The International Pharmacopoeia

Third Edition

Volume 1
General methods of analysis

World Health Organization 1979

THE INTERNATIONAL PHARMACOPOEIA

THIRD EDITION

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CONTENTS

PREFACE

The *International Pharmacopoeia* is published by the World Health Organization by virtue of resolution WHA3.10[1] of the Third World Health Assembly. The first edition was published in two volumes, the first in 1951 and the second in 1955, followed by a Supplement in 1959; all of these were issued in English, French and Spanish. German and Japanese translations have also been published. The second edition was published in 1967, followed by a Supplement in 1971. These were issued in English, French, Russian and Spanish.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations, in its 25th and 26th reports, has reviewed the organization of work on the revision of the *International Pharmacopoeia* and on the production and review of quality specifications published by the World Health Organization. It recommended suitable procedures and established priorities with a view to the implementation of World Health Assembly resolutions WHA20.34,[2] which requested the Director-General "to continue work on analytical control specifications", and WHA28.66,[3] which requested the Director-General "to continue to develop activities related to the establishment and revision of international standards, requirements and guidelines for prophylactic and therapeutic substances".

Following these recommendations, work has been proceeding on the preparation of the third edition of the *International Pharmacopoeia*, which will be published in several volumes. Volume 1 contains the description of general methods of analysis; it will be followed by volumes containing the monographs, i.e., quality specifications for individual drugs, primarily for those most widely used in general health care.

The selection of the methods and procedures included in volume 1 of the third edition was based on their utility for the purpose of assuring the quality of pharmaceuticals. Numerous alterations have been made in the methods retained from previous editions to bring them into line with progress in the development of new analytical tools. Full account was, however, taken of various technical and economic constraints, and in the choice of recommended procedures optimum solutions were sought that will, it is hoped, permit their use by drug quality control laboratories located in developing countries as well.

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[1] *WHO Handbook of Resolutions and Decisions*, vol. I, 1973, p. 127.
[2] *WHO Handbook of Resolutions and Decisions*, vol. I, 1973, p. 132.
[3] *WHO Handbook of Resolutions and Decisions*, vol. II, third edition, 1979, p. 52.

The revision of the general methods of analysis included in Volume 1 of the third edition was carried out with the help of the members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists. The process of revision was carried out in a series of meetings held during the period 1974-1977 and by correspondence. In July 1978 the draft text of volume I of the third edition of the *International Pharmacopoeia* was sent for final comments to all WHO Member States, to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, and to other specialists.

The following specialists participated both in person and by correspondence in the above-mentioned discussions, and commented on the final draft: Professor E.A. Babayan, Ministry of Health, Moscow, USSR; Dr D. Banes, The United States Pharmacopoeia, Rockville, MD, USA; Dr. I. Bayer, National Institute of Pharmacy, Budapest, Hungary; Dr T. Bićan, Institute for the Control of Drugs, Zagreb, Yugoslavia; Mr J.Y. Binka, Government Chemical Laboratory, Accra, Ghana; Professor W.H. Briner, Duke University Medical Center, Durham, NC, USA; Mr J.R. Buriánek, State Institute for the Control of Drugs, Prague, Czechoslovakia; Dr T. Canbäck, Swedish Pharmacopoeia Commission, Stockholm, Sweden; Dr J.C. Charlton, The Radiochemical Centre, Amersham, England; Professor Y. Cohen, Atomic Energy Commission, Saclay, Gif-sur-Yvette, France; Dr D. Cook, Drug Research Laboratories, Ottawa, Ontario, Canada; Dr N. Diding, WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden; Dr L.F. Dodson, National Biological Standards Laboratory, Department of Health, Canberra, Australia; Dr K. Florey, The Squibb Institute for Medical Research, New Brunswick, NJ, USA; Ms M.A. Garth, National Center for Antibiotics Analysis, Food and Drug Administration, Washington, DC, USA; Dr A.R. Gennaro, The Philadelphia College of Pharmacy and Science, Philadelphia, PA, USA; Dr T. George, Ciba-Geigy Research Centre, Goregaon, Bombay, India; Mr W. Hewitt, Cheltenham, England; Mr Kang Hu, Peking Institute for the Control of Pharmaceutical and Biological Products, Peking, People's Republic of China; Dr T. Inoue, National Institute of Hygienic Sciences, Tokyo, Japan; Miss S. Johansson, WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden; Mr C.A. Johnson, British Pharmacopoeia Commission, London, England; Mr H.G. Kristensen, The Danish Pharmacopoeia Council, Brønshøj, Denmark; Dr K. Kristensen, The Isotope Pharmacy, Brønshøj, Denmark; Dr C.S. Kumkumian, Bureau of Drugs, Food and Drug Administration, Rockville, MD, USA; Dr E. Lang, Ciba-Geigy SA, Basle, Switzerland; Professor J. Laszlovszky, National Institute of Pharmacy, Budapest, Hungary; Dr T. Layloff, National Center for Drug Analysis, Food and Drug Administration, St Louis,

MO, USA; Dr J.W. Lightbown, National Institute for Biological Standards and Control, London, England; Dr A.J. Liston, Drugs Directorate, Ottawa, Ontario, Canada; Mr W.J. Mader, Alza Corporation, Palo Alto, CA, USA; Professor M.D. Maškovskij, Pharmacopoeia Committee of the USSR, Moscow, USSR; Dr E. Nieminen, Lääkelaboratorio, Helsinki, Finland; Dr A.N. Obojmakova, Pharmacopoeia Committee of the USSR, Moscow, USSR; Mr B. Öhrner, WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden; Dr T. Olawuyi Oke, Federal Drug Quality Control Laboratory, Yaba, Lagos State, Nigeria; Professor X. Perlia, Institut de Pharmacie, Zurich, Switzerland; Dr M. Pesez, Roussel Uclaf SA, Romainville, France; Professor J. Richter, Institut für Arzneimittelwesen der DDR, Berlin-Weissensee, German Democratic Republic; Dr G. Schwartzman, Bureau of Drugs, Food and Drug Administration, Washington, DC, USA; Professor S.D. Sokolov, All-Union Chemico-Pharmaceutical Research Institute, Moscow, USSR; Dr I. Suzuki, National Institute of Hygienic Sciences, Tokyo, Japan; Mr Tien Sung-chiu, Peking Institute for the Control of Pharmaceutical and Biological Products, Peking, People's Republic of China; Mr Tu Kuo-shih, Peking Institute for the Control of Phamaceutical and Biological Products, Peking, People's Republic of China; Dr M.M. Tuckerman, School of Pharmacy, Temple University, Philadelphia, PA, USA; Professor H. Vanderhaeghe, Rega Pharmaceutical Institute, Leuven, Belgium; Dr R. Vasiliev, State Institute for Drug Control and Pharmaceutical Research, Bucharest, Romania; Dr A. Végh, Hungarian Pharmacopoeia Commission, Budapest, Hungary; Mr W.J. Welsh, Radiation Medicine Division, Ottawa, Ontario, Canada; Dr B.A. Wills, Allen & Hanburys Ltd., Ware, England; Dr W.W. Wright, Bureau of Drugs, Food and Drug Administration, Washington, DC, USA.

Furthermore, comments were obtained from the International Atomic Energy Agency, the Austrian Pharmacopoeia Commission, the Danish Pharmacopoeia Council, the French National Pharmacopoeia Commission, the Pharmacopoeia Commission of the Federal Republic of Germany, the Hungarian Pharmacopoeia Commission, and the United States Pharmacopoeia; from the Ministries of Health of Bulgaria, Romania and Sweden; and also from the National Biological Standards Laboratory, Canberra, Australia, the Drug Research Laboratories, Ottawa, Ontario, Canada, and the Department of Scientific and Industrial Research, Wellington, New Zealand. In addition, some professional associations provided comments and suggestions.

The World Health Organization takes this opportunity to express its gratitude to all those persons and institutions who took part in the preparation of this volume.

Mr C.A. Johnson served as Chairman at the above-mentioned meetings of the WHO Expert Committee on Specifications for Pharmaceutical

Preparations. The functions of Secretary to the Committee were assumed by Mr O. Wallén, Chief Pharmaceutical Officer, WHO, and by Dr W. Wieniawski, Senior Pharmaceutical Officer, assisted by Miss M. Schmid, Technical Assistant.

Volume 1 of the third edition of the *International Pharmacopoeia* contains the description of 42 general methods of analysis. For most of the physical and physicochemical methods an introductory description is given followed by recommended procedures. This general description is designed to facilitate the utilization of these methods for the purpose of drug quality assurance, even outside the scope of specifications published in the *International Pharmacopoeia.*

In accordance with resolution WHA30.39[1] of the Thirtieth World Health Assembly the units of measurement used in the third edition of the *International Pharmacopoeia* are based on the International System of Units (SI) (see page 13).

The general notices that precede volume I of the third edition concern primarily terms and provisions applicable in connexion with the general methods of analysis and will be expanded in subsequent volumes.

In accordance with World Health Assembly resolution WHA3.10 mentioned above, the *International Pharmacopoeia* constitutes a collection of recommended methods and specifications that are not intended to have a legal status as such in any country, unless expressly introduced for that purpose by appropriate legislation, but are offered to serve as references so that national requirements can be established on a similar basis in any country. Any Member State of the World Health Organization may include all or part of these provisions in its national requirements.

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

GENERAL NOTICES

Quantities and their precision

The quantities of substances and reagents to be used in the tests, assays, and procedures have to be measured with adequate precision. The required precision is indicated by the number of decimals given in the text. For example, 20 indicates a value not less than 19.5 and not greater

[1] *WHO Handbook of Resolutions and Decisions, vol. II, third edition, 1979, p. 99.*

than 20.5; 2.0 indicates a value not less than 1.95 and not greater than 2.05; and 0.20 a value not less than 0.195 and not greater than 0.205.

Temperature measurements and their precision

The required precision of temperature measurements is indicated in a manner similar to that given for the quantities of substance.

pH values and their precision

The required precision of pH values is indicated in a manner similar to that given for the quantities of substance.

Calculation of results

The results of assays should be calculated to one decimal place more than indicated in the requirement and then rounded up or down as follows: if the last figure calculated is 5 to 9, the preceding figure is increased by 1; if it is 4 or less, the preceding figure is left unchanged. Other calculations, for example, in the standardization of volumetric solutions, are carried out similarly.

Solutions

Unless otherwise specified, all solutions indicated in the tests and assays are prepared with distilled or demineralized water.

Solubility

Statements about the solubility of a substance refer to the approximate solubility at 20 °C, unless otherwise indicated. The expression "part" has to be understood as describing the number of millilitres of the solvent, represented by the stated number of parts, in which 1 g of the solid is soluble.

Descriptive terms are sometimes used to indicate the solubility of a substance. The following table indicates the meaning of such terms:

Descriptive term	*Number of millilitres of the solvent required for 1 g of the solid*
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1 000
Very slightly soluble	From 1 000 to 10 000
Practically insoluble	More than 10 000

Loss on drying

In determining the loss on drying, unless another amount of substance is specified, 1.0 g is dried under the conditions indicated.

Constant weight

The expression "dry to constant weight" means that the drying process should be continued until the results of two consecutive weighings do not differ by more than 0.5 mg per g of the substance taken for the determination, the second weighing being made after an additional hour of drying at the prescribed conditions. The expression "ignite to constant weight" has a similar meaning, the second weighing following further ignition.

Containers

The container and its closure must not interact physically or chemically with the substance it holds so as to alter its purity or strength. The following terms describe additional requirements for the permeability of containers:

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

Tightly closed container. It must protect the contents from extraneous matter, from loss of the substance, and from efflorescence, deliquescence, or evaporation under ordinary or customary conditions of handling, shipment, or storage, and shall be capable of tight reclosure.

Protection from light

The substance required to be kept protected from light should be maintained in a light-resistant container that shields the contents against the effects of light, either by reason of the inherent properties of the material from which the container is composed, or because a special coating has been applied to the container. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering.

Patents and trademarks

The inclusion in the *International Pharmacopoeia* of any product subject to actual, or potential, patent or similar rights, or the inclusion of any name that is a trademark in any part of the world, does not and shall not be deemed to imply or convey permission, authority, or licence to

exercise any right or privilege protected by such patent or trademark, including licence to manufacture, without due permission, authority, or licence from the person or persons in whom such rights and privileges are vested.

Use of trade names

Reference to a particular trade name in the description of certain materials used in assays and tests does not imply that other, equivalent, materials are not also suitable.

Reagents, test solutions and volumetric solutions

The letters R, IR, TS and VS following the names of reagents, test solutions and volumetric solutions indicate that they are described in the list commencing on p. 167.

UNITS OF MEASUREMENT

The names and symbols for units of measurement used by the *International Pharmacopoeia* are those of the *Système international d'Unités* (International System of Units) (SI), a practical system of units that has been developed through the efforts of the General Conference of Weights and Measures (CGPM) and other international organizations. The 11th General Conference (1960) adopted the international abbreviation SI for this system of units[1].

The SI units used in the third edition of the *International Pharmacopoeia*, as well as their multiples and submultiples, are in many cases identical to the units used for the respective units of measurement in the second edition. In other cases, however, the SI has introduced differently defined units; this is especially true for derived units. In such situations, to promote better understanding of the procedures and limits related to quality requirements, the third edition of the *International Pharmacopoeia* gives, in addition to the SI units, the units previously used in the second edition, together with appropriate conversion of numerical values.

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[1] Complete information on SI units is contained in *A guide to international recommendations on names and symbols for quantities and on units of measurement*, by D.A. Lowe, Geneva, World Health Organization, 1975; a more concise account is given in *The SI for the health professions*, Geneva, World Health Organization, 1977.

The following multiplicative prefixes, which indicate decimal multiples and submultiples of the SI units, are used in the *International Pharmacopoeia:*

giga	(G)	10^9
mega	(M)	10^6
kilo	(k)	10^3
centi	(c)	10^{-2}
milli	(m)	10^{-3}
micro	(μ)	10^{-6}
nano	(n)	10^{-9}
pico	(p)	10^{-12}

The use of these prefixes is illustrated by the following units, multiples and submultiples, that are employed in the third edition of the *International Pharmacopoeia:*

Units of length

metre	(m)
centimetre	(cm)
millimetre	(mm)
micrometre	(μm)
nanometre	(nm)

Units of volume (capacity)

litre	(l)	= 1 000 cm^3
millilitre	(ml)	= 1 cm^3
microlitre	(μl)	= 0.001 cm^3

Units of temperature

Kelvin	(K)
degree Celsius	(°C)

Units of mass

kilogram	(kg)
gram	(g)
milligram	(mg)
microgram	(μg)
nanogram	(ng)

Units of time

year	(a)
day	(d)
hour	(h)
minute	(min)
second	(s)
millisecond	(ms)
microsecond	(μs)

Units of pressure

kilopascal	(kPa)
pascal	(Pa)

The following non-SI units of pressure are also used in some special cases:

pound-force per square inch (lbf/in^2 or, incorrectly, psi)	≈ 0.69 kPa
millimetre of mercury (mmHg)	≈ 133 Pa

Units of radioactivity [1]

gigabecquerel	(GBq)	= 27.03 mCi
megabecquerel	(MBq)	= 27.03 μCi
becquerel	(Bq)	= 27.03 pCi
curie	(Ci)	= 37 GBq
millicurie	(mCi)	= 37 MBq
microcurie	(μCi)	= 37 kBq

Units of electric current

ampere	(A)
milliampere	(mA)
nanoampere	(nA)

Units of electric potential

volt	(V)
millivolt	(mV)

Unit of resistance

ohm	(Ω)

[1] The definition of units of radioactivity is given under "Radiopharmaceuticals" (see pages 52-55).

PHYSICAL METHODS