could be of considerable value. The nature of the data which might be required had been discussed at previous sessions of the Expert Committee, but there remained the problem of how WHO could obtain such information rapidly.

Members reported that draft monographs might be obtained from pharmacopoeia commissions in those countries where the drugs were first developed and introduced on the market. The drafts might then be distributed to members of the panel, for comment, and the preparation of provisional specifications. For WHO to issue annually such provisional specifications as were ready would be of great value to authorities requiring such specifications at the national level. Copies should be made available quickly to governments and their pharmacopoeia commissions, members of the Expert Advisory Panel, and national laboratories dealing with quality control, and additionally, a notice might be inserted in the WHO Chronicle offering to supply copies to other interested parties. The provisional specifications might be issued as loose sheets or mimeographed documents.

Comments would be invited from users of these provisional specifications, which would be considered in preparing the monographs for publication in future editions of the International Pharmacopœia.

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<sup>1</sup> See item 10, unpublished working documents, No. 11.

Thus by directing efforts towards the issue of various kinds of information (1) preliminary data, (2) provisional specifications, and (3) specifications of the International Pharmacopoeia, maximum assistance would be provided in the establishment of specifications on a national basis.

#### 5. Authentic Chemical Substances

A report was received from the WHO Centre for Authentic Chemical Substances, Stockholm, and members expressed their appreciation of the work accomplished by the Centre. Requests for reference specimens continue to be dealt with by this Centre, and arrangements were being made to replace the supply of tubocurarine chloride, as stocks of it were nearing exhaustion. There is a steady increase in the number of requests received. The digitoxoside which is held for distribution has a purity of about 97 per cent., and it was reported that a preparation of higher purity could now be obtained. It was agreed, however, to continue using the present material which is already more highly purified than much of the commercial material used in medicine, and to reconsider replacement later.

The Centre had proposed providing a series of substances for use in standardizing melting-point determinations and it was agreed that the Centre should be asked to obtain suitable specimens, submit them to collaborative testing, and hold them for distribution as Authentic Chemical Substances. Members agreed to suggest laboratories which would collaborate in testing these standards.

The Expert Committee recommended that work should be continued on the development of a series of authentic chemical substances for use as reference materials in infra-red and ultra-violet spectrophotometric assay methods and identification tests. Members drew up a tentative list<sup>1</sup> of substances which should be included in the collection as soon as possible. It was recommended that the names of these substances should be forwarded to the WHO Centre, as well as any others for which requests were received, so that the specimens might be obtained, examined in collaboration with other laboratories, and held for distribution. It was further suggested that WHO could approach the United States Pharmacopoeia or other authorities to ascertain if some of the substances can be obtained from them.

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<sup>1</sup> Annex 5

## 6. Research Programme

Consideration was given to various aspects of research which might be usefully supported by WHO after consideration by a Medical Research Advisory Committee. It was agreed that suitable programmes could be prepared on the following subjects:

### 6.1 Training personnel for the analysis of pharmaceutical preparations

The availability of well-trained staff is essential to any laboratory charged with the control of drugs. The Expert Committee found that there is a widespread scarcity of such staff capable of conducting analyses of pharmaceutical preparations by the procedures now in use. The scarcity appears to be due in large measure to certain shortcomings in the training of pharmaceutical analysts. It was concluded that by overcoming these deficiencies, and so providing adequate facilities for the quality control of drugs in government institutions and manufacturing concerns, there would be a distinct benefit to public health generally both in developed and in developing countries.

The Committee agreed that the situation might be greatly improved if guidance be offered to training centres, such as universities, colleges and institutes, so that prospective analysts may receive the kind of training best fitting them for present-day needs.

The problem appears to reflect no serious shortage of general facilities in educational institutions, but rather a lack of appreciation of the exact needs. Study may reveal, however, that a limited amount of financial assistance would greatly increase the output of chemists and pharmacists adequately trained for pharmaceutical analyses.

The Committee recommended that the situation justifies research on the part of WHO into current needs for trained analysts and the most effective and economical means of providing that training.

### 6.2 Analysis of complex specialities

The analysis of complex pharmaceutical specialities presents many difficult problems. Modern techniques, such as chromatography on paper or on columns and electrophoresis, are available and a programme of research might yield valuable results in offering methods of quality control of products of this type.

### 6.3 Vegetable drugs

It was agreed that three lines of approach might usefully be followed, based on the chemico-taxonomic survey of the vegetable kingdom to trace the development of useful chemical groups in the evolution of plant families. Information resulting from this survey would provide a valuable starting point for more specific investigations. Investigations could be carried out on the flora of selected areas to determine which plants yield constituents of interest in medicine, and plants used in the folk-medicine of certain countries might be investigated with a view to isolating active principles with a useful pharmacological action. Specialists might be sent by WHO to assist in the collection of plants for chemical and pharmacological investigation or to carry out special techniques. Institutes concerned with this type of research might be granted assistance. The Committee agreed that organization of a chemico-taxonomic survey would be a type of basic research which WHO could usefully sponsor. It was suggested that three specialists should meet and prepare such a programme to be submitted to the WHO Medical Research Advisory Committee.

Other possible lines of research are as follows:

(a) Since satisfactory methods of assay are not available for a number of important vegetable drugs, WHO might also assist in the development of new analytical methods which would be of value in investigating the constituents of medicinal plants.

(b) In certain instances the yield of active constituents of the drug can be considerably improved by selecting suitable strains and the best conditions for harvesting, preserving and drying the plant material. The investigation of these factors offers another line of research in which WHO might participate.

### 6.4 Stability of drugs and preparations

The Expert Committee agreed that WHO might sponsor work on the effect of factors such as heat, light, moisture and pH on new substances, their solutions and their preparations, including perhaps the effect of heat during sterilization procedures and the use of suitable preservatives and packaging materials. Special attention might be given to the problems of transport and storage of pharmaceutical products in the tropics.

### 6.5 Development of new pharmaceuticals

The Expert Committee suggested that a survey might be undertaken to determine whether there was a need to develop new drugs for the prophylaxis and treatment of specific diseases, additional to the investigations which are at present being undertaken by government or industrial research laboratories. According to the results of the survey it might be appropriate to sponsor the development of new drugs for special purposes. The fact that a great deal of work on these lines is being undertaken considerably limits the possibilities.

### 6.6 Identification methods

The increasing number of chemical substances used in medicine makes their identification more difficult, and in many cases conventional methods are no longer adequate to establish proof of identity. Hence there is a need for techniques of wide application and WHO might initiate research in this direction by sponsoring the investigation of a system based on the determination of melting-points and eutectic melting-points; perhaps about two thousand compounds could be examined in the first instance and the data examined statistically to evaluate such methods as a means of proving the identity of compounds in pharmaceutical use.

### 6.7 Adverse drug reactions

It was agreed that information on adverse reactions to drugs should be made widely available, and that WHO might assist by assembling data. Much of this information would be available from practising physicians and hospitals, and might be collected through hospital pharmacies and compiled for examination, tabulation and analysis on the national, and later, on the international level.

## 7. Use of Specifications

The Expert Committee noted that the First Edition is consulted by the authorities preparing specifications for pharmaceutical preparations in various countries, who wish to use the recommended specifications as a basis for preparing their own monographs. Volumes I and II are available in English, French and Spanish editions published by WHO, while the Supplement is available in English and French, and was presented at the XIX International Congress of Pharmaceutical Sciences of the International Pharmaceutical Federation, Zurich, September 1959. Volume I is also available in German, Japanese and Korean translations and volume II in German and Japanese.

A Spanish translation of the Supplement is being prepared by WHO, and a publishing house is undertaking the preparation of a German translation under the supervision of a member of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

8. Poison Control Centres

The Expert Committee noted with satisfaction that the development of centres, from which information may be obtained rapidly on poisons and the treatment of poisoning, was continuing, particularly in Canada and the United States of America, and expressed a hope that more such centres would be established, as they are of great value to physicians in emergencies.

9. International Non-Proprietary Names

The Expert Committee examined the ninth report of its Sub-Committee on Non-Proprietary Names<sup>1</sup> submitted by the Chairman of this Sub-Committee. It noted that 108 names had been selected as proposed international non-proprietary names, and that a review had been made of the principles used in devising names in different countries. The Committee expressed appreciation of the work done by the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated to deal with the selection of names, and noted that the names were being increasingly used in regulations, pharmacopoeias and other volumes of specifications, thus helping to avoid confusion resulting from the application of several non-proprietary names to the same preparation. It further noted that a recapitulative list of all names for pharmaceutical preparations so far proposed or recommended by WHO was in course of preparation.

10. Unpublished Working Documents

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|---|---|
| Canbäck, T.   | Collaborative testing of the monographs of the Second Edition of the International Pharmacopoeia (WHO/Pharm/Ed.Sec./78) |
| Canbäck, T.<br>Denston, T. C.<br>Miller, L. C.<br>(Secretariat) | Monographs, Revision (WHO/Pharm/Ed.Sec./73 and Adds 1, 2, 3)  |

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<sup>1</sup> WHO/Pharm/372 (Distribution restricted)



## DRAFT GENERAL NOTICES

for the Second Edition of the I.Ph.

### Nomenclature

Unless otherwise indicated, the monograph title is the singular Latin form of the International Non-Proprietary Name (INN). The Latin names of chemical elements correspond to the chemical symbols given in the Table of International Atomic Weights. The Latin names of salts or esters begin with the name of the base or alcohol in the genitive case, followed by the name of the acid radical in the nominative, and certain other binomial titles are formed in a similar way. Exceptionally, for salts in which the principal pharmacological action is due to the acid radical, this is the first word of the title (in the nominative).

In Latin titles of drugs consisting of plant organs, the name of the organ is preceded by the name of the plant.

Where a second name is also in general use, it is given as a synonym.

For preparations, the first part of the title indicates the nature of the preparation.

The English, French and Spanish equivalents of the Latin titles are used in the monograph texts of the respective editions of the International Pharmacopoeia.

### Standards for drugs and preparations

All statements contained in the monographs, with the exceptions given below, constitute standards for the pharmacopoeial substances. A substance is not of pharmacopoeial quality unless it complies with all the requirements stated, except the chemical formula given at the beginning of the monograph and the statements given under the side headings "Solubility" and "Storage".

A synthetic chemical entity may be substituted for a substance defined as derived from a natural source provided that it complies with all other specifications given in the monograph.

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Chemical formulae

When the chemical composition of a pharmacopoeial substance is known or generally accepted, the molecular chemical formula and the molecular weight are given at the beginning of the monograph for purposes of information. For organic substances the graphic formula when known or generally accepted is also given. The Chemical formulae and molecular weights given at the beginning of the monographs are those of the chemically pure substances and are not to be regarded as an indication of the purity of the pharmacopoeial drug. Elsewhere, in statements of specifications of purity and strength, and in descriptions of processes of assay, it is evident from the context that the formulae denote the pure chemical substances.

Application of standards

The specifications of purity and strength of the Pharmacopoea Internationalis apply to articles which are intended for medicinal use but not necessarily to articles which may be sold under the same name for other purposes.

Atomic weights

The atomic weights adopted are the values given in the International Table of Atomic Weights for 19.. The values are based upon the atomic weight of oxygen taken as 16.0000.

Solubility

In stating the solubilities of chemical substances, the term "soluble" is necessarily used sometimes in a general sense, irrespective of concomitant chemical changes.

Statements of solubilities are not regarded as part of the specification unless indicated by a special heading.

Statements of solubilities which are expressed as a precise relation of weight of dissolved substances to volume of solvent, are intended to apply at 20°. Statements of approximate solubilities, for which no figures are given, are intended to apply at ordinary room temperatures.

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Pharmacopoeial chemicals, when brought into solution, may show slight mechanical impurities, such as fragments of filter-papers, fibres, and dust particles, unless excluded by definite tests in the individual monographs.

When the exact solubility of a pharmacopoeial substance is not known, a descriptive term is used to indicate its solubility. The following table indicates the meanings of such terms:

<u>Descriptive terms</u>	<u>Relative quantities of solvent for 1 part of solute</u>	
Very soluble	Less than	1 part
Freely soluble	From 1 to	10 parts
Soluble	From 10 to	30 parts
Sparingly soluble	From 30 to	100 parts
Slightly soluble	From 100 to	1 000 parts
Very slightly soluble	From 1 000 to	10 000 parts
Practically insoluble	More than	10 000 parts

Interpretation of figures

The number of significant figures given in statements in this pharmacopoeia depends on the degree of precision to be attained.

For example: the statement 100 per cent. means a proportion exceeding 99.5 per cent. but not exceeding 100.5 per cent. and the statement 100.0 per cent. means a proportion exceeding 99.95 per cent. but not exceeding 100.05 per cent. If no upper limit for an assay result is given a limit of 100.5 per cent. is to be understood.

Quantities to be weighed or measured

In stating the quantities to be used for tests or assays an appropriate amount is specified. The word "about" is used to indicate that this amount need not be the exact quantity specified but it should not deviate more than plus or minus 10 per cent. This quantity is accurately weighed or measured and the result of the test or assay is based upon this exact weight or volume.

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### Water

When water is referred to in the tests, distilled water or demineralized water is to be used.

### Impurities

The requirements are not framed to provide against all possible impurities. It is not to be presumed, for example, that an unusual impurity is tolerated which is not precluded by the prescribed tests should rational considerations and good pharmaceutical practice require that it be absent. The tests have been adopted to detect or determine the impurities to which attention is more particularly needed, to fix the limits of those which are tolerated to a given extent, and to indicate convenient methods of ensuring the absence of certain others for which no tolerance is approved.

### Drying to constant weight

The term "dried to constant weight" when applied to the determination of loss on drying means that two consecutive weighings do not differ by more than 0.0005 g per g of substance taken for the determination, the second weighing following an additional hour of drying.

### Containers

The container and its closure must not interact physically or chemically with the substance which it holds so as to alter the strength, quality, or purity of the substance; if interaction is unavoidable, the alteration must not be so great as to bring the substance below the pharmacopoeial requirements.

Well-closed container. A well-closed container must protect the contents from extraneous matter or from loss of the substance under ordinary or customary conditions of handling, shipment, storage or sale.

Tightly-closed container. A tightly-closed container must protect the contents from contamination by extraneous matter or moisture, from loss of the substance and from efflorescence, deliquescence, or evaporation under the ordinary or customary

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conditions of handling, shipment, storage or sale, and shall be capable of tight reclosure. Where a tightly-closed container is specified, it may be replaced by a hermetically-closed container for a single dose of the substance.

Hermetically-closed container. A hermetically-closed container must be impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, or sale.

Storage

Protection from light. The substance must be kept in an opaque container or in a bottle of black, dark-red, or dark-brown glass.

Special protection from light. In certain specified instances, when additional protection against light is necessary, the bottle must further be covered with black paper.

(Other specifications on storage are under revision.)

Percentage solutions

The expression "per cent." is used, according to circumstances, with one of four different meanings.

In order that the meaning to be attached to the expression in each instance may be clear, the following notation, which has long been employed by pharmacists, is used.

Per cent. w/w (percentage, weight in weight) expresses the number of g of active substance in 100 g of product.

Per cent. w/v (percentage, weight in volume) expresses the number of g of active substance in 100 ml of product.

Per cent. v/v (percentage, volume in volume) expresses the number of ml of active substance in 100 ml of product.

Per cent. v/w (percentage, volume in weight) expresses the number of ml of active substance in 100 g of product.

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Temperatures

The Celsius thermometric scale is used in expressing temperatures.

Crude drugs

The term "foreign organic matter" is used to designate organic matter which does not form part of the drug as defined by the monograph.

Vegetable drugs are to be substantially free from insects and other animal matter, and from animal excreta, and to show no abnormal odour, colour, sliminess, moulds, or other evidence of deterioration. No poisonous, dangerous, or otherwise noxious foreign substances may be present.

In commerce it is, however, not always possible to obtain vegetable and animal drugs in a state of absolute purity, and a very small amount of innocuous extraneous matter adhering to the drug, or contained in it or admixed with the drug, is usually not detrimental.

If, in exceptional cases, some of the dimensions given in the description of the morphological and microscopical characters in this pharmacopoeia are exceeded by a relatively small amount, but otherwise the drug corresponds to all other requirements of the pharmacopoeia, it may be considered as conforming to the pharmacopoeia.

In determining the ash, ethanol-soluble extractive, and water-soluble extractive of powdered vegetable drugs, the calculations are made with reference to the drug which has not been specially dried.

When it is found necessary to dry a drug before it can be reduced to powder for the purpose of the assay, a correction is made for the loss on drying, and the content of active principle is calculated with reference to the drug which has not been dried.

Standard medicine dropper

The standard dropper shall be one which, at a temperature of 20°, delivers a drop of distilled water weighing between 0.0475 g and 0.0525 g. The instrument shall consist of a glass tube to which a reservoir bulb may be fixed at a distance of at least 5 mm from the outflow surface. The orifice shall be circular, with an external diameter of 3 mm. The drops of liquid must always fall clear.

Annex 1

Biological assays and determinations of potency

For each biological assay or determination of potency, the International Biological Standard or the International Biological Reference Preparation specified may be replaced by a national biological standard or a national biological reference preparation, the potency of which has been determined by suitably adequate comparative tests in relation to the International Biological Standard or the International Biological Reference Preparation and expressed in International Units.

Potency declarations in biological units

Where, in individual monographs, it is specified under "Labelling" that declarations of potency shall be in International Units, the appropriate National Unit may be used if it is substantially identical with the corresponding International Unit and when conditions make it impractical to refer to International Units.

PROVISIONAL LIST OF ADDITIONS AND DELETIONS<sup>1</sup>

The following additions were proposed:

Adonidis Vernalis Herba	Hydralazinum
Aloe	Hydroxyzinum
Althaeae Radix	Meralluridum
Bacitracinum	Mercaptomerinum
Bemegridum	Neomycinum
Chlorotrianisenum	Oleandomycinum
Corticotrophinum	Phenylbutazonum
Dimenhydrinas	Pholcodinum
Diprophyllinum	Pralidoximi methiodidum
Gluthetimidum	Sennae Folium
Glycyrrhizae Radix et Rhizoma	Sennae Fructus
Gummi Arabicum	Tetrahydrozolinum
Gummi Tregacanthae	Tretaminum
	Valerianae Radix

The following deletions were proposed:

Aconitinum	Ferri et Ammonii Citras
Aetheroleum Chenopodii	Hydrargyri Bichloridum
Conessini Hydrobromidum	

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<sup>1</sup> See also document WHO/Pharm/Ed.Sec./64.

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION

Resolution 2, ISO/TC 85 SC 4, Radioisotopes

"The SUB-COMMITTEE will take note of the activities in the field of radioisotopes of other international organizations, for example the International Atomic Energy Agency and the World Health Organization, as well as other ISO Committees and Sub-Committees, in particular Sub-Committee ISO/TC 85 SC 2. The Secretariat of ISO/TC 85 SC 4 will endeavour to ensure any necessary co-ordination.

Appendix to Resolution 2

The Sub-Committee will consider specifications for pharmaceutical forms of radioisotopes to be used in medical/diagnostic and therapeutic/applications, in conjunction with the World Health Organization in order to avoid discrepancies with monographs published in the International Pharmacopoeia."

EXAMPLES OF SPECIFICATIONS FOR REAGENTS  
USED IN THE I.Ph.

A. "ACETIC ACID, GLACIAL R."  $\text{CH}_3\text{COOH}$ . A clear, colourless liquid, having an irritating and characteristic odour. Miscible with water, with ethanol (95 per cent.) R, and with ether R. Specific gravity: 1.050. Boils at  $118^\circ$ .

Assay. Its congealing temperature (page 00) is not below  $16^\circ$ , indicating not less than 99.6 per cent. of  $\text{CH}_3\text{COOH}$ .

Dilution test. Dilute 1 volume with 3 volumes of water: no turbidity appears within one hour.

Residue on evaporation. Evaporate 100 ml on a water-bath, and dry at  $105^\circ$  for one hour; the residue weighs not more than 1.0 mg (0.001 per cent.).

Chloride (page 00). Dilute 5 ml with 25 ml of water, and add 3 ml of nitric acid R and 1 ml of silver nitrate TS: any turbidity produced does not exceed that of a control containing 0.01 mg of added Cl (0.0002 per cent.).

Sulfate (page 00). To 12.5 ml add 10 mg of sodium carbonate R, and evaporate on a water-bath to dryness. Take up the residue in 5 ml of water, filter, and make up to 10 ml. Add 0.5 ml of N hydrochloric acid and 1 ml of barium chloride TS: any turbidity produced does not exceed that of a control containing 0.05 mg of added  $\text{SO}_4$  (0.0004 per cent.).

Substances reducing permanganate. Dilute 2 ml with 10 ml of water and 0.1 ml 0.1 N potassium permanganate: the pink colour is not entirely discharged within two hours.

Heavy metals (page 00). Transfer 20 ml to a beaker, add about 10 mg of sodium carbonate R, and evaporate on a water-bath to dryness. Take up the residue in 1 ml of dilute acetic acid R, dilute to 40 ml, and add 10 ml of hydrogen sulfide TS: any colour produced is not darker than that of a control containing 0.02 mg of added Pb (0.0001 per cent.).

Iron (page 00). To 10 ml add 10 mg of sodium carbonate R, and evaporate to dryness. Take up the residue in 2 ml of saturated hydrochloric acid R, and dilute to 50 ml. Add about 50 mg of ammonium persulfate R and 3 ml of ammonium thiocyanate TS: any red colour produced is not darker than that of a control containing 0.01 mg of added Fe (0.0001 per cent.).

Annex 4

B. "AMMONIUM CHLORIDE R."  $\text{NH}_4\text{Cl}$ . Colourless crystals, or a white, granular powder.

Insoluble matter (page 00). 20 g, dissolved in 200 ml of water, shows not more than 1.0 mg of insoluble matter (0.005 per cent.).

Residue on ignition. To 20 g in a porcelain or silica dish add 2 ml of sulfuric acid R, heat at a temperature that will require at least one hour to volatilize the salt, then ignite at low red heat for five minutes, cool, and weigh: the residue weighs not more than 2 mg (0.01 per cent.). Retain the residue.

Neutrality. Dissolve 5 g in 50 ml of freshly-boiled and cooled water, and add 1 drop of methyl red TS: if a red colour is produced, not more than 0.10 ml of 0.1 N alkali is required to change it to yellow.

Phosphate (page 00). To 2 g add 3 ml of nitric acid R, and evaporate on a water-bath to dryness. Take up the residue in 25 ml of 0.05 N sulfuric acid, add 1 ml each of phosphate reagents A and B and allow to stand for two hours at room temperature: any blue colour produced is not darker than that of a control containing 0.02 mg of added  $\text{PO}_4$  (0.001 per cent.).

Sulfate (page 00). Dissolve 5 g in 50 ml of water, add 1 ml of dilute hydrochloric acid and 1 ml of barium chloride solution and allow to stand for 6 hours. No turbidity or precipitate is produced. (0.01 per cent.)

Heavy metals (page 00). Its heavy metals limit is 0.0005 per cent.

Iron (page 00). The limit for iron is 0.0002 per cent.

C. "BENZENE R."  $\text{C}_6\text{H}_6$ . A colourless, transparent, flammable liquid, having a characteristic aromatic odour. Specific gravity: about 0.876. Insoluble in water. Miscible with ethanol (95 per cent.) R and with ether R.

Boiling-range (page 00). Distil 100 ml: not less than 95 ml distils between  $79.5^\circ$  and  $80.5^\circ$ .

Annex 4

Congealing-temperature (page 00). The congealing-temperature is not below  $5.0^{\circ}$ .

Residue on evaporation. Evaporate 57 ml on a water-bath, and dry at  $105^{\circ}$  to  $110^{\circ}$  for 30 minutes: the residue weighs not more than 1.0 mg (0.002 per cent.).

Water. By Karl Fischer titration, not more than 0.05 per cent.

Sulfur compounds. Place 30 ml of ethanolic potassium hydroxide TS in an Erlenmeyer flask, add 6 ml of sample, and boil the mixture gently for 30 minutes under a reflux condenser. Detach the condenser, dilute with 50 ml of water, and heat on a water-bath until the benzene and ethanol are evaporated. Add 50 ml of bromide TS, and heat for 15 minutes longer. Transfer the solution to a beaker, neutralize with diluted saturated hydrochloric acid R (1 in 4), add an excess of 1 ml of the acid, and concentrate to about 50 ml. Filter if necessary, heat the filtrate to boiling, add 5 ml of barium chloride TS, heat on a steam-bath for two hours, and allow to stand overnight. If a precipitate is formed, filter through a small filter-paper, wash with water until the last washing does not react with silver nitrate TS and ignite: the residue weighs not more than 2.0 mg, correction being made for a blank (0.005 per cent. as S).

Substances darkened by sulfuric acid. Shake 25 ml with 15 ml of sulfuric acid R for 15-20 seconds, and allow to separate: no darkening is observed in either layer.

Thiophene. Repeat the test for substances darkened by sulfuric acid, dissolving a few mg of isatin R in the sulfuric acid before mixing with the benzene: the acid layer does not acquire a blue or green colour within one hour.

D. "SODIUM CARBONATE, ANHYDROUS, R."  $\text{Na}_2\text{CO}_3$ . A white, hygroscopic powder. Soluble in water: insoluble in ethanol (95 per cent.) R.

Insoluble matter (page 00). 10 g shows no more than 1.0 mg of insoluble matter (0.01 per cent.). Do not use a glass filter.

Loss on ignition. Ignite 1 g at  $270$  to  $300^{\circ}$ : it loses not more than 10 mg of its weight (1.0 per cent.).

Annex 4

Chloride (page 00). Dissolve 1 g in water and 3 ml of nitric acid R, and dilute to 60 ml: 20 ml of the solution shows no more than 0.01 mg of Cl (0.003 per cent.).

Nitrate. Dissolve 1 g in 10 ml of water containing 5 mg of sodium carbonate R, and add 0.1 ml of indigo carmine TS and 10 ml of sulfuric acid: the blue colour is not entirely discharged within five minutes (about 0.003 per cent.).

Phosphate (page 00). Dissolve 2 g in 10 ml of water, add 5 ml of saturated hydrochloric acid R, and evaporate on a water-bath to dryness: the residue shows no more than 0.02 mg of  $PO_4$  (0.001 per cent.).

Sulfur compounds. Dissolve 10 g in 100 ml of water, add 5 drops of bromine TS, and boil for five minutes. Cool, neutralize with saturated hydrochloric acid R, add an excess of 1 ml, and filter. Boil the filtrate, add 5 ml of barium chloride TS, digest on a water-bath for two hours, and allow to stand overnight. If a precipitate is present, filter, wash thoroughly, ignite, and weigh: the residue weighs not more than 1.1 mg more than that obtained in a blank (0.005 per cent. as  $SO_4$ ).

Arsenic (page 00). Dissolve 3 g in a few ml of water, neutralize with sulfuric acid R, and determine the arsenic content as directed: the stain produced is not darker than that produced by 0.003 mg of As (0.0001 per cent.).

Calcium and magnesium. Dissolve 5 g in 80 ml of water and 20 ml of 5 N hydrochloric acid; boil for 5 minutes, cool and neutralize to pH 7.0 with 5 N sodium hydroxide solution (about 1 ml). Add 1 ml of standard magnesium solution (1 ml = 0.1 mg Mg) and sufficient borate buffer solution (about 2 ml) to adjust the pH to 10.0. Add 0.1 ml of Eriochrome black T solution and titrate slowly with shaking with 0.01 M disodium edetate, using a micro-burette, until a pure blue colour is obtained. Not more than 1.6 ml of 0.01 M disodium edetate is required.

Annex 4

Heavy metals. Dissolve 3 g in 20 ml of water, and slowly add 8 ml of saturated hydrochloric acid R (A). Dissolve 1 g in 20 ml of water, and add 0.02 mg of Pb (page 00) and 8 ml of saturated hydrochloric acid R (B). Evaporate both solutions on a water-bath to dryness, take up each residue in 20 ml of water, add 1 drop of phenolphthalein TS, and neutralize with 0.1 N sodium hydroxide. Add, to each, 1 ml of dilute acetic acid R, dilute to 40 ml, and add 10 ml of hydrogen sulfide TS: any brown colour produced in (A) is not darker than that of (B) (0.002 per cent.).

Iron. Dissolve 1 g in 10 ml of water, and slowly add 3 ml of saturated hydrochloric acid R. Evaporate on a water-bath to dryness. Take up the residue in 2 ml of saturated hydrochloric acid R, and dilute to 50 ml. Add 50 mg of ammonium persulfate R and 3 ml of ammonium thiocyanate TS: any red colour produced is not darker than that of a control containing 0.01 mg of added Fe (page 00) (0.001 per cent.).

Ammonium (0.0002 per cent.). Dissolve 5 g in 40 ml of water, add 9 ml of hydrochloric acid, boil to remove carbon dioxide, cool and add 2 ml of sodium hydroxide solution and 2 ml of Nessler's reagent to 50 ml of water containing 1 ml of standard ammonium solution (1 ml = 0.01 mg  $\text{NH}_4$ ).

Potassium. Dissolve 1 g in 15 ml of water, add 3 ml of saturated hydrochloric acid R, evaporate on a water-bath to dryness, and heat for thirty minutes at  $120^\circ$ . Dissolve the residue in water to make 10 ml. To 5 ml of the solution add 5 ml of sodium cobaltinitrite TS and 10 ml of ethanol (95 per cent.) R: any turbidity formed within thirty minutes does not exceed that of a control containing 0.1 ml of standard potassium solution<sup>1</sup> and the residue from the evaporation of 3 ml of saturated hydrochloric acid R (0.02 per cent.).

Alternatively potassium may be determined with the use of the flame photometer.

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<sup>1</sup> Prepared by dissolving 1.907 g of potassium chloride R in sufficient water to produce exactly 1000 ml.

LIST OF SUBSTANCES TO BE STUDIED FOR INCLUSION IN THE  
COLLECTION OF THE CENTRE FOR AUTHENTIC CHEMICAL SUBSTANCES

Cortisone Acetate  
Desoxycorticosterone Acetate  
Dienestrol  
Diethylstilboestrol  
Estradiol Benzoate  
Ethinyl Estradiol  
Ethinisterone  
Hydrocortisone  
Hydrocortisone Acetate  
Hydrocortisone Sodium Succinate  
Liothyronine Sodium  
Methyltestosterone  
Prednisolone  
Prednisone  
Progesterone  
Testosterone Propionate

## LIST OF REVISED MONOGRAPHS

Sulfonamides

Phthalysulfathiazolum, Sup.  
 Succinylsulfathiazolum, vol.I  
 Compressi Succinylsulfathiazoli, vol.II  
 Sulfadiazinum, vol.I  
 Compressi Sulfadiazini, vol.II  
 Sulfadiazinum Natricum, vol.I  
 Injectio Sulfadiazini Natrici, vol.II  
 Sulfadimidinum, Sup.  
 Compressi Sulfadimidini, Sup.  
 Sulfguanidinum, vol.I  
 Compressi Sulfguanidini, vol.II  
 Sulfamerazinum, vol.I  
 Compressi Sulfamerazini, vol.II  
 Sulfamerazinum Natricum, vol.I  
 Injectio Sulfamerazini Natrici, vol.II  
 Sulfanilamidum, vol.I  
 Compressi Sulfanilamidi, vol.II  
 Sulfathiazolum, vol.I  
 Compressi Sulfathiazoli, vol. II  
 Sulfathiazolum Natricum, vol.I  
 Injectio Sulfathiazoli Natrici, vol. II

Barbiturates

Amobarbitalum, Sup.  
 Compressi Amobarbitali, Sup.  
 Amobarbitalum Natricum, Sup.  
 Amobarbitalum Natricum pro Injectione, S  
 Barbitalum Natricum, vol.I  
 Compressi Barbitali Natrici, vol.II  
 Hexobarbitalum, vol.II  
 Hexobarbitalum Natricum, vol.II  
 Phenobarbitalum, vol.I  
 Compressi Phenobarbitali, vol.II  
 Phenobarbitalum Natricum, vol.I  
 Compressi Phenobarbitali Natrici, vol.II  
 Phenobarbitalum Natricum pro Injectione,  
 vol.II  
 Injectio Phenobarbitali Natrici, vol.II  
 Secobarbitalum Natricum, Sup.  
 Compressi Secobarbitali Natrici, Sup.  
 Thiopentalum Natricum cum Natrii  
 Carbonate, vol.I  
 Thiopentalum Natricum cum Natrii  
 Carbonate pro Injectione, vol.II  
 Injectio Thiopentali Natrici cum  
 Natrii Carbonate, Vol.II

Annex 6

Adrenaline and related compounds

Adrenalini Bitartras, vol.II  
Injectio Adrenalini, vol.II  
Adrenalinum, vol.I  
Amphetamini Sulfas, vol.I  
Compressi Amphetamini Sulfatis, vol.II  
Amphetaminum, vol.I  
Dextro Amphetamini Sulfas, Sup.  
Compressi Dextro Amphetamini Sulfatis, Sup.  
Ephedrini Hydrochloridum, vol.I  
Compressi Ephedrini Hydrochloridi, vol.II  
Isoprenalini Hydrochloridum, vol.II  
Isoprenalini Sulfas, vol.II  
Compressi Isoprenalini Sulfatis, Sup.  
Levarterenoli Bitartras, vol.II  
Injectio Levarterenoli, vol.II  
Methamphetamini Hydrochloridum, Sup.  
Compressi Methamphetamini Hydrochloridi,  
Sup.  
Methoxamini Hydrochloridum, Sup.

Antihistaminics

Antazolini Hydrochloridum, vol.II  
Chlorcyclizini Hydrochloridum, Sup.  
Compressi Chlorcyclizini Hydrochloridi,  
Sup.  
Diphenhydramini Hydrochloridum, vol.II  
Mepyramini Maleas, vol.II  
Compressi Mepyramini Maleatis, Sup.  
Promethazini Hydrochloridum, vol.II  
Compressi Promethazini Hydrochloridi, Sup.  
Tripeleammamini Hydrochloridum, vol.II