II. INTRODUCTION

The European Pharmacopoeia (Ph. Eur.) 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 39 member states (Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Republic of Moldova, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Türkiye, Ukraine, United Kingdom) and the European Union.

The preparation of the Ph. Eur. is the responsibility of the European Pharmacopoeia Commission ('Ph. Eur. Commission', the 'Commission'), appointed in accordance with Article 5 of the above-mentioned Convention. It is composed of delegations nominated 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.

The Convention is open for signature by member states of the Council of Europe 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. Observers from non-member states and international organisations are admitted to sessions of the Commission in accordance with the Rules of Procedure. The list of observers can be found on the EDQM website.

The 11th Edition of the Ph. Eur. 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 800 experts in pharmaceutical sciences from all around the world. Participation by experts and stakeholders in the Ph. Eur. public standard-setting process is vital for the elaboration and revision 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:

(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."

The European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe supports the Commission in the elaboration and revision of Ph. Eur. 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 and general chapters. The EDQM is also active in a number of other areas related to public health protection, 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 Ph. Eur. become the official standards applicable within their respective territories.

PURPOSE OF THE EUROPEAN PHARMACOPOEIA

The purpose of the Ph. Eur. is to promote public health by the provision of recognised common standards for the quality of medicinal products and their components. As these standards ensure that medicinal products reaching the market are safe for use by patients, it is essential that they are fit for purpose. Such standards also facilitate the free movement of medicinal products in Europe and beyond.

Ph. Eur. monographs and other texts are designed to meet the needs of:

- regulatory authorities;
- individuals 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 substances for pharmaceutical use and medicinal products. To respond to these challenges, the Ph. Eur. 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 Ph. Eur. Commission holds its meetings in Strasbourg, the seat of the Council of Europe.

GENERAL PRINCIPLES

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

The general working principles applied during elaboration and revision of Ph. Eur. texts are laid down in different procedures (*Rules of procedure, Guide for work and Code of practice*) and in Technical Guides that are freely available on the EDQM website. The latter are revised regularly, when needed, generally without retrospective application, which means that monographs already published may not always match 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 Ph. Eur.; in these circumstances, users are advised to consult the relevant technical guide, which gives extensive information on the application of many of the analytical procedures.

General and individual monographs. Ph. Eur. standards are published in 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 medicinal product is subject to the provisions of both a general monograph and an individual monograph, the two

are complementary. In exceptional cases, an individual monograph may 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, such 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.

Monographs on medicinal products. The general monograph *Pharmaceutical preparations (2619)* is intended to be a reference source of Ph. Eur. standards on active substances, excipients and dosage forms that are to be applied during the manufacture/preparation of medicinal products. It is not intended as a guide on how to manufacture the products it covers: specific guidance describing methods of manufacture and associated controls is provided elsewhere.

Harmonisation and standardisation for medicinal products is dealt with in general dosage form monographs setting out elements common to all types of medicinal products covered by the monograph, and via standard analytical procedures used to test medicinal products. This provides competent authorities and manufacturers with a common basis for the preparation and evaluation of marketing authorisation applications. In addition, 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 medicinal products when the conditions stated in general chapter *5.12. Reference standards* are fulfilled.

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, wherever possible, the use of animals in pharmacopoeial testing, and encourages its stakeholders to seek alternative analytical 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.

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 Commission's current general policy 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*.

Elemental impurities. The strategy for the control of elemental impurities has been aligned with 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 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)*, medicinal products for parenteral administration must comply with the test for bacterial endotoxins.

Individual 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 analytical procedure 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.

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 gathered in a dedicated section of the Ph. Eur. It is understood that when the same substance is used in both homoeopathic and other preparations, the monograph in the main body of the Ph. Eur. applies.

Herbal drugs and herbal drug preparations (including traditional Chinese medicines). All relevant monographs are gathered in a dedicated section of the Ph. Eur.

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 Ph. Eur. of articles subject to patent protection does not confer or imply any right to the use of such patents by any individuals other than the proprietors of the patents concerned.

WORK PROGRAMME

The work programme (elaboration of new monographs or general chapters or revision of existing texts) is decided by the Commission at the three annual sessions. In general, whenever two member states express a wish to elaborate a text, the Commission adds the item to the work programme. Changes to the work programme are published on both the EDQM and Pharmeuropa websites. Information is also provided to industry associations registered with the Secretariat, 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 in which they wish to become involved.

Revision programme. Proposals to revise a text of the Ph. Eur. may be submitted by a delegation, by the Chair of the Commission, by the chair of a group of experts or 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 website. Proposals must be accompanied by sufficient data to justify the need for the revision. Monographs and other texts of the Ph. Eur. are revised as necessary following a decision of the Commission. Draft revised texts are published in Pharmeuropa.

CERTIFICATION PROCEDURE

The procedure for the certification of suitability to the monographs of the Ph. Eur. 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 on the EDQM website). The procedure 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 (CEP) 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 on the EDQM website. A daily updated list of the certificates granted is available on the EDQM website, including voided or suspended certificates.

PUBLICATIONS

The official version of the Ph. Eur. is available in English and in French in print and online versions. A new edition is published every third year, with three supplements published in each intervening year (supplements 1-8).

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 a edition or supplement of the Ph. Eur., a specific Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care is issued. The Resolution, including the full text to be implemented, is posted on the EDQM website and the text is also published on the Pharmeuropa website for information.

Pharmeuropa is the Ph. Eur. forum. Texts issued for public consultation are available in French and English on the Pharmeuropa Online platform. There are four issues per year (published in January, April, July and October) with a minimum deadline for comments of three months. The public consultation is an important tool for the elaboration and revision of relevant texts and it is extremely important that manufacturers and users of the Ph. Eur. provide feedback on the proposed draft texts. In addition, the Pharmeuropa website is a platform for information on pharmacopoeial and related matters. It also incorporates Pharmeuropa Bio & Scientific Notes, a publication indexed by bibliographic services, that includes scientific papers related to the establishment of biological reference preparations and validation of biological procedures within the Biological Standardisation Programme of the EDQM, but also to various aspects of pharmaceutical analysis and other subjects relevant to the Ph. Eur. The entire content of the platform is freely accessible.

Knowledge database. This database contains a variety of information related to monographs and other texts that is intended to facilitate their proper use. It can be accessed via the dedicated icon, directly from the online version of a Ph. Eur. text. 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;
- useful guidance for applying some of the analytical procedures;
- suppliers of reagents, e.g. brand names of chromatography columns used in the validation of the corresponding analytical procedure and equipment where this is considered useful. NOTE: This information is given for guidance and does not imply that columns, equipment or reagents other than those specified are not suitable;
- the revision history of the text, starting with the 5th Edition;
- harmonisation status;
- list of relevant reference standards;
- other relevant topics.

Archives (online). The Ph. Eur. archives contain copies of the previous editions in PDF format. They are available to all Ph. Eur. subscribers with an up-to-date subscription and a registered EPID code.

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

HelpDesk. Any technical and other enquiries should be submitted to the EDQM via the HelpDesk website. The Ph. Eur. Secretariat will deal with enquiries that are related to the use of monographs and other texts of the Ph. Eur. The HelpDesk also contains Frequently Asked Questions that should be consulted by users before submission of a new enquiry.

COMBISTATS

Certain analytical procedures in monographs, particularly biological assays, require statistical analysis of the results. The EDQM has developed a computer programme, CombiStats, that 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 medicinal products amongst regions and countries. Amongst other harmonisation initiatives, the Ph. Eur. is engaged in a process of harmonisation of selected general chapters and excipient monographs with the Japanese Pharmacopoeia and the United States Pharmacopeia, within an informal structure referred to as the Pharmacopoeial Discussion Group (PDG).

General chapter *5.8 Pharmacopoeial harmonisation* provides users with general guidance on the work of the EDQM in this field and details of the information included in harmonised Ph. Eur. general chapters and monographs.

Where harmonisation of general chapters is carried out, the aim is to arrive at interchangeable analytical procedures or requirements so that demonstration of compliance using a general chapter from one of the three 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 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). In November 2018, the PDG took over the responsibility for and the maintenance of the existing Q4B annexes.

Where harmonisation of monographs is carried out, the aim is to agree on identical requirements for all attributes of a substance. Any non-harmonised attributes/provisions and any local requirements (i.e. attributes/provisions that are present only in the Ph. Eur. text) are indicated in the relevant Ph. Eur._ general chapters and monographs.

Information on the harmonisation status of each individual pharmacopoeial text is available on the EDQM website. Information on individual non-harmonised provisions and attributes or on specific local requirements of one of the PDG pharmacopoeias may also be available.