European Pharmacopoeia

5.0

volume 1

01/2005

EUROPEAN PHARMACOPOEIA

FIFTH EDITION

Volume 1

Published in accordance with the
Convention on the Elaboration of a European Pharmacopoeia
(European Treaty Series No. 50)

Council of Europe
Strasbourg

The European Pharmacopoeia is published by the Directorate for the Quality of Medicines of the Council of Europe (EDQM).

ISBN: 92-871-5281-0

Printed in France by Aubin, Ligugé

I. PREFACE

The European Pharmacopoeia was inaugurated in 1964 through the Convention on the Elaboration of a European Pharmacopoeia. The present Fifth Edition of the European Pharmacopoeia is therefore published at the time where the 40th Anniversary of the Pharmacopoeia can be celebrated. The work on the Pharmacopoeia has gone through a remarkable development since the first difficult years. Elaboration and approval of monographs and other texts proceed by an effective and smoothly running process producing public quality standards that keep pace with scientific progresses. The work is remarkable because of its volume - the Fifth Edition presents close to 2000 monographs and other texts - and because all technical requirements have to be adopted by the European Pharmacopoeia Commission by unanimous decision. The monographs of the Pharmacopoeia are legally enforced in the countries being signatories to the Convention on the Elaboration of a European Pharmacopoeia. In addition to the 31 European countries and the European Union now being parties to the Convention, the work on the Pharmacopoeia is followed by 16 European and non-European countries and the WHO as observers. The quality standards of the European Pharmacopoeia have, therefore, an impact on the quality of medicines, which goes far beyond the European region.

The Fifth Edition of the European Pharmacopoeia will become effective on 1st January 2005. Like the Fourth Edition, the present main volumes will be added to by three annual supplements implementing the decisions of each of the three annual Sessions of the European Pharmacopoeia Commission. The presentation of the Pharmacopoeia in a main volume and three annual supplements was initiated by the publication of the Fourth Edition. The intention was to increase the flexibility of the publication scheme and, in particular, to shorten the time span between adoption and enforcement. The shortening of the time span, which has indeed been successful, is possible only thanks to a very flexible attitude by those countries that make national translations of the European Pharmacopoeia monographs. A very low number of rapid revisions implemented in the past three years is another result of the new publication scheme. The Fourth Edition is completed with the publication of Supplement 4.8 since it is impracticable to work with more than the eight supplements. The Commission decided therefore to proceed to the Fifth Edition by consolidation of the Fourth Edition after three years, only. The change from First to Second Edition was caused by major changes in the general methods, while the change from Second to Third Edition was due to the wish to consolidate the work achieved and to change the form of presentation from a loose-leaf format into a main volume followed by annual supplements. The change from Fourth Edition to Fifth Edition continues the work of making the publication of the Pharmacopoeia as user-friendly as possible. It is assumed that the publication of this Fifth Edition will proceed by publication of supplements over the next three years.

The eight founder countries of the Convention realised in 1964 that manufacturing and quality control standards for medicinal products on the European market had to be harmonised for reasons of public health and to facilitate the free movement of medicines. Since 1964 the world has changed and the market for medicinal products has become global. Accordingly, international harmonisation among the three major pharmacopoeias of the world, the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia, has been in progress since 1990 when the Pharmacopoeial Discussion Group was set up to co-ordinate the harmonisation work. In the first years, the work was focused on the harmonisation of monographs on widely used excipients. In the absence of harmonised general methods this was a difficult work, which has now been speeded up by 'harmonisation by attribute' meaning that there may be tests that cannot be fully harmonised before the concerned general method is harmonised. At the stage where the monographs are harmonised, detailed information will be provided in the monograph and in a chapter of the Pharmacopoeia devoted to information on international harmonisation. In recent years, harmonisation of a wide range of general methods has been in progress, partly because of an impact from the International Conference on Harmonisation (ICH). Implementation in the Pharmacopoeia of harmonised general methods, for example for a dosage form specification, needs careful consideration because the specification must be met by products already on the market as well as new products submitted to the regulatory process.

The European Pharmacopoeia Commission supports strongly the international harmonisation. It is not the harmonisation work itself that gives rise to the greatest problems, rather the implementation, which has to be decided in mutual agreement with the registration authorities. The links between the European Pharmacopoeia Commission and European regulators have been steadily strengthened during the years, as have the links with the pharmaceutical manufacturers and their associations.

The new European Directives 2001/82/EC and 2001/83/EC on medicines for human use and veterinary use maintain the mandatory character of the European Pharmacopoeia monographs in the preparation of dossiers for marketing authorisation of medicines, which was instituted in the first directive 75/318/EEC in 1975. It means that the monographs of the European Pharmacopoeia must therefore be updated to keep pace with products on the market, with scientific progress, and with regulatory developments. In the field of active pharmaceutical substances, the European Pharmacopoeia Commission decided at its March 2002 Session that the principles and terminology of the revised ICH Q3A impurity testing guideline *Impurities in new drug substances* should as far as possible be implemented in the monographs on active substances, both new and already published. A change in terminology has been introduced in the Impurities section of monographs published in Supplement 4.6 and later where the term 'specified impurities' is used for impurities that have a defined individual acceptance criterion. A revision of the general monograph *Substances for pharmaceutical use (2034)* was also presented in Supplement 4.6 to implement the threshold values for reporting, identification and qualification of organic impurities in active substances of the revised ICH guideline. For the Fifth Edition a new chapter, *5.10. Control of impurities in substances for pharmaceutical use* has been developed with great assistance by the chairs of the chemical Groups of Experts and other experts from the Commission, and by consultations of the Groups of Experts. The next step will be revision of monographs to ensure that they contain related substances tests and lists on specified and other detectable impurities. Monographs containing a related substances test based on TLC will be considered for revision. Major revision work will thus proceed during the coming years. Hopefully, these revisions can be completed with the publication of the Sixth Edition. In the meantime, users of the Pharmacopoeia must consult the new Chapter *5.10*

on impurity control for the interpretation of monographs published in the past and therefore adapted to a style that has now been changed as described above. Users can in addition find information on representative chromatograms, reagents and columns used in drafting the monographs on the EDQM web site.

The aim of the revision is to ensure that the related substances test and impurity lists reflect the purity of pharmaceutical substances being authorised for the European market. The goal cannot be met without close collaboration with the registration authorities and consultations regarding the specifications for impurities. A procedure for co-operation with the CPMP/CVMP Quality Working Party has been established. It will certainly contribute to ensure the validity of the European Pharmacopoeia monographs. The Certification of Suitability of Monographs of the European Pharmacopoeia might be a valuable source of information on the purity of pharmaceutical substances. The procedure is, however, confidential and will be kept so. In cases where a new impurity is present and calls for revision of the monograph, this can be done only when the manufacturer provides the concerned Group of Experts with the information required for updating.

The growing number of monographs on pharmaceutical substances and the need to keep them updated means a great workload on the Groups of Experts. In 2001, the number of chemical groups was increased and some reallocations of experts between the groups took place. There is, however, still a need for more experts with access to experimental facilities as permanent members of the Groups of Experts or as members on an *ad hoc* basis. In addition to the reorganisation of the system of Groups of Experts and Working Parties the working procedures for the elaboration of monographs have been expanded. In addition to Procedure 1, the traditional elaboration by a Group of Experts, and Procedure 2, adaptation of national monographs, which is now considered almost complete, Procedures 3 and 4 have been established in recent years. Procedure 3 applies to substances produced by only one manufacturer and which are close to patent expiry. The manufacturer and the national pharmacopoeia authority of the country where the substance is produced carry out the preliminary drafting stages and check the requirements experimentally. The draft is reviewed by the working party also responsible for the adaptation procedure and then processed in the usual way by public inquiry. Procedure 3 has proved successful. The Commission decided in 2002 to establish a modified version, Procedure 4. This procedure implies collaboration between the manufacturer of the substance and the EDQM on the draft monograph and experimental checking by the EDQM laboratory and laboratories of national pharmacopoeia authorities before publication for public inquiry. At present, Procedure 4 is run as a pilot project supervised by members of the European Pharmacopoeia Commission. It is the aim of the Commission to have a full coverage of monographs on substances no longer subject to a patent and being present on more than one European market. It requires the collaboration with the innovators and manufacturers of active substances, which has been established during recent years.

The Fifth Edition of the European Pharmacopoeia has a number of excipient monographs containing a non-mandatory section on functionality-related characteristics. The aim is to provide users with a list of physical and physicochemical characteristics that are critical to the typical uses of the concerned excipient, and to provide the general methods required to assess these characteristics. The section does not necessarily give acceptance criteria for the concerned properties; this is usually left as an option for labelling by the manufacturers and where specified, the values are indicative only. This is a new development which is in agreement with the policy of the European Pharmacopoeia Commission to make monographs and other texts appropriate to the needs of regulatory authorities and manufacturers of starting materials and medicinal products. The intention is to provide manufacturers of excipient materials and manufacturers of medicinal products a 'common language', to facilitate the establishment of product-specific specifications, and to provide regulators with data generated by methods that have been independently assessed.

It is the intention of the European Pharmacopoeia Commission to continue the work by drafting sections on functionality-related characteristics in monographs on excipients available in more than one physical grade. Introduction of the concept of functionality-related characteristics presupposes that the relevant general methods are available in the Pharmacopoeia. The European Pharmacopoeia Commission has therefore established a Working Party on synthetic polymers to investigate the need for general methods for polymers and a Working Party on powder characterisation methods. The provision of the needed general methods, for example in the field of powder characterisation, is also included in international harmonisation among the pharmacopoeias.

The achievements of the European Pharmacopoeia Commission during the past three years would not have been possible without the participation of the great number of experts from industry, academia and national authorities, who have given their time and expertise to the work of Groups of Experts and Working Parties. The Commission is indebted to all these experts whose work is given on a voluntary basis. The Commission is equally indebted to the Chairs of the Groups and Working Parties who have the responsibility of guiding the work through and bringing it to term according to tight time limits. The Chairs are thanked for their contributions within the Groups and also for their advice and counsel to the Commission itself.

The work of the European Pharmacopoeia Commission is strongly dependent on an effective Secretariat. The role of the Secretariat is to obtain and process all the information and reports needed for the Groups of Experts, Working Parties and for the Commission, to undertake laboratory work to support the experts and to ensure the availability of all the reference standards needed to allow the requirements in the monographs to be tested. The prompt publication of the Pharmacopoeia main volumes and Supplements and the on-line electronic version is possible, only, because of dedicated and hard work by the staff at the Secretariat.

Along with the growing volume of the European Pharmacopoeia and its adjustment to the regulatory process, the use of the Pharmacopoeia and its interpretation has become rather complex. The journal of the European Pharmacopoeia, *Pharmeuropa*, is a valuable source of information. General chapters for information will appear in the Pharmacopoeia during the publication of the Fifth Edition as a result of the international harmonisation, and because the European Pharmacopoeia Commission has agreed on the elaboration of other chapters for information. During the past two years, the staff at the EDQM have offered training courses to users of the Pharmacopoeia. The Commission is grateful to the EDQM for having taken this initiative, which also strengthens the role of the Pharmacopoeia and the links to its users. The links to users of the Pharmacopoeia are also strengthened by

the frequent workshops and conferences organised by the EDQM. This activity is highly valued by the Commission as it gives the opportunity to Commission members to exchange viewpoints and to discuss new developments with experts from authorities, industry and academia. The EDQM web site is another valuable source for information on the work programme and other activities of the Commission, its Groups and the EDQM.

During the past three years I have had the honour to serve the European Pharmacopoeia Commission as its elected chair. The task has been challenging but, certainly, rewarding because of the insight it has given me into the many quality aspects of the development, manufacture and marketing of medicinal products. I wish to thank members of the European Pharmacopoeia Commission for their support and collaborative spirit within and in between the Sessions of the Commission. The two vice-chairs of the Commission are thanked for good collaboration and support during the years we have joined the Presidium. I will also thank the staff at the EDQM, in particular the secretaries to the Groups, for their kindness, enthusiasm and hard work for the benefit of the Pharmacopoeia. Finally, I wish to express warm thanks to the Director of EDQM, Dr. Agnes Artiges, and her deputy as secretary to the European Pharmacopoeia Commission, Mr. Peter Castle. I have appreciated our collaboration during the three years and wish to express heartfelt thanks to both for their support to the chair and for the tremendous work they are doing to develop the European Pharmacopoeia and its role in the European regulatory system.

Professor, Dr. Henning G. Kristensen

Chair 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 and Herzegovina, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Norway, Portugal, Romania, Serbia and Montenegro, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, "the Former Yugoslav Republic of Macedonia", Turkey, the United Kingdom, 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 3 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 Procedures. Observers are at present admitted from: Albania, Algeria, Australia, Bulgaria, Canada, China, Georgia, Lithuania, Malaysia, Malta, Morocco, Poland, Senegal, Syria, Tunisia, Ukraine, and the World Health Organisation.

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 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 substances, preparations and spectra 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, but wherever an issue with impact on public health is identified, monographs are revised.

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 standards of the European Pharmacopoeia are represented by general and specific monographs. The use of general monographs has developed in recent years to provide standards that best fulfil the aims stated above and meet the needs of users. It is now usually necessary to apply one or more general monographs along with any specific monograph. Since it is not practically possible to include in each specific monograph a cross-reference to applicable or potientially applicable general monographs, cross-referencing has been discontinued except where it is necessary to avoid ambiguity.

A list of general monographs is included in each new edition and supplement to aid users in identifying those that are needed for use with a specific 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. Considerable progress was made in this area while the 4th Edition was in force and while the 5th Edition was being prepared.

Hydrates. With the publication of the 4th Edition, the policy on monograph titles for hydrated forms was changed. For all monographs published for the first time in the 4th Edition or subsequent editions, the degree of hydration, where applicable, is 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, 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 shows 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 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)* and *5.9. Polymorphism* 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. Following a review of policy on control of impurities, a new general chapter *5.10. Control of impurities in substances for pharmaceutical use* has been included in the 5th Edition. Together with the general monograph *Substances for pharmaceutical use (2034)*, it describes the policy of controlling impurities in specific monographs and provides explanations on how the limits in the related substances test should be understood. Currently the test is a limit test (comparison of peaks areas). In the future (next Edition) and in order to be in line with licensing practice and international collaboration, this test will progressively be changed to utilise a quantitative acceptance criterion. At present, some of the current monographs already satisfy this approach.

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.

Chromatographic columns. As an aid to users, information is made available via the web site www.pheur.org on chromatographic columns that have been found satisfactory during development of monographs and general methods. Information is also given on other equipment and reagents where this is considered useful. This information is given without warranty and does not imply that other columns, equipment or reagents than those specified are not suitable.

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 substances, reference preparations and reference spectra. Where necessary for application of a monograph, reference substances, reference preparations and reference spectra are established and provided to users. They 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 substances and preparations, 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 substances, preparations and spectra 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 to take account of future standards developed within the framework of the Directive. The monographs on surgical sutures 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 2nd Edition. A number of monographs on substances used in homoeopathic preparations are now 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 (www.pheur.org)] as an aid to the use of monographs in applications for marketing authorisation. The certification procedure also applies to herbal drugs, herbal drug preparations and 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. A daily updated list of certificates granted is available on-line on the EDQM web site. A list of voided or suspended certificates is also published in *Pharmeuropa*.

PUBLICATIONS

The European Pharmacopoeia is available in English and French versions in the form of a book with 3 supplements per year, and in electronic form (internet and CD-ROM).

Pharmeuropa, the European Pharmacopoeia Forum, is published 4 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 (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 6 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 web site as part of the Resolution.

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. Pharmacopoeial harmonisation*. 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 30 NOVEMBER 2003

CHAIR AND VICE-CHAIRS OF THE COMMISSION

Chair	Henning G.	KRISTENSEN
Vice-chairs	Dries	DE KASTE
	Liisa	TURAKKA

MEMBERS OF THE COMMISSION

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	Jan Willem	DORPEMA
	Pieter H.	VREE
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	Randi	WINSNES
Portugal	José Manuel	CORREIA NEVES SOUSA LOBO
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Spain	Franco	FERNANDEZ GONZALEZ
	Jordi	RUIZ COMBALIA
	Alexandra	VARDULAKI
Sweden	Lennart	AKERBLOM
	Marianne	EK
	Christina	GRAFFNER

Switzerland	Werner	ERNI
	Silvia	WEBER BRUNNER
	Helena	WINDEMANN
"The Former Yugoslav Republic of Macedonia"	Aneta	DIMITROVSKA
	Tatjana	PERUSEVSKA
Turkey	Orhan	CANBOLAT
	Yilmaz	CAPAN
	Hayriye	MIHCAK
United Kingdom	Derek H.	CALAM
	Gerard	LEE
	A.David	WOOLFSON
European Commission	Nicolas	ROSSIGNOL
EMEA	Emer	COOKE

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	Josef	TRENKER
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The European Pharmacopoeia Commission and the European Directorate for the Quality of Medicines also wishes to thank the Secretariat for their contribution towards the publication:

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IV. CONTENTS OF THE 5th EDITION

The 5th Edition consists of all texts published in the 4th Edition, which may subsequently have been revised or corrected, and new texts.

For the information of the reader, lists are given below of monographs and general chapters that are new, or that have been revised, corrected or deleted, and texts whose title has been changed for the 5th Edition.

The version date (01/2005 for volume 5.0) and the reference number (four digits for monographs and five digits for general chapters) are specified above the title of each text (monographs and general chapters). The version date makes it possible to identify the successive versions of revised texts in different volumes of the 5th Edition. Corrections that are indicated by the word "corrected" under the version date are to be taken into account from the publication date of the volume.

For the 5th Edition, the following systematic modifications have been made to the texts of the Pharmacopoeia.

- The term "specified impurities" has replaced "qualified impurities" in the Impurities section of monographs in accordance with the texts on *Substances for pharmaceutical use (2034)* and *5.10. Control of impurities in substances for pharmaceutical use*. This term, which is compliant with the ICH guidelines, applies to impurities for which a specific acceptance criterion has been defined.
- In cases covered by the general monograph on *Substances for pharmaceutical use (2034)*, the test for sterility and the corresponding information in the Labelling section are no longer included in specific monographs.
- Chromatograms published for information no longer appear in the Pharmacopoeia; they are now available on the Internet site: www.pheur.org.
- A reference to available biological reference preparations has been added to the monographs concerned.
- The solubility in ether has been deleted from the Characters section and from the reagent descriptions.
- The reference to storage in a cool place has been deleted from the monographs and reagent descriptions.

A vertical line in the margin indicates where part of a text has been revised or corrected. A horizontal line in the margin indicates where part of a text has been deleted. It is to be emphasized that these indications, which are not necessarily exhaustive, are given for information and do not form an official part of the texts. Editorial changes are not indicated.

Individual copies of texts will not be supplied.

NEW TEXTS INCLUDED IN THE 5th EDITION

GENERAL CHAPTERS

2.4.30. Ethylene glycol and diethylene glycol in ethoxylated substances

2.6.24. Avian viral vaccines: tests for extraneous agents in seed lots *(previously texts 2.6.3, 2.6.4, 2.6.5 and 2.6.6)*

2.6.25. Avian live virus vaccines: tests for extraneous agents in batches of finished product *(previously texts 2.6.3, 2.6.4, 2.6.5 and 2.6.6)*

5.9. Polymorphism

5.10. Control of impurities in substances for pharmaceutical use

5.11. Characters section in monographs

MONOGRAPHS

The monographs below appear for the first time in the European Pharmacopoeia. They will be implemented on ***1 January 2005*** *at the latest.*

Monographs

Botulinum toxin type A for injection (2113)

Ciprofibrate (2013)

Clioquinol (2111)

Clofazimine (2054)

Closantel sodium dihydrate for veterinary use (1716)

Colestyramine (1775)

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Dipivefrine hydrochloride (1719)

Dodecyl gallate (2078)

Edrophonium chloride (2106)

Formoterol fumarate dihydrate (1724)

Human coagulation factor VIII (rDNA) (1643)

Hydromorphone hydrochloride (2099)

Insulin aspart (2084)

Insulin lispro (2085)

Isradipine (2110)

Lactobionic acid (1647)

Lysine acetate (2114)

Mitomycin (1655)

Octyl gallate (2057)

Oleyl alcohol (2073)

Oxeladin hydrogen citrate (1761)

Propylene glycol dicaprylocaprate (2122)

REVISED TEXTS IN THE 5th EDITION

GENERAL CHAPTERS

MONOGRAPHS

The monographs below have been technically revised since their last publication. They will be implemented on ***1 January 2005****.*

General monographs

Monographs