INTRODUCTION

The publication of this, the second volume of the European Pharmacopoeia, marks an important stage in the "progressive elaboration" of a pharmacopoeia common to the countries concerned, as envisaged in the Convention of July 1964 and desired by the eight signatory States.

This volume, like the first, is the result of the patient and energetic efforts of specialists in all our countries who have voluntarily contributed their expert knowledge and the services of their laboratories to the work of the Commission. Its importance lies in the number of monographs it contains and in their quality and variety.

During this stage the Commission has been confronted by a number of often fundamental and difficult administrative and legal problems concerning, for example, methods of biological assay, the use of reference substances and the procedure to be followed for revising monographs.

The style of presentation adopted in the first volume has been retained; however, attention is drawn to the detailed summary of contents included at the beginning of the book, and to the index which is cumulative for the two volumes.

A number of corrections to the texts of the first volume have been included as a separate chapter, except in the case of corrections to reagents: the latter will be found in the Reagents chapter.

The General Notices have been revised and extended and, for convenience, are printed in full in Volume II. They are applicable without distinction to both volumes.

In presenting the nomenclature and structural formulae of chemical substances, the rules of the International Union for Pure and Applied Chemistry have been followed wherever possible. Resonance formulae have not been shown. The stereochemistry of compounds has been shown when this affects their pharmacological activity or when it is justified in connection with the analytical identification of certain isomers.

The chapter on analytical methods has been enlarged, particularly by the introduction of amperometry, fluorimetry and gas chromatography and the application of infra-red spectrophotometry and of thin-layer chromatography in the identification and purity tests of the steroid hormones.

Of the monographs a large proportion has been devoted to antibiotics, steroid hormones and vaccines and immunosera.

When fiducial limits are prescribed, it is intended that a statistical analysis using recognised mathematical techniques shall be applied to the experimental results of the assays. The Commission has decided that it would be useful to publish, for information in the Annex, a section on the statistical interpretation of the results of biological assays, giving examples.

Surgical dressings and ligatures are the subject of a number of monographs which have presented particular problems. It is interesting to note the new system which has been introduced to indicate the diameters of surgical ligatures, using a decimal number which corresponds to the diameter expressed in tenths of a millimetre.

The completion of these monographs has called for a considerable amount of research on the part of the experts: this and the discussions which have taken place in the Commission have been characterised throughout by a real and unanimous desire to arrive at conclusions acceptable to all concerned.

The elaboration of a common Pharmacopoeia is now well advanced: it constitutes an irreversible phenomenon. The work is continuing and it is hoped that in the not too distant future the stage will be reached where the task will consist only of keeping it up to date.

It is with great satisfaction that I associate in my appreciation and thanks the members of the Commission, the members of the Groups of Experts and the officers of the Technical Secretariat, each of whom in his own special sphere has undertaken a heavy task, sometimes hazardous but always exhilarating, and has carried it out with conviction, care and patience, happy through the European Pharmacopoeia, to make his contribution to the building of a united Europe.

CARL STAINIER

Chairman of the Commission 1968-1971

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GENERAL NOTICES

The present volume is complementary to the first volume of the European Pharmacopoeia, published in November 1969. It is published under the same conditions and has the same official status.

These General Notices replace those of Volume I and apply to both volumes.

The word "pharmacopoeia" without qualification means the European Pharmacopoeia (Ph. Eur.)

APPLICATION

For the purposes of the pharmacopoeia a medicine is regarded as being any substance or compound described as possessing curative or preventive properties in relation to human or animal diseases.

Any substance or compound capable of being administered to human beings or animals for purposes of medical diagnosis or in order to restore, correct or modify their organic functions is also regarded as a medicine.

All specifications given in the monographs, with the exception of those included under the heading STORAGE, constitute the definitions of substances or articles intended for human or veterinary use, unless specifically restricted to one or other of these uses. The requirements given under the heading CHARACTERS are to be interpreted in a broad sense and do not comprise analytical standards. Any medicine or article described in a monograph of the pharmacopoeia is only regarded as official if it conforms to these specifications.

The requirements are not framed to take account of all possible impurities. It is not to be presumed, for example, that an unusual impurity which is not detectable by means of the prescribed tests is tolerated if common sense and good pharmaceutical practice require that it be absent.

The inclusion in the pharmacopoeia of substances subject to protection by patents does not confer or imply any right to the use of such patents by any person or persons other than the proprietors of the patent concerned.

The text of the Convention on the Elaboration of a European Pharmacopoeia deals only with the elaboration of the pharmacopoeia and its entry into force in the member States. The requirements of the pharmacopoeia form an integral part of national law and international agreements without creating contradictions.

TITLES OF MONOGRAPHS

The titles of monographs in the pharmacopoeia are in Latin and under these are given the names in English or French in the respective versions. As far as possible the International Non-Proprietary Names (INN) recommended by the World Health Organisation have been used.

Each national authority may add in its pharmacopoeia any synonyms commonly used in its country.

In the titles of monographs on aqueous solutions and alcoholic tinctures the nature of the solvent is not mentioned. For solutions and tinctures prepared with other solvents, the nature of the solvent is stated.

ATOMIC WEIGHTS

The atomic weights adopted are those of the International Table of Atomic Weights published in 1967 by the International Union for Pure and Applied Chemistry. The figures represent the average atomic weights of the natural mixtures of isotopes with reference to the relative atomic mass of the isotope $^{12}C = 12$.

MOLECULAR WEIGHTS

The molecular weights of compounds (or, where appropriate, atomic weights) are given at the beginning of the monographs. The number of significant figures in these molecular weights is determined as follows: first, the atomic weights, or multiples thereof, are added together using all the figures of the International Table of Atomic Weights; the total is then rounded off to four significant figures if the initial digit is 1, 2, 3, 4 or 5, or to three significant figures if the initial digit is 6, 7, 8 or 9; the last figure is increased by one when the part rejected exceeds one half-unit. When the part rejected is equal to or less than a half-unit, the last figure taken is not modified. The molecular weights shown in the monographs are theoretical values and neither these nor the molecular and graphic formulae constitute analytical standards for the substances described.

EQUIVALENT WEIGHTS

The equivalent weights stated in the monographs are calculated from the molecular weights without rounding off the numbers. The result is then rounded off in the manner described under MOLECULAR WEIGHTS.

CONTENT OF A CHEMICAL SUBSTANCE

Where the monograph does not state an upper limit for content, it is understood that this content shall be 100·5 per cent, determined by the method of assay prescribed in the monograph.

SOLUBILITY, SOLUTIONS AND SOLVENTS

In stating the solubilities of chemical substances, the term "soluble" is sometimes used in a general sense, irrespective of concomitant chemical changes. Statements of solubility which are expressed as a precise relation of weight of dissolved substance to volume of solvent are intended to apply at 20°. Statements of approximate solubilities for which no figures are given are in-

tended to apply at room temperature, and are indicated by a descriptive phrase. The following table indicates the meanings of such phrases:

Descriptive terms	Approximate quantities of solvent by volume for 1 part of solute by weight
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

Solutions Where the name of the solvent is not mentioned, the term " solution " indicates a solution in water.

Water Where the term " water " is used with reference to identification, tests and assays and for reagents, it is to be interpreted as referring to water prepared by distillation and complying with the requirements in the monograph on Aqua Purificata.

Ethanol and Alcohol The term " ethanol " without other indication means absolute ethyl alcohol. The term " alcohol " used without other indication means alcohol 95 per cent v/v. Where other strengths are intended the term " alcohol " is used followed by the statement of the strength.

Neutrality of solvents used in tests and assays When a blank test is not prescribed, solvents must be previously neutralised using the indicator used in the test or assay concerned.

EXPRESSION OF CONCENTRATION

In defining concentrations, the expression " per cent " is used according to circumstances with one of four meanings.

— Per cent w/w (percentage, weight in weight) expresses the number of grammes of substance in 100 grammes of final product.

— Per cent w/v (percentage, weight in volume) expresses the number of grammes of substance in 100 millilitres of final product.

— Per cent v/v (percentage, volume in volume) expresses the number of millilitres of substance in 100 millilitres of final product.

— Per cent v/w (percentage, volume in weight) expresses the number of millilitres of substance in 100 grammes of final product.

MELTING POINT

Melting points are determined by the capillary method, unless otherwise prescribed in the monograph.

TESTS AND ASSAYS

The tests and assays described are the official methods upon which the standards of the European Pharmacopoeia are based.

When a monograph on a biological substance refers to a strain, a test, a method, a substance, etc., using the qualifications " suitable " or " appropriate " without further definition in the text, the choice of such strain, test, method, substance, etc. is made in accordance with any national regulations or international agreements affecting the subject concerned.

Quantities. In stating the quantity of a substance to be examined in an assay, an appropriate amount is prescribed in the monograph. The word " about " in this context is used to indicate that the amount used should be within ± 10 per cent of the quantity specified. The quantity to be used is accurately measured with the appropriate precision and the result is calculated with reference to it.

This precision is indicated by the number of decimals in the text, for example:

— 1·0 indicates a value not less than 0·95 and not greater than 1·05
— 1·00 indicates a value not less than 0·995 and not greater than 1·005
— 1·000 indicates a value not less than 0·9995 and not greater than 1·0005.

The results of assays are calculated to one place of decimals more than that indicated in the monograph and then rounded to the required number of decimal places. If the last figure calculated is 5, 6, 7, 8, or 9, the preceding figure is increased by 1; if it is below 5, it is deleted.

Limits of impurity The quantity of impurity represented by the limit tests is expressed in parts per million (ppm). When the limit is greater than 500 ppm, it is expressed as a percentage. These limits are approximations only and are related to the conditions of the test.

STANDARDS AND REFERENCE SUBSTANCES

Certain tests and assays are carried out using a Standard or a Chemical or Biological Reference Substance.

(a) Chemical Reference Substances (CRS)

(b) International Biological Standards
International Biological Reference Preparations
These substances are established by the World Health Organisation.

(c) European Pharmacopoeia Biological Standards
European Pharmacopoeia Biological Reference Preparations
These substances are established under the authority of the European Pharmacopoeia Commission.

International Biological Standards and International Biological Reference Preparations are supplied only to national authorities and to the Technical Secretariat of the European Pharmacopoeia, both of which may prepare and issue under their own authority similar reference substances standardised in relation to the International Substances.

Biological Standards and Biological Reference Preparations and Chemical Reference Substances of the European Pharmacopoeia are issued by the Technical Secretariat[1]. They are the official reference substances to be used in cases of arbitration within the States party to the Convention.

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(1) Technical Secretariat, The European Pharmacopoeia Commission, Council of Europe, 67 - Strasbourg, France.

Local laboratory standards may be prepared for use in routine analysis in place of the designated reference substances, provided they are standardised with reference to those issued by the Technical Secretariat.

DRYING

The term " dried to constant weight " means that two consecutive weighings do not differ by more than 0·0005 g, the second weighing following an additional hour of drying, unless otherwise prescribed in the monograph.

When the result of a test or assay is referred to the " anhydrous " or the " dried " substance, the determination of water content or of the loss on drying is carried out by the method prescribed under the heading WATER or LOSS ON DRYING respectively in the monograph concerned.

For dried vegetable drugs, the sulphated ash, water soluble matter, alcohol soluble matter, water content, content of volatile substances and alkaloid content are calculated with reference to the air-dried drug, unless otherwise prescribed in the monograph.

STORAGE

The substances and preparations described are stored in such a way as to prevent contamination and, as far as possible, deterioration. Where special conditions of storage are necessary, they are prescribed in the monograph.

LABELLING

In general, the labelling of medicines is controlled by national regulations and international agreements. In certain cases, necessary information which must be stated on the label is specified in the monograph.

UNITS OF MEASUREMENT

Length

— metre : m
— decimetre : dm
— centimetre : cm
— millimetre : mm = 10^{-3} m
— micrometre : µm = 10^{-6} m
— nanometre : nm = 10^{-9} m

Volume

— litre : l
— millilitre : ml
— microlitre : µl

Mass

— kilogramme : kg
— gramme : g
— decigramme : dg
— centigramme : cg
— milligramme : mg
— microgramme: µg

Pressure

The pressure is expressed in Torr.

— 1 Torr is the pressure exerted by a column of 1 mm of mercury.

Temperature

All temperatures are expressed in degrees centigrade (Celsius).

General expressions used to describe temperatures	
In deep-freeze	-15° to 0°
In a refrigerator	0° to 6°
Cold or cool	6° to 15°
Room temperature	15° to 25°

In the absence of any specific indications, the term " water bath " means a bath of boiling water. This may be replaced by any other means of heating which gives a temperature of about, but not higher than, 100°.

ABBREVIATIONS AND SYMBOLS OF PHYSICAL CONSTANTS

Acidity or alkalinity : pH

Melting point : mp

Boiling point : bp

Relative density	: d_{20}^{20}
Viscosity	: η
Optical rotation at 20°	: α_{λ}^{20}
Specific optical rotation	: $[\alpha]_{\lambda}^{t}$
Wavelength	: λ
Extinction	: E
Specific extinction	: $E_1^{1\ \text{per cent}}$ $_{1\ \text{cm}}$
Coefficient of molar extinction	: ε
Refractive index	: n_{λ}^{t}

OTHER ABBREVIATIONS

AW Atomic Weight

MW Molecular Weight

ppm Parts per million (ppm is expressed by weight in weight w/w, unless otherwise indicated).

R Substance or solution defined under " Reagents ".

RV Substance or solution used as a standard in " Volumetric analysis ".

Rf Used in chromatography to indicate the relation between the distances traversed by the substance and the solvent front.

CRS Chemical Reference Substance of the European Pharmacopoeia.

I.U. International Unit.