The International Pharmacopoeia

Third edition

Volume 5

Tests and general requirements for dosage forms

Quality specifications for pharmaceutical substances and tablets

World Health Organization
Geneva

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THIRD EDITION

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Editio tertia

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Preface

The International Pharmacopoeia[1] comprises a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances, excipients, and dosage forms that is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status only if a national authority expressly introduces it into appropriate legislature.

The policies and aims of the third edition of *The International Pharmacopoeia*, together with general notices and methods of analysis, are set out in detail in the prefaces of previous volumes.[2] It has been emphasized that pharmacopoeial specifications represent only one element of the quality assurance of drugs. Increasingly, the selection of monographs is determined by those substances included in the current *WHO Model List of Essential Drugs*.[3]

Pharmaceutical substances and dosage forms for human use, as described in a monograph of *The International Pharmacopoeia*, should be manufactured according to the requirements of Good Manufacturing Practices (GMP), whether those recommended by WHO or those laid down by the competent national (regional) authority in the country of manufacture. The processes, premises, equipment, and installations should also comply with the provisions of the product licence or marketing authorization, relevant regulations and, in the case of products destined for export, with any binding international norms that would affect their entry onto the market. In many cases this compliance cannot be verified by analysing a sample of the final product against a pharmacopoeial monograph. The national authority will need to ensure that these instructions have been followed by any means at its disposal, including use of appropriate certificates, inspection of the manufacturing site or testing of samples beyond specifications.

Pharmaceutical preparations that are produced on a large scale and will

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[1] Published in accordance with World Health Assembly resolution WHA3.10, *WHO Handbook of Resolutions and Decisions*, Vol. 1, 1977, p. 127.

[2] *The International Pharmacopoeia*, 3rd ed. Geneva, World Health Organization.
Volume 1: *General methods of analysis*, 1979.
Volume 2: *Quality specifications*, 1981.
Volume 3: *Quality specifications*, 1988.
Volume 4: *Tests, methods, and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms*, 1994.

[3] WHO Technical Report Series, No. 882, 1998.

be stored before use should undergo testing to show physical and chemical stability during storage over the claimed shelf-life.[1] The requirements of the monographs are not framed to detect all possible impurities. The present tests are designed to determine impurities on which attention should be focused, to fix the limits of those that are tolerable to a certain extent, and to indicate methods for ensuring the absence of those that are undesirable. It is therefore not to be presumed that an impurity can be tolerated because it has not been precluded by the prescribed tests. In some purity tests, limits are indicated additionally in brackets in percentage terms: such limits are given for information only.

The degree of protection provided by compendial standards will depend not only on their technical content but also to a great extent on how they are utilized. The specified tolerances and limits allow for the inherent variations that occur during production and packaging, as well as for subsequent degradation within normal handling and storage conditions and for any acceptable variance of analytical results.

When pharmaceutical standards are used to establish the compliance of products with regulatory requirements, the following principles should apply:

- The interpretation of a monograph must be in accordance with all general requirements and testing methods, texts, or notices pertaining to it as found in this edition.
- No further tolerances are to be applied to the limits prescribed.
- A product is not of pharmaceutical quality unless it complies with all the requirements stated.

As stated in the Twenty-sixth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,[2] a distinction exists between pharmacopoeial standards and manufacturers' release specifications. Although release specifications must be based on and be compatible with pharmacopoeial specifications, they may differ in several respects, and it is generally the case that manufacturers' specifications for a drug are more exacting than corresponding pharmacopoeial requirements. The manufacturer is entitled to use other methods for routine testing and, on occasions, certain analytical procedures can be omitted by the manufacturer when testing for compliance with pharmacopoeial standards as long as in-process controls and manufacturing process validation studies have already provided the necessary assurances.

The present volume contains quality specifications for 37 pharmaceutical substances and 20 dosage forms as tablets. There is a new and separate section on antimalarial drugs (7 substances and 8 dosage forms, as identified by the Malaria Unit of WHO), which was included in order to help combat malaria.

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[1] *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials*. Volume 1. Geneva, World Health Organization, 1997.

[2] WHO Technical Report Series, No. 614, 1977, p. 18.

These specifications were developed with the help of special advisers and experts in the field.

There are also general requirements for dosage forms for ophthalmic preparations and for suppositories, and seven additional tests for dosage forms. The specific requirements for the dissolution test for tablets and capsules are still being developed and the Secretariat of *The International Pharmacopoeia* therefore recommends that dissolution requirements for individual monographs be established with regard to the actual biopharmaceutical characteristics of the representative products on the world market. Until publication of specific requirements, the limits provided by the world's leading compendia should be followed.

The new guidelines for microbial purity of pharmaceutical preparations are intended only to provide information and guidance for manufacturers, essentially for process validation, and those involved in quality assurance within the drug distribution system, for periodic monitoring of finished products.

The test method for bacterial endotoxins is intended for substances for parenteral or sterile administration, and replaces the pyrogen test used so far. The limits are currently being evaluated and, where appropriate, have been added to certain monographs. The test for visible particulate contamination is provided for use only as a simple batch acceptance criterion in commerce, and occasionally for random checking of products in the distribution system to ensure quality control during storage. It should be noted that this test is not suitable for use by manufacturers for the purposes of batch release.

Changes to monographs published in Volumes 2, 3, and 4 have been included in the Amendments, which also provide an updated text on "High-performance liquid chromatography". This brings the method into line with the current situation. Modern analytical techniques such as high-performance liquid chromatography have been recognized in some cases to be more sensitive, more rapid, and more robust, and could potentially save costs. Where resources permit, the more technically advanced methods might be provided as the first choice and the less advanced methods as the alternative.

Reagents presenting a potential health risk, such as chloroform, have been replaced as far as possible.

Furthermore, the present volume has an entirely new section of "Supplementary information", which includes lists of available International Chemical Reference Substances and International Infrared Reference Spectra and guidelines for establishing and distributing International Chemical Reference Substances. There are also annotated references to information on International Nonproprietary Names (INN) for pharmaceutical substances and how they are devised and selected, and to information on how to represent chemical formulae graphically in INN publications.

A questionnaire on how *The International Pharmacopoeia* was used was included in Volume 4, which was published in 1994; the same questionnaire was distributed to a number of relevant institutions in WHO Member States. Results showed that *The International Pharmacopoeia* was generally used by both

industrialized and developing countries as a reference source for developing national standards, for quality testing imported pharmaceutical products, and for quality testing locally manufactured drugs. Other uses included its partial or total adoption, mostly in developing countries, as the national pharmacopoeial or similar standard for product licensing and procurement of pharmaceuticals.

The International Chemical Reference Substances referred to in the monographs may be obtained from the WHO Collaborating Centre for Chemical Reference Substances, Apoteket AB, Produktion & Laboratorier, Centrallaboratoriet (ACL), Prismavägen 2, S-141 75 Kungens Kurva, Sweden. International Infrared Reference Spectra are available from the same source. The purpose of chemical reference substances and infrared reference spectra is to achieve the accuracy and reproducibility of analytical results that are required in the context of pharmacopoeial testing and pharmaceutical control in general.

All comments and suggestions concerning the contents of *The International Pharmacopoeia* will be examined and, should amendments be proposed, they will be considered for inclusion in subsequent volumes.

History

The history of *The International Pharmacopoeia* dates back to 1874 when the need to standardize terminology and to specify dosages and composition of drugs led to attempts to produce an international pharmacopoeial compendium. The first conference, called by the Belgian Government and held in Brussels in 1902, resulted in the Agreement for the Unification of the Formulae of Potent Drugs, which was ratified in 1906 by 19 countries. The outcome considerably influenced the subsequent publication of national pharmacopoeias.

A second agreement, the Brussels Agreement, was drawn up in 1925 and ratified in 1929. This 41-article agreement stipulated that the League of Nations would be responsible for the administrative work to produce a unified pharmacopoeia, and a permanent secretariat of an international organization would coordinate the work of national pharmacopoeial commissions. General principles for the preparation of galenicals, maximal doses, nomenclature, and biological testing of arsenobenzones were included in the articles of this agreement, as was a table of dosage strengths and descriptions for 77 drug substances and preparations.

In response to repeated calls from pharmaceutical experts in various countries that the Brussels Agreement be revised and extended to cover an international pharmacopoeia, the Health Organization of the League of Nations set up a Technical Commission of Pharmacopoeial Experts in 1937. This first committee comprised seven experts from Belgium, Denmark, France, Netherlands, Switzerland, the United Kingdom (Chairman), and the United States of America.

In 1947 the Interim Commission of WHO took over the work on pharmacopoeias previously undertaken by the Health Organization of the League of Nations, and set up an Expert Committee on the Unification of Pharmacopoeias to continue the work of the League's Technical Commission. The aim of the Expert Committee was to produce a draft international agreement for the unification of pharmacopoeias, modifying and extending the existing Agreement for the Unification of the Formulae of Potent Drugs.

In 1948 the First World Health Assembly approved the establishment of the Expert Committee by the Interim Commission. In 1951 this became the Expert Committee on the International Pharmacopoeia; and subsequently, in 1959, the Expert Committee on Specifications for Pharmaceutical Preparations. The panel has always been named the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

Article 2 of the WHO Constitution states that one of the functions of the Organization is "to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". *The International Pharmacopoeia* falls clearly into this category. In this context also the Third World Health Assembly in 1950 adopted a resolution to create the International Nonproprietary Names (INN) Programme in order to identify pharmaceutical substances unambiguously on a worldwide basis and to provide a single nonproprietary name to be used in monographs.

First edition

The Third World Health Assembly, held in May 1950, formally approved the publication of the *Pharmacopoea Internationalis* and recommended, in accordance with Article 23 of the WHO Constitution, "the eventual inclusion of its provisions by the authorities responsible for the pharmacopoeias". It was thus recommended that the *Pharmacopoea Internationalis* was not intended to be a legal pharmacopoeia in any country unless adopted by the pharmacopoeial authority of that country. From that moment the World Health Organization constituted the Permanent International Pharmacopoeia Secretariat.

The first edition, published with the aim of creating a worldwide, unified pharmacopoeia, relied on collaboration with national pharmacopoeia commissions for its preparation. It was published in two volumes (1951 and 1955) and a supplement (1959) in English, French and Spanish, and was also translated into German and Japanese. Altogether, it included 344 monographs on drug substances, 183 monographs on dosage forms (capsules, injections, tablets and tinctures) and 84 tests, methods, and general requirements.

A large number of national pharmacopoeias and official lists were examined and assistance was also obtained from the International Pharmaceutical Federation (FIP) to determine the selection of substances and products to be described in the pharmacopoeia. Latin was chosen for the monograph titles because of its distinction as an international language. Experts collaborated with the WHO Expert Committee on Biological Standardization with regard to biological products, and with those working in specific divisions, e.g. malaria, maternal and child health, mental health, and venereal diseases, to help collate the required information.

Second edition

The second edition was published in 1967 as *Specifications for the Quality Control of Pharmaceutical Preparations*, with a subtitle classifying it as the second edition of *The International Pharmacopoeia*.

Owing to the development of new analytical techniques such as infrared spectroscopy, chromatography (column, paper and thin-layer), non-aqueous titration, and radioactivity, the second edition incorporated numerous alterations and constituted a revision of the first edition.

The selection of monographs and appendices was based largely on the availability, at the time of preparation, of specifications intended for publication in

national pharmacopoeias and in other volumes of specifications for pharmaceutical quality control. Specifications for 162 pharmaceutical preparations not included in the first edition were introduced in the second edition, while 114 monographs were deleted, based on feedback from the first edition. New analytical methods were also added. The specifications and methods in the monographs were tested in a number of national pharmacopoeial and pharmaceutical quality control laboratories, in pharmaceutical manufacturers' laboratories, and at various pharmacopoeial institutes.

Special thanks were expressed to the authorities of the British Pharmacopoeia and the United States Pharmacopeia.

Third edition

In 1975 the purpose of *The International Pharmacopoeia* was reconsidered. It was decided that the publication should focus more on the needs of developing countries and recommend only simple, classical chemical techniques that had been shown to be sound. Priority would be given to drugs that were widely used throughout the world, with emphasis on the therapeutic value of these drugs. High priority would be accorded to drugs important to WHO health programmes, and to those likely to contain impurities arising from degradation or due to difficulties in their manufacture. Wherever possible, classical procedures would be used in the analytical methods so that the pharmacopoeia could be applied without the need for expensive equipment. Where a sophisticated analytical method was suggested, an alternative, less complex method would also be proposed.

Since 1979, the drugs appearing in *The International Pharmacopoeia* have been selected from the list of essential drugs based on the first report of the WHO Expert Committee on the Selection of Essential Drugs. Specifications are provided in the monographs for the identification, purity, and content of the essential drugs appearing in the WHO Model List of Essential Drugs, and their updates.

The International Pharmacopoeia currently stands at five volumes: Volume 1 contains general methods of analysis; Volumes 2 and 3, quality specifications for the majority of essential drug substances in the WHO Model List of Essential Drugs; and Volume 4, information on tests, methods, and general requirements and quality specifications for pharmaceutical substances, excipients, and dosage forms. Volume 5, the present volume, contains tests and general requirements for dosage forms and quality specifications for pharmaceutical substances and tablets, which will practically complete the list of monographs for active pharmaceutical substances, and a section on antimalarial drug substances and their most widely used dosage forms.

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