European Pharmacopoeia

4th Edition
2002

EUROPEAN PHARMACOPOEIA

Fourth Edition

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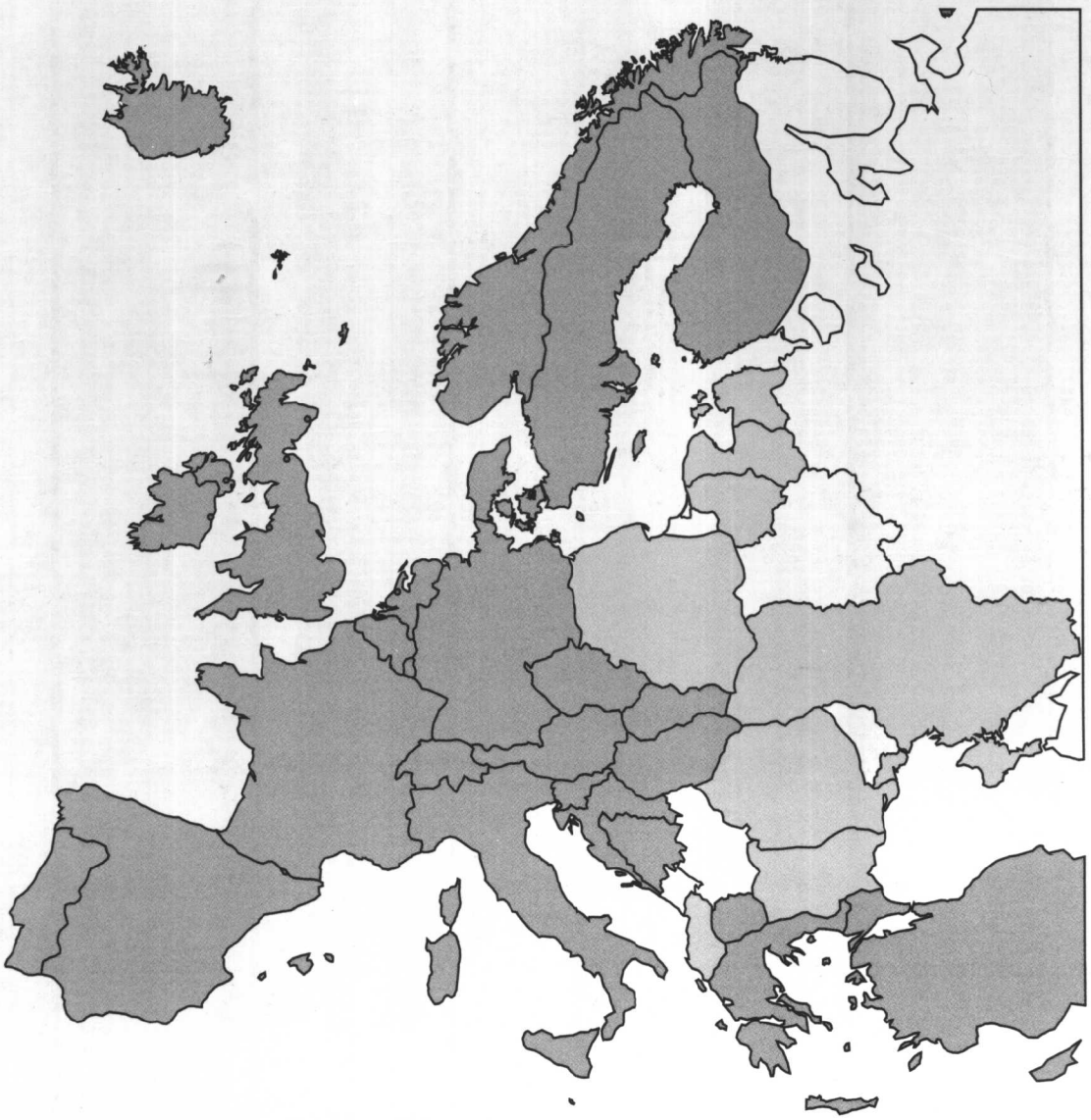

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** All reference substances required for application of the monographs are available from the EDQM. A catalogue of reference substances is available on request; this catalogue is included in the Pharmeuropa subscription; the catalogue can also be consulted on the EDQM internet site.

European Pharmacopoeia

Fourth Edition

published 20th September 2001

replaces the Third Edition on 1 January 2002

This publication constitutes the Fourth Edition of the European Pharmacopoeia. It will be complemented by 2 **non-cumulative** supplements in 2002 and by three supplements in each of the subsequent years.

If you are using the Fourth Edition at any time later than 1 April 2002, make sure that you have all the published supplements and consult the index of the most recent volume to ensure that you use the latest versions of the monographs and general chapters.

European Pharmacopoeia

CD-ROM

The Fourth Edition is also available as a CD-ROM with all the monographs and general chapters contained in the book. With the publication of each supplement the CD-ROM is replaced by a new fully updated version.

Pharmeuropa

Quarterly Forum Publication

Pharmeuropa contains preliminary drafts of all new and revised monographs proposed for inclusion in the European Pharmacopoeia and gives an opportunity for all interested parties to comment on the specifications before they are finalised. Pharmeuropa also contains information on the work programme, the list of Certificates of Suitability of the Monographs of the European Pharmacopoeia issued by the EDQM, scientific articles on pharmacopoeial matters and other articles of general interest. Pharmeuropa is available on subscription from the EDQM (see opposite).

International Harmonisation

Refer to information given in chapter *5.8. Pharmacopoeial Harmonisation.*

KEY TO MONOGRAPHS

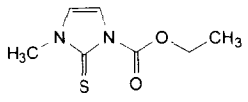
Monograph is applicable from 1 January 2002

01/2002:0884

CARBIMAZOLE

Monograph reference number

Carbimazolum



$C_7H_{10}N_2O_2S$ M_r 186.2

DEFINITION

Ethyl 3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazole-1-carboxylate.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Application of the first and second identification is defined in the General Notices (chapter 1)

Appearance: white or yellowish-white, crystalline powder.

Solubility: slightly soluble in water, soluble in acetone and in alcohol.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 122 °C to 125 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *carbimazole CRS*

Chemical reference substance available from the Secretariat (see inside front cover)

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 10 mg of *carbimazole CRS* in *methylene chloride R* and dilute to 10 ml with the same solvent.

Plate: *TLC silica gel GF_{254} plate R.*

Reagents described in chapter 4

Mobile phase: *acetone R*, *methylene chloride R* (20:80 *V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air for 30 min.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in a mixture of 50 ml of *water R* and 0.05 ml of *dilute hydrochloric acid R*. Add 1 ml of *potassium iodobismuthate solution R*. A red precipitate is formed.

TESTS

Impurity A and other related substances. Liquid chromatography (*2.2.29*).

Reference to a general chapter

Test solution. Dissolve 5.0 mg of the substance to be examined in 10.0 ml of a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*. Use this solution within 5 min of preparation.

Reference solution (a). Dissolve 5 mg of *thiamazole R* and 0.10 g of *carbimazole CRS* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 100.0 ml with the same mixture of solvents. Dilute 1.0 ml of this solution to 10.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (b). Dissolve 5.0 mg of *thiamazole R* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 ml with the same mixture of solvents. Dilute 1.0 ml of this solution to 100.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Column:

- *size*: *l* = 0.15 m, Ø = 3.9 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R*, *water R* (10:90 *V/V*).

Flow rate: 1 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl.

Run time: 1.5 times the retention time of carbimazole.

Retention time: carbimazole = about 6 min.

System suitability: reference solution (a):

- *resolution*: minimum 5.0 between the peaks due to impurity A and carbimazole.

Limits:

- *impurity A*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
- *any other impurity*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

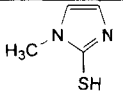
Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator over *diphosphorus pentoxide R* at a pressure not exceeding 0.7 kPa for 24 h.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in *water R* and dilute to 500.0 ml with the same solvent. To 10.0 ml add 10 ml of *dilute hydrochloric acid R* and dilute to 100.0 ml with *water R*. Measure the absorbance (*2.2.25*) at the maximum at 291 nm. Calculate the content of $C_7H_{10}N_2O_2S$ taking the specific absorbance to be 557.

IMPURITIES



A. 1-methyl-1*H*-imidazole-2-thiol (thiamazole).

List of impurities controlled by the tests (see chapter 1 General Notices)

IMPORTANT NOTICE

GENERAL MONOGRAPHS

The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see *1. General Notices*, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia.

Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the section General Monographs (unless otherwise stated). This list is updated where necessary and republished in each Supplement.

Allergen products (1063)

Dosage Forms monographs
(published in the section Dosage Forms)

Extracts (0765)

Herbal drug preparations (1434)

Herbal drugs (1433)

Herbal teas (1435)

Homoeopathic preparations (1038)
(published in the Homoeopathy section)

Immunosera for human use (0084)

Immunosera for veterinary use (0030)

Products of fermentation (1468)

Products with risk of transmitting agents of animal spongiform encephalopathies (1483)

Radiopharmaceutical preparations (0125)

Recombinant DNA technology, products of (0784)

Substances for pharmaceutical use (2034)

Tinctures (0792)

Vaccines for human use (0153)

Vaccines for veterinary use (0062)

Vegetable fatty oils (1579)

I. PREFACE

It gives me great pleasure to introduce this Fourth Edition of the European Pharmacopoeia. During the period since the Convention establishing the European Pharmacopoeia was signed in 1964, the contents of the Pharmacopoeia which represents the output from all the activities of the European Pharmacopoeia Commission have grown to about 2000 monographs. Since all the technical requirements have to be adopted by unanimous agreement between all parties to the Convention (currently 28), this is a remarkable and unique achievement.

The First Edition was published over a period of about thirteen years in a series of volumes and supplements, the last of which appeared in 1977. The Second Edition covered the period from 1980 to 1996 and was presented as a series of loose-leaf fascicules on an approximately annual basis. This presentation became increasingly unwieldy as individual monographs were revised. Consequently the Commission decided that the format of the Third Edition would change to a main volume, that came into effect in 1997, to which were added a series of cumulative annual supplements until 2001. This allowed the reader to find all current requirements by consulting only two volumes. However, the annual supplement with a single date of implementation each year has proved to be somewhat inflexible. It has been found that rapid developments in regulatory requirements and the need for rapid revision of existing monographs, as well as implementation of some new ones, could not be achieved as promptly as necessary.

For the Fourth Edition, therefore, this main volume, effective from 1st January 2002, will be added to by means of three supplements per year, implementing decisions from each of the three sessions per year of the European Pharmacopoeia Commission about one year after the meeting. This speeds considerably the implementation of

[illegible] during the period between the Third and Fourth Edition[illegible]

individual monographs is difficult especially with the implementation of the new general monograph for *Substances for pharmaceutical use*. The Commission has decided, therefore, to remove almost all cross-references and instead provide a list of general monographs in the cover pages, together with a running footer directing the reader to this list and the relevant general notice. Thus the user is able to identify the general monograph or monographs that are relevant in a given case.

Another development has been the introduction of a general monograph on *Products with risk of transmitting agents of animal spongiform encephalopathies*. In view of the public health concerns surrounding this issue, the Commission has implemented the CPMP/CVMP Note for Guidance on minimising the risk of transmission of animal spongiform encephalopathies as a general chapter *5.2.8*. The monograph defines the scope of products covered and then refers to the general chapter under a Production section. In this way, the Note for Guidance has been given mandatory status not only within the countries in the European Community but also in other countries party to the Convention on the European Pharmacopoeia. The availability of the general monograph has been an essential factor in allowing application of the procedure for *Certification of compliance with monographs of the European Pharmacopoeia* to affected products whether or not they are subject to an individual monograph. By this means, it has been possible to employ the Certification procedure to allow manufacturers to comply with the Directives 1999/82/EC and 1999/104/EC, relating to human and veterinary medicines respectively, that require demonstration of minimisation of risk for the products concerned by various dates in 2000 and 2001.

During the period between the Third and Fourth Editions, steps have been taken to implement achievements in

Harmonisation of a different kind has also been achieved during the course of preparation of the Fourth Edition of the European Pharmacopoeia. The programme for adaptation of national monographs began in 1992 as a means of harmonising European requirements for a substance for which one or more national pharmacopoeial monographs exist. With the publication of the Fourth Edition, monographs are now included for all substances previously subject to three or more individual national monographs as well as for more than 85% of all those subject to two national monographs. During the life of the Fourth Edition it is expected that the remainder will be brought through as harmonised European requirements. The substances for which there is one national monograph but none in the European Pharmacopoeia will be introduced where priority and demand justify the work. For some minor products of limited interest, the preparation of European requirements may not be necessary.

The procedure for adaptation of national monographs was the second mechanism for developing monographs, in addition to the usual route of drafting by a Group of Experts. In the last few years a so-called 'third way' procedure has also been employed for drafting monographs. By this procedure, a manufacturer collaborates with a national authority to carry out the preliminary stages of drafting and checking requirements experimentally. The draft is then reviewed by the Group also responsible for the adaptation procedure, then published in Pharmeuropa and processed in the usual way. Although more limited use has been made of this procedure than anticipated, it has proved successful and a modified and expanded version is under consideration for the preparation of the Fifth Edition.

Expansion of the contents of the European Pharmacopoeia has brought with it a greatly increased work-load for the Secretariat, Groups of Experts and Working Parties and the European Pharmacopoeia Commission. The growing responsibilities of the Secretariat in recent years, which include the Certification procedure, begun as a pilot phase in 1992 and fully adopted in 1994, the programme for Biological Standardisation to prepare reference materials and to improve analytical methods for these complex medicines, and the establishment and operation of the network of Official Medicines Control Laboratories, have been reflected in the decision of the Council of Europe to establish the European Directorate for the Quality of Medicines (EDQM). The main activity of the Directorate remains preparation of the European Pharmacopoeia but the wider role of the Secretariat is now formally recognised.

The staff numbers of the Directorate have increased to absorb the greater work-load. Together with the growing numbers of delegations and observers to the Commission and the larger number and size of meetings, the point has been reached that the 'new' premises are fully occupied and are no longer adequate for their purpose. A decision has been taken in principle by the Council of Europe to provide enlarged premises, a decision for which the delegations to European Pharmacopoeia Commission are very grateful. However, the funding and selection of site and building have yet to be concluded. It is to be hoped that this initiative can be supported by the Member States to allow the necessary further decisions to be taken rapidly so that the work and role of EDQM as a vital and influential partner in the European medicines system can continue to expand.

The achievements of the European Pharmacopoeia Commission and the European Directorate for the Quality of Medicines during the past five years would not have been possible without the enthusiasm, dedication and participation of many people.

The role of the Secretariat has been critical in discharging effectively all their responsibilities in obtaining and processing information, in undertaking the laboratory work necessary to support the experts and to obtain and prepare all the reference materials necessary to allow the requirements in the monographs to be tested, and in the timely and efficient production of all the publications including working documents, *Pharmeuropa*, the European Pharmacopoeia itself and the expanding electronic systems. In addition there has been a growing programme of conferences and specialist meetings, efficiently and effectively organised, whose proceedings have appeared in a timely manner so providing a valuable resource for the work of the Commission. To all the staff of EDQM, both those in the foreground as participants at meetings and secretaries of Groups and those in the background in the laboratory and offices, the European Pharmacopoeia Commission owes an enormous debt of gratitude for their dedication and commitment given willingly and cheerfully.

The Commission is equally indebted to the more than 450 experts from government, industry and academic establishments who have given their time and expertise to the work of the Groups and Working Parties. This work is given voluntarily and in addition to often very heavy work schedules and commitments. Without their contributions, the technical output of the Commission would be greatly diminished. Their effectiveness depends on support from the Secretariat and also on the contribution of the Chairmen of the Groups and Working Parties who have the onerous responsibility of guiding the work and bringing it to fruition. The European Pharmacopoeia Commission is most grateful to all the Chairmen for their contributions within their Groups and also for their wise advice and counsel to the Commission itself.

During the past three years it has been my privilege and honour to serve the European Pharmacopoeia Commission as its elected Chairman. My task has been lightened by the enormous amount of support, goodwill and friendship shown by the members of the Commission, other experts, staff of EDQM and in particular the Director, Dr Artiges, and her deputies as Secretary to the European Pharmacopoeia Commission, firstly Dr Schorn and latterly Mr Castle. My heartfelt thanks go to them all. Together we have achieved much but there is still more to do. With a new Presidium, a review of the working systems and Group structure, and renewed work programme, the future direction towards the Fifth Edition looks exciting and I wish all those taking part in this stimulating and rewarding task every success.

Prof. Derek Calam

Chairman of the European Pharmacopoeia Commission

II. INTRODUCTION

The European Pharmacopoeia is prepared under the auspices of the Council of Europe in accordance with the terms of the *Convention on the elaboration of a European Pharmacopoeia* (European Treaty Series No. 50) as amended by the Protocol to the Convention (European Treaty Series No. 134), signed by the Governments of Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, "the Former Yugoslav Republic of Macedonia", Turkey, the United Kingdom of Great Britain and Northern Ireland, and by the European Community.

The preparation of the Pharmacopoeia is the responsibility of the *European Pharmacopoeia Commission* ("the Commission"), appointed in accordance with Article 5 of the above-mentioned Convention. It is composed of delegations appointed by the Contracting Parties. Each delegation consists of not more than three members chosen for their competence in matters within the functions of the Commission.

Observers from non-Member States and international organisations are admitted to Sessions of the Commission in accordance with the Rules of Procedure.

The functions of the Commission established by Article 6 of the Convention as amended by the Protocol are:

Article 6

"Subject to the provision of Article 4 of the present Convention, the functions of the Commission shall be:

(a) to determine the general principles applicable to the elaboration of the European Pharmacopoeia;

(b) to decide upon methods of analysis for that purpose;

(c) to arrange for the preparation of and to adopt monographs to be included in the European Pharmacopoeia and;

(d) to recommend the fixing of the time limits within which its decisions of a technical character relating to the European Pharmacopoeia shall be implemented within the territories of the Contracting Parties."

In accordance with the terms of the Convention, the Contracting Parties undertake to take the necessary measures to ensure that the monographs of the European Pharmacopoeia shall become the official standards applicable within their respective territories.

PURPOSE OF THE EUROPEAN PHARMACOPOEIA

The purpose of the European Pharmacopoeia is to promote public health by the provision of recognised common standards for use by health-care professionals and others concerned with the quality of medicines. Such standards are to be of appropriate quality as a basis for the safe use of medicines by patients and consumers. Their existence:

- facilitates the free movement of medicinal products in Europe;
- ensures the quality of medicinal products exported from Europe.

European Pharmacopoeia monographs and other texts are designed to be appropriate to the needs of:

- regulatory authorities;
- those engaged in the control of quality;
- manufacturers of starting materials and medicinal products.

The European Pharmacopoeia is widely used internationally. It is the intention of the Commission to work more closely with users of the Pharmacopoeia in order to satisfy better their needs and facilitate their co-operation. To this end improved procedures are being developed for obtaining advice on priorities for elaborating new monographs and enhancing the quality of the Pharmacopoeia.

TECHNICAL SECRETARIAT AND LABORATORY

The European Pharmacopoeia Commission has a Technical Secretariat with scientific and administrative staff, situated in Strasbourg. The European Pharmacopoeia Laboratory is situated within the Secretariat and, amongst other duties, is in charge of the establishment and monitoring of all reference materials needed for the monographs of the Pharmacopoeia. The Technical Secretariat is an administrative division of the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe.

GENERAL PRINCIPLES

General rules for interpretation of the texts of the Pharmacopoeia are given in the General Notices. The following information should also be noted.

The general principles applied in the elaboration of monographs of the European Pharmacopoeia are laid down in technical guides. The *Technical Guide for the Elaboration of Monographs*, which deals mainly with monographs on chemical substances, is available as a special issue of *Pharmeuropa* (see below under Publications). Other technical guides are being prepared to deal with aspects specific to monographs on other groups of products. The principles applied are revised from time to time without complete retrospective application so that monographs published already may not always follow the latest recommendations.

The procedures for the tests and assays published in the individual monographs have been validated, according to current practice at the time of their elaboration, for the purpose for which they are intended.

It is recognised that general chapters are used elsewhere than in the monographs of the Pharmacopoeia; in these circumstances users are recommended to consult the Technical Guide which gives extensive information on the application of many of the methods.

General monographs. The Pharmacopoeia contains a number of general monographs covering classes of substances or preparations or types of dosage forms. In the Third Edition, the scope of many general monographs was limited to substances and preparations for which there was a specific monograph in the Pharmacopoeia. With the implementation of the Fourth Edition, this situation will change and general monographs will apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the Pharmacopoeia.

During the course of the Third Edition, a number of new general monographs were introduced and the Fourth Edition contains, *inter alia* a new general monograph *Substances for Pharmaceutical Use (2034)*, whose provisions affect many monographs on individual active substances and excipients. In previous editions, references to relevant general monographs were included in the individual monographs concerned, for example those on immunosera, radiopharmaceuticals and vaccines. These references were not completely systematic. If the practice were to be continued the increasing number of general monographs would require an excessively large number of cross-references. Moreover, since the application of some general monographs depends on the manufacturing process and full information on this is not necessarily available to the Commission, the cross-references would in all likelihood be incomplete. In view of these considerations, the Commission has decided to delete virtually all the cross-references, exceptions being made where it is necessary to clarify the application of a general monograph. To aid users in identifying the general monographs that apply, a list of general monographs is given in the cover pages of the 4th Edition and its Supplements, and via an alert for the electronic versions. It is essential therefore that users familiarise themselves with this list and the monographs concerned before using the monographs on individual substances or preparations.

The general monograph on *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)* presents a particular difficulty in regard to its application. In the 3rd Edition, a number of monographs on substances concerned had a reference to this general monograph but these references were not complete, nor is it an easy matter to identify all substances concerned without a full knowledge of their method of preparation or synthesis. Moreover, the general monograph also applies to substances that are used during manufacture but not covered by an individual monograph. The previous references have therefore been deleted and to aid users in identifying substances potentially within the scope of the general monograph a list has been drawn up of substances that may be or are concerned; this list is published for information in *Pharmeuropa* and is posted on the EDQM web site (http://www.pheur.org). It has to be emphasised that the list is *not exhaustive* and it remains the responsibility of the user to ascertain whether a given substance, even if not included in the list, is within the scope of the general monograph.

Use of animals. In accordance with the *European Convention on the protection of animals used for experimental and other scientific purposes (1986)*, the Commission is committed to the reduction of animal usage, wherever possible, in pharmacopoeia testing and encourages those associated with its work to seek alternative procedures. An alternative or modified method is adopted by the Commission once it has been clearly demonstrated that it offers satisfactory control for pharmacopoeial purposes.

Hydrates. With the publication of the Fourth Edition, the policy on monograph titles for hydrated forms has been changed. For all monographs published for the first time in the Fourth Edition, the degree of hydration, where applicable, will be indicated in the monograph title. In previous editions, the policy was to indicate the degree of hydration only where several forms exist. If a monograph on both an anhydrous and a hydrated form of a given substance are published, then "anhydrous" will be included in the title of the relevant form. In order to avoid placing an unnecessary burden on manufacturers for relabelling and similar work, this policy will not be applied retrospectively to monographs published already, unless there is reason to believe that this is justified as a public health measure, notably for safety reasons where the substance contains a large proportion of water.

Chiral substances. Monographs on chiral substances that describe a particular enantiomer have a test to confirm enantiomeric purity, usually by measurement of optical rotation. Monographs that describe racemates are, in this respect, heterogeneous because of changes of policy during the 3rd Edition. Older monographs do not always have a test to show racemic character. During the course of the 3rd Edition, a test for racemic character was included in all new and revised monographs on racemates, using measurement of optical rotation. When it was shown that in many cases a test for optical rotation, even with narrow limits

around zero rotation, was not necessarily sufficiently discriminating because of the low specific optical rotation of the enantiomers, the Commission modified the policy applied. A test for racemic character using optical rotation is now included only if there is information on the specific optical rotation of the enantiomers that indicates that such a test would be discriminating in terms of enantiomeric purity. If other techniques, such as circular dichroism, can serve the intended purpose, they will be prescribed instead of optical rotation.

Polymorphism. Where a substance may show polymorphism, this is usually stated under Characters. In general, no particular crystalline form is required in monographs; exceptionally, in a few monographs, the crystalline form required is specified, for example, via an infrared absorption spectrophotometric identification test where the spectrum is required to be recorded using the substance in the solid state without recrystallisation, the chemical reference substance (CRS) provided being of the required crystalline form. However, for substances other than these exceptional cases, depending on the use of a given substance in a dosage form, it may be necessary for a manufacturer to ensure that a particular crystalline form is used. The information given under Characters is intended to alert users to the need to evaluate this aspect during the development of a dosage form. The monograph on *Substances for pharmaceutical use (2034)* should also be consulted.

Specificity of assays. For the elaboration of monographs on chemical substances, the approach generally preferred by the Commission is to provide control of impurities via a well designed Tests section rather than by the inclusion of an assay that is specific for the active moiety. It is therefore the full set of requirements of a monograph that is designed to ensure that the product is of suitable quality.

Impurities. Many monographs, particularly those recently published, now have appended a list of known or potential impurities shown to be controlled by the tests. Known impurities (also referred to as 'actual impurities') are those that have been observed in batches of the substance; potential impurities are those that although they might be expected to occur, from knowledge of the manufacturing process, have not in fact been observed in batches during elaboration of the monograph. This list is intended to facilitate use of the monograph, especially during the licensing process for medicines (see *Impurities in new drug substances*, ICH tripartite note for guidance, May 1995 and subsequent revisions). A series of impurities for a substance obtained by a given manufacturing process may be compared with the list to establish whether the monograph provides sufficient control. It is the intention of the Commission to include such lists wherever possible in new monographs and to add them to existing monographs during revision.

Except where required for the application of the monograph, in which case the name is followed by "CRS", impurities are not provided as reference substances nor can they be provided for experimental purposes.

Residual solvents. The requirements for residual solvents are given in the monograph *Substances for pharmaceutical use (2034)* together with the general chapters *2.4.24 Identification and control of residual solvents* and *5.4 Residual solvents*. Thus all active substances and excipients are subject to relevant control of residual solvents, even where no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic.

Reference materials. Where necessary for application of a monograph, reference materials are established and provided to users. These reference materials are chosen for their suitability for the purposes stated in the monograph and are not necessarily suitable for other uses. Any necessary information for proper use is given, for example a declared content, but no complete certificate of analysis is provided since this is not relevant for the intended use. No expiry date is attributed to reference materials, which are subjected to regular periodic monitoring to ensure their continued suitability. Where an assigned value for a given attribute, for example chemical content, is provided, no uncertainty for the assigned value is indicated. The reference materials are provided to enable the analyst to determine compliance or otherwise with a monograph. The uncertainty of an assigned value is not to be taken into account when judging compliance, since the uncertainty is already allowed for in the prescribed limits.

Medical devices. All editions of the Pharmacopoeia have contained monographs on articles that are regarded as medical devices. For Member States of the European Union, a unified framework for standardisation of medical devices is now provided by a Directive (93/42/EEC). Following an agreement between the various parties involved, the Commission has decided that the monographs on medical devices will be deleted once standards have been developed as foreseen by the Directive. Specifications included in the section on containers will be adapted or, in some instances, deleted, to take account of future standards developed within the framework of the Directive. The monographs on surgical sutures are to remain in the Pharmacopoeia but they have been modified to conform to the requirements of the Directive and are now to be seen as standards of the type foreseen there. This adaptation of the monographs has involved deletion of some monographs on specific types of sutures in favour of a more general approach.

Homoeopathic preparations. A general monograph on homoeopathic preparations was added to the Pharmacopoeia during the Second Edition. In the Fourth Edition, a number of monographs on substances used in homoeopathic preparations are also included and further monographs are in preparation. All of these texts have been grouped in a separate section. It is understood that when the same substance is used in both homoeopathic and other preparations then the monograph in the main body of the Pharmacopoeia applies.

Patents. The description in the Pharmacopoeia of articles subject to protection by patent does not confer or imply any right to the use of such patents by any person or persons other than the proprietors of the patents concerned.

Protected species. Monographs, notably those on herbal drugs, may cover material obtained from protected species. Inclusion of these monographs is without prejudice to the provisions for protection of these species by national and international law.

CERTIFICATION PROCEDURE

A procedure for the certification of suitability of monographs of the Pharmacopoeia with respect to control of the purity of a product from a given source has been established [see Public Health Committee (Partial Agreement) Resolution AP-CSP (99) 4 or any subsequent revision available from EDQM and on the web site] as an aid to the use of monographs in applications for marketing authorisation. The certification procedure has recently been extended to cover transmissible spongiform encephalopathy (TSE) risk. Certificates may be granted with respect to published monographs. Details of the operation of this scheme are available from the Secretariat and on the EDQM web site (http://www.pheur.org). A list of certificates granted is published in *Pharmeuropa* and on the EDQM web site.

PUBLICATIONS

The **European Pharmacopoeia** is available in English and French versions in the form of a book with three supplements per year, and as a CD-ROM.

Pharmeuropa, the European Pharmacopoeia Forum, is published four times per year as an aid in the elaboration of monographs and as a vehicle for information on pharmacopoeial and related matters. It is available on subscription from EDQM.

Web site. Information on activities and many other aspects of the European Pharmacopoeia is to be found on the EDQM web site (http://www.pheur.org).

Implementation. The date on which monographs are to be implemented is fixed by a resolution of the Public Health Committee (Partial Agreement) of the Council of Europe, following a recommendation by the Commission. This date is usually about six months after publication. Where a monograph is to be implemented at a date earlier than the next publication date of the Pharmacopoeia or a supplement, a Resolution of the Public Health Committee gives the full text to be implemented. The text is also published in *Pharmeuropa* for information and posted on the EDQM web site.

Revision programme. Monographs and other texts of the Pharmacopoeia are revised as necessary following a decision of the Commission. Revision proposals are published in *Pharmeuropa.*

INTERNATIONAL HARMONISATION

The European Pharmacopoeia is engaged in a process of harmonisation with the Japanese Pharmacopoeia and the United States Pharmacopeia, within an informal structure referred to as the Pharmacopoeial Discussion Group (PDG). The activities are developed in co-ordination with those of the International Conference on Harmonisation (ICH). Information on the status of harmonised texts is given in chapter *5.8.* Harmonised general chapters have a preliminary statement indicating interchangeability with the other two pharmacopoeias.

III. EUROPEAN PHARMACOPOEIA COMMISSION

COMPOSITION OF THE COMMISSION, LIST OF EXPERTS AND OF THE SECRETARIAT AS OF 28TH FEBRUARY 2001

Chair: Derek H. CALAM **Vice-chairs:** Henning G. KRISTENSEN - Alexandra TSOKA

MEMBERS OF THE COMMISSION

Austria	Kristof LISZKA Ernst LUSZCZAK Andreas MAYRHOFER
Belgium	Luc ANGENOT Jos HOOGMARTENS Paule JACQMAIN
Bosnia-Herzegovina	A. MEHMEDAGIC
Croatia	Dragica BEGIC I. STARESINIC-SERNHORST
Iceland	G. BALDURSDOTTIR I.J. PETERSEN
Ireland	T.A. McGUINN Michael MORRIS Joan O'RIORDAN
Italy	M. CIGNITTI Anna FARINA Graziella OREFICI
Luxembourg	Jacqueline GENOUX-HAMES

"The Former Yugoslav Republic of Macedonia"	N. POPOSKI Angel SIMOV
Turkey	Orhan CANBOLAT Enver IZGÜ
United Kingdom	John A. GOLDSMITH R.C. HUTTON J. M. MIDGLEY
European Commission EMEA	Maurice ROBERT Steven FAIRCHILD

ALTERNATE MEMBERS

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Finland	N. SEVON
France	Thierry BOURQUIN Hendrick Jan DE JONG Corinne SAINT-REQUIER
Germany	Gerhard FRANZ Rainer MOHR M. SCHWANIG
Hungary	Tamas L. PAÀL Ilona TÖRÖK
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Slovenia	Barbara RAZINGER-MIHOVEC
Sweden	Christina GRAFFNER
Switzerland	Eugen WACHBERGER
United Kingdom	Aileen M.T. LEE Marie L. RABOUHANS M. I. ROBERTSON

LIST OF EXPERTS DESIGNATED BY NATIONAL AUTHORITIES TO PARTICIPATE IN THE WORK OF THE EUROPEAN PHARMACOPOEIA (GROUPS OF EXPERTS OR CONSULTATION BY CORRESPONDENCE)

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Jean-Marc AIACHE
Ferhan AKTAN
Concepcion ALONSO
Rolf Josef ALTERMATT-MÜLLER
H. ALTORFER
Denis AMIOT
Hanspeter AMSTUTZ
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D. BAYLOCQ-FERRIER
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T. BRINGHAMMAR
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G. COLLI
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G. DUGO
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A. ECKLE
Kurt EGER
Erling EHRIN
Marianne EK
Mohamed EL HAJJI
Jean-Pierre ETCHEGARAY
Øystein EVENSEN
B. EVERETT
Brigitte EVRARD
José Luis FABREGAS
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Gemma L.M. FEENSTRA-BIELDERS
Peter FEIGENWINTER
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Rainer FENDT
Ton FÖRCH
L. FOSSE
Isabelle FOURASTÉ
Jean-Paul FOURNIER
Bruno FRANK
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GUERIS
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Marylène KOBISCH
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Franciscus Gerardus KORSE
Hilda KÖSZEGI-SZALAI
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