

II. INTRODUCTION

The European Pharmacopoeia is prepared under the auspices of the Council of Europe in accordance with 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 38 member states (Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Republic of Moldova, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom) and the European Union. 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 Procedure. Observers are at present admitted from Albania, Algeria, Argentina, Armenia, Australia, Azerbaijan, Belarus, Brazil, Canada, China, Georgia, Guinea, India, Israel, Japan, Kazakhstan, Republic of Korea, Madagascar, Malaysia, Morocco, Russian Federation, Senegal, Singapore, South Africa, Syrian Arab Republic, Tunisia, United States of America, Uzbekistan, Taiwan Food and Drug Administration (TFDA) and the World Health Organization (WHO).

The Convention is open for signature by European countries and observer status can serve to familiarise European countries intending to become signatories with the working methods of the Commission. The Commission recognises that interactions with countries outside Europe are essential in view of the globalisation of the supply chain for pharmaceuticals. Observer status for non-European countries helps to foster these interactions by facilitating regulatory partnerships and the exchange of information and working documents as well as participation in the scientific work of the Commission. The 10th Edition of the European Pharmacopoeia contains nearly 3000 monographs and general texts. This would not have been possible without the contributions from and dedication of a network of more than 700 experts in pharmaceutical sciences from all around the world. Participation by experts and stakeholders in the European Pharmacopoeia's public standard-setting process is vital for the development of authoritative and relevant monographs.

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

Article 6

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

- to determine the general principles applicable to the elaboration of the European Pharmacopoeia;
- to decide upon methods of analysis for that purpose;
- to arrange for the preparation of and to adopt monographs to be included in the European Pharmacopoeia and;
- 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." The European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe supports the Commission in the elaboration and revision of European Pharmacopoeia texts by providing the Scientific Secretariat. In addition, it is responsible for the

establishment, production, monitoring and distribution of reference standards needed when applying the monographs. The EDQM is also active in a number of other areas related to the protection of public health, for example in certifying the quality of active pharmaceutical ingredients from specific sources and in biological standardisation.

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 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 the quality of medicines and their components. As these standards ensure that medicines reaching the market are safe for use by patients, it is essential that they are appropriate. Their existence also facilitates the free movement of medicinal products in Europe and beyond.

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

- regulatory authorities;
- those engaged in the quality control of medicinal products and their constituents;
- manufacturers of medicinal products and their individual components.

Globalisation gives rise to new challenges in terms of the quality of pharmaceutical substances and medicines. To respond to these challenges, the European Pharmacopoeia has extended its international outreach and works closely with all its stakeholders to produce quality standards appropriate for medicinal products developed in an increasingly global world.

SEAT OF THE EUROPEAN PHARMACOPOEIA COMMISSION

The European Pharmacopoeia Commission holds its meetings in Strasbourg, the seat of the Council of Europe.

GENERAL PRINCIPLES

General rules for interpretation of the texts of the European Pharmacopoeia are given in the General Notices. These rules are to be applied in conjunction with the information given below.

The general principles applied during elaboration of European Pharmacopoeia texts are laid down in procedures (Rules of procedure, Guide for work and Code of practice) and in Technical Guides freely available on the EDQM website. These principles are revised regularly, generally without retrospective application, so that monographs already published may not always follow the latest recommendations; however, wherever an issue with an impact on public health is identified, monographs are revised immediately.

It is recognised that general chapters are also used independently of the monographs of the Pharmacopoeia; in these circumstances users are recommended to consult the relevant technical guide, which gives extensive information on the application of many of the methods.

General and individual monographs. The standards of the European Pharmacopoeia take the form of general and individual monographs. General monographs provide standards that best fulfil the aims stated above and meet the needs of users. It is usually necessary to apply one or more general monographs along with any individual monograph. Where a substance or a pharmaceutical preparation is subject to the provisions of both a general monograph and an individual monograph, the two are complementary.

An individual monograph may, exceptionally, include an exemption from one or more provisions of a general monograph.

Since, for practical reasons, it is not possible to include a cross-reference to applicable or potentially applicable general monographs in each individual monograph, cross-references are not included, except where they are necessary to avoid ambiguity. A list of general monographs is included in each new edition and supplement to help users identify those required for use with an individual monograph.

Use of animals. In accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (CETS No. 123), elaborated under the auspices of the Council of Europe, the Commission is committed to reducing the use of animals wherever possible in pharmacopoeial testing, and encourages its stakeholders to seek alternative procedures. An animal test is included in a monograph only if it has been clearly demonstrated that it is absolutely necessary to achieve satisfactory control for pharmacopoeial purposes and no alternative is available.

Hydrates. When monographs refer to a hydrate form, either well-defined or not, the corresponding degree of hydration (mono-, di-, tri-, *n*-hydrate or hydrate) is indicated in the title, the chemical formula and the chemical name. For non-hydrates, 'anhydrous' is not specified in the title unless otherwise justified. When monographs cover both non-hydrates and hydrates, nothing is added to the title or the chemical name, but 'xH₂O' is stated in the chemical formula.

Chiral substances. Monographs on chiral substances that describe a particular enantiomer include a test to confirm enantiomeric purity, usually by chiral liquid chromatography. A test for racemic character using optical rotation is 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 chiral liquid chromatography, can serve the intended purpose, they are 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; in rare cases, however, a monograph may cover a specific crystalline form and describe, for example, an infrared absorption spectrophotometric identification test. In these cases, the spectrum is to be recorded using the substance in the solid state without recrystallisation and the chemical reference substance described is of the required crystalline form. In addition to these exceptional cases, depending on the function of a given substance in a pharmaceutical preparation, 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 pharmaceutical preparation. The general monograph *Substances for pharmaceutical use (2034)* and general chapter 5.9. *Polymorphism* should also be consulted.

Impurities. Together with the general monograph *Substances for pharmaceutical use (2034)*, general chapter 5.10. *Control of impurities in substances for pharmaceutical use* describes the policy for the control of impurities in individual monographs and explains how the limits in the related substances test are to be understood.

The current general policy of the Commission for substances for pharmaceutical use is to include quantitative tests for impurities in monographs. Most of the older monographs that predate this policy have been revised to introduce quantitative methods. Where a monograph does not conform to the general policy, compliance with the general monograph *Substances for pharmaceutical use (2034)* implies that the individual monograph requirements need to be supplemented

by the user, using the decision tree provided in general chapter 5.10.

Monographs on medicinal products containing chemically defined active substances describe limits for degradation products arising during manufacture and shelf-life of the medicinal product, including those synthesis impurities that are also degradation products. To this end, quantitative tests are included in the monographs.

Elemental impurities. The strategy for the control of elemental impurities has been aligned to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3D guideline and the core principles of this guideline are reproduced in general chapter 5.20. *Elemental impurities*. The requirements for the control of elemental impurities, which is strongly based on risk management, are given in the general monographs on *Pharmaceutical preparations (2619)* and on *Substances for pharmaceutical use (2034)*, while to a certain extent tests for elemental impurities have been removed from individual monographs (e.g. 2.4.8. *Heavy metals*).

Residual solvents. The requirements for residual solvents are given in the general monograph *Substances for pharmaceutical use (2034)* and in general chapter 5.4. *Residual solvents*. Thus, all active substances and excipients are subjected to relevant control of residual solvents, whether or not a test is specified in the individual monograph. The requirements are aligned with the ICH Q3C guideline.

Bacterial endotoxins. In June 2014, the Commission approved a new policy on bacterial endotoxins in substances for pharmaceutical use. The general monograph *Substances for pharmaceutical use (2034)* states that a substance must comply with the bacterial endotoxins test (BET) if it is labelled as 'bacterial endotoxin-free', or if it is intended for use in the manufacture of parenteral preparations or preparations for irrigation without a further appropriate procedure for the removal of bacterial endotoxins. The monograph references general chapters 2.6.14. *Bacterial endotoxins* and 5.1.10. *Guidelines for using the test for bacterial endotoxins*. According to the general monograph on *Parenteral preparations (0520)*, pharmaceutical preparations for parenteral administration must comply with the test for bacterial endotoxins.

Monographs for substances for pharmaceutical use elaborated after the implementation of this policy do not describe a test for bacterial endotoxins, this aspect being covered by the requirements of the general monograph on *Substances for pharmaceutical use (2034)*. There is an exception to this rule: the test is maintained in new monographs when, for example, a specific sample preparation must be used or a specific method applied. In such cases, no limit is given. For all monographs for substances for pharmaceutical use published before the implementation of the policy, the test for bacterial endotoxins is retained: existing limits remain in these monographs to maintain the use of well-established limits.

Equipment, reagents. As an aid to users, information is made available via the Knowledge database (see below) on chromatographic columns that have been found to be 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 as a guide and does not imply that other columns, equipment or reagents than those specified are not suitable.

Homoeopathic preparations. A monograph on methods of preparation of homoeopathic stocks and potentisation, general monographs on homoeopathic preparations, mother tinctures for homoeopathic preparations and herbal drugs for homoeopathic preparations, and individual monographs on raw materials and stocks for homoeopathic preparations are included in a separate section of the European Pharmacopoeia. It is understood that when the same substance is used in both homoeopathic and other preparations, the monograph in the main body of the European Pharmacopoeia applies.

Herbal drugs and herbal drug preparations (including traditional Chinese medicines). All relevant monographs are grouped together in a separate section of the European Pharmacopoeia.

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 under national and international law.

Patents. The description in the European Pharmacopoeia of articles subject to patent protection 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.

MONOGRAPHS ON PHARMACEUTICAL PREPARATIONS

The general monograph *Pharmaceutical preparations (2619)* is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls.

Harmonisation and standardisation for pharmaceutical preparations is dealt with via the drafting of general dosage form monographs setting out elements common to all preparations covered by the monograph, and via the development of standard test methods used to test medicinal products. The inclusion of these general monographs and methods in the European Pharmacopoeia provides competent authorities and manufacturers with a common basis for the preparation and evaluation of marketing authorisation applications. In addition, after a successful pilot phase, individual monographs on medicinal products containing chemically defined active substances are now elaborated on a regular basis.

Reference standards established for the assay of active substances and excipients may be suitable for use as assay standards for preparations when the conditions stated in general chapter 5.12. *Reference standards* are fulfilled.

WORK PROGRAMME

The work programme (elaboration of new monographs or general chapters or revision of existing texts) is decided by the Commission at the 3 annual sessions. In general, whenever 2 member states express a wish to elaborate a monograph, the Commission adds the item to the work programme.

Changes to the work programme are published on the EDQM website and in *Pharmeuropa*. Information is also provided to industry associations registered with the Secretariat and to manufacturers' liaison contacts and in the EDQM Knowledge database (including reasons for the revision). Interested parties are invited to contact the Secretariat for any items where they wish to be involved in the work.

CERTIFICATION PROCEDURE

The procedure for the certification of suitability to the monographs of the Pharmacopoeia allows suppliers to demonstrate that the quality of their substance is suitably controlled by the relevant monographs (see Public Health Committee (Partial Agreement) Resolution AP-CSP (07) 1 or any subsequent revision, available from the EDQM and on its website) and is an aid to the use of monographs in marketing authorisation applications where relevant, complemented by additional tests appended to the certificate. The certification procedure also applies to herbal drugs, herbal drug preparations and any substance subject to the risk of transmissible spongiform encephalopathy (TSE). Certificates of suitability are issued by the EDQM only for substances produced under a suitable quality system. Certificates are granted with respect to published monographs. Details on how this scheme is run are available from the Secretariat and

on the EDQM website. A daily updated list of the certificates granted is available online on the EDQM website, including voided or suspended certificates.

PUBLICATIONS

The official version of the European Pharmacopoeia is available in English and in French. Three additional supplements are published every year.

Implementation. The date on which monographs are to be implemented is fixed by a Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care (Partial Agreement) of the Council of Europe, following a recommendation by the Commission. This date is usually 1 year after adoption and about 6 months after publication. Where a monograph is to be implemented at a date earlier than the next publication date of the European Pharmacopoeia or a supplement, a Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care gives the full text to be implemented. The text is also published in *Pharmeuropa* for information and posted on the EDQM website as part of the Resolution.

Pharmeuropa is the European Pharmacopoeia Forum. Texts are published for public enquiry 4 times per year (with deadlines for comments) as an aid to the elaboration of monographs and as a vehicle for information on pharmacopoeial and related matters. It is therefore extremely important that manufacturers and users of the substances provide feedback on the draft monographs. *Pharmeuropa Bio & Scientific Notes*, a publication indexed by bibliographic services, includes scientific papers related to the establishment of biological reference preparations and validation of biological methods within the Biological Standardisation Programme of the EDQM, and to various aspects of pharmaceutical analysis and other subjects relevant to the Pharmacopoeia. Both of these are only available online as free publications.

Knowledge database. The EDQM website provides access to a database containing a variety of information related to monographs and other texts and intended to facilitate their proper use. Information is provided on:

- the status (e.g. whether the text is under elaboration or a revision is ongoing, together with a brief description, if deemed appropriate);
- typical chromatograms (or other raw data) obtained for certain chromatographic separations and brand names of chromatography columns used in monograph development;
- suppliers of reagents and equipment that may be difficult to find for some users;
- revisions of the texts on a historical basis, starting with the 5th Edition;
- harmonisation status;
- other relevant topics.

Archives (online). The European Pharmacopoeia Archives contain copies of the 1st to the 9th Editions in PDF format. They are available to all European Pharmacopoeia subscribers with an up-to-date subscription and a registered EPID code.

Website. Information on activities and many other aspects of the European Pharmacopoeia can be found on the EDQM website (www.edqm.eu).

HelpDesk. Many technical and other enquiries are addressed to the EDQM by users. They should be submitted via the HelpDesk on the EDQM website. The EDQM will deal with enquiries that are related to the use of monographs and other texts of the European Pharmacopoeia. The HelpDesk has a section of Frequently Asked Questions that should be consulted by users before submission of an enquiry.

Revision programme. Proposals to revise a text of the European Pharmacopoeia may be submitted by a delegation, by the Chair of the Commission, by the chair of a group of

experts or a working party, by a user or by the Secretariat. Requests for revision may be submitted via the national pharmacopoeia authority of a member state or, where this is not possible, to the EDQM via the HelpDesk. Proposals must be accompanied by sufficient data to justify the need for the revision. Monographs and other texts of the European Pharmacopoeia are revised as necessary following a decision of the Commission. Draft revised texts are published in Pharmeuropa.

COMBISTATS

Certain tests in monographs, particularly biological assays, require statistical analysis of the results. The EDQM has developed a computer programme, CombiStats, which can be used for statistical analysis of results of biological dilution assays. Information on the programme, with conditions of access and use, is available on the EDQM website.

INTERNATIONAL HARMONISATION

In an increasingly globalised world, the need for global quality standards has become ever more pressing. Standards are a vital instrument for marketing authorisation, market surveillance and the free movement and trade of medicines amongst regions and countries. Amongst other harmonisation

initiatives, the European Pharmacopoeia is engaged in a process of harmonisation with the Japanese Pharmacopoeia and the United States Pharmacopoeia, within an informal structure referred to as the Pharmacopoeial Discussion Group (PDG).

Where harmonisation of general chapters is carried out, the aim is to arrive at interchangeable methods or requirements so that demonstration of compliance using a general chapter from one of the 3 pharmacopoeias implies that the same result would be obtained using the general chapter of either of the other pharmacopoeias. To help regulatory authorities and other users recognise the interchangeability of selected harmonised general chapters, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has issued topic-specific annexes with information about a limited number of these texts in order to facilitate their implementation. More information is available from the ICH website (ich.org).

Where harmonisation of monographs is carried out, the aim is to arrive at identical requirements for all attributes of a product. Information on any non-harmonised attributes and local requirements is included in the relevant European Pharmacopoeia general chapters and monographs.