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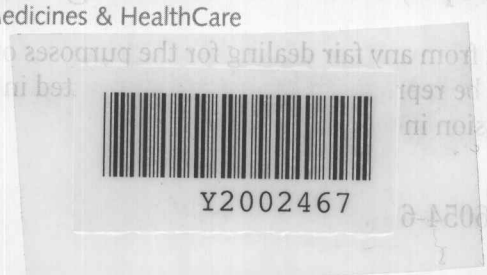

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I. PREFACE

The European Pharmacopoeia was inaugurated in 1964 through the Convention on the Elaboration of a European Pharmacopoeia under the auspices of the Council of Europe. The 6th Edition of the European Pharmacopoeia is published at a time coinciding with the 43rd Anniversary of the Pharmacopoeia Convention and marks the occupation of the new purpose-designed headquarters building of the EDQM, the European Directorate for the Quality of Medicines & HealthCare, in Strasbourg. The work of the Pharmacopoeia has gone through a remarkable development, from the early publications of the 1st Edition to the strong position of the 4th, 5th and 6th Editions that follow the current three-year cycle of publication with intermittent thrice-yearly supplements.

The monographs of the Pharmacopoeia, both specific and general, together with other texts made mandatory by virtue of reference in monographs, are applicable throughout the 37 Member States including the European Union itself, which is also a signatory to the European Pharmacopoeia Convention. This means that the European Pharmacopoeia holds a special place in the regulatory processes within the European Union, its text being made mandatory or given 'mandatory' applicability by virtue of reference in European Council Directives. In addition to the 37 signatories to the European Pharmacopoeia Convention, there are also a large number (20) of observer countries. Consequently, the quality standards developed through the Pharmacopoeia have an impact on the quality of medicinal products and substances used across a large part of the globe.

Since the 5th Edition (2004), the European Pharmacopoeia in paper copy has had to be lodged in a two-volume set for simple practical reasons. The 6th Edition will become effective on 1 January 2008 and be augmented with eight supplements, three per annum, implementing on a rapid basis the decisions of interim meetings of the European Pharmacopoeia Commission. This flexible publication schedule has allowed a shortening of the time span between adoption of monographs by the Commission and their publication and official status. This reduced time span becomes possible only due to the very flexible attitude of those countries that make national translations of those European Pharmacopoeia monographs, which are published bilingually by the European Pharmacopoeia only in its working languages of English and French. The European Pharmacopoeia is of course also available in CD-ROM format as well as electronically online. Electronic versions are becoming increasingly popular and therefore tend to dictate the way the Pharmacopoeia is produced to meet modern expectations. The three-year publication schedule that began with the 4th Edition continues with this current edition and will be the pattern set for the foreseeable future. By this process the stability and flexibility of the publication schedule is maximised and the publication remains user-friendly.

Elaboration and approval of monographs and other texts proceeds through an efficient and transparent, smooth-running process, based on scientific co-operation between the members of the various Groups of Experts and Working Parties assigned by the European Pharmacopoeia Commission, the governing body of the Pharmacopoeia. These experts give of their time, expertise and experience to produce the highest-level quality standards available to the public, standards that are continually revised in line with scientific developments. This co-operation between the experts from industry, academia, regulatory authorities and official government laboratory scientists represents the pinnacle of scientific co-operation to produce a high standard of technical monographs and chapters. The current edition will contain in excess of two-thousand monographs, each of which has gone through the painstaking elaboration and/or revision process ultimately directed by the Commission and subject to extensive and transparent public consultation through the medium provided by *Pharmeuropa*, the quarterly publication of the EDQM. Furthermore, the technical requirements adopted by the Pharmacopoeia Commission are based upon a unanimous decision-making process – each Member State of the Pharmacopoeia Commission has the right to veto, should they choose to exercise it.

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 pharmaceutical world has changed radically 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 Pharmacopoeia, 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 task, which has now been speeded up by 'harmonisation by attribute', meaning that there may be tests that cannot be fully harmonised before the general method concerned is harmonised. At the stage where the monographs are harmonised, detailed information will be provided in the monograph and in the general chapter *5.8. Pharmacopoeial harmonisation*, which is devoted to information on international harmonisation. In recent years, harmonisation of a wide range of general methods has been in progress, partly because of the impact from the International Conference on Harmonisation (ICH) and in particular the work of its guideline on specification-setting (Q6A). Implementation in the Pharmacopoeia of harmonised general methods, for example for a dosage form specification, needs careful consideration however, 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 initiative. It is not the harmonisation work itself that gives rise to the greatest problems, rather the implementation, which has to be decided by mutual agreement with the European regulatory authorities. In response 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 European Pharmacopoeia has a particular statutory role in the EU Medicines legislative system, which helps to strengthen the harmonisation initiative, notwithstanding that the Pharmacopoeia has an audience wider than the EU Member States.

The growing number of monographs on pharmaceutical substances and the need to keep them updated means an increased workload for the Groups of Experts. There

continues to be 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 also been expanded to four different procedures.

- *Procedure 1*, the traditional elaboration by Groups of Experts.
- *Procedure 2*, adaptation of national monographs.
- *Procedure 3*, applying to substances produced by only one manufacturer, usually close to patent expiry. In this procedure, the manufacturer and national pharmacopoeial authority in the country where the substance is produced carry out the preliminary drafting stages and check the requirements experimentally. The draft is then reviewed by a Working Party and processed in the usual way by public enquiry.
- *Procedure 4*, a modified version of Procedure 3, introduced by the Commission in 2002 to further streamline the process. Procedure 4 involves collaboration between the manufacturer of the substance and the EDQM to prepare a draft monograph with experimental checking by the EDQM laboratory before publication for public enquiry.

  A Working Party has been set up to supervise this process and prepare the draft monographs in the usual way, but with the ability to have direct collaboration between the manufacturer and the EDQM laboratory in refining the experimental method. This results in rapid preparation of monographs on substances still under patent. The collaboration with innovators and manufacturers of such active substances established in recent years has proved to be very successful.

For the 6th Edition, the normal procedures now used for production of monographs are in effect Procedures 1 and 4, since the processes of adaptation of national monographs and the Procedure 3 route have been largely exhausted and the work done through these two procedures is largely complete.

The codified European Directives 2001/83/EC and 2001/82/EC as amended, on medicines for human and veterinary use, maintain the mandatory character of the European Pharmacopoeia monographs in the preparation of dossiers for marketing authorisation of medicines. It is therefore essential that the monographs of the European Pharmacopoeia be updated to keep pace with product development, with scientific progress, and with regulatory requirements. In the field of active pharmaceutical substances, the European Pharmacopoeia Commission has decided 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 since Supplement 4.6, where the term 'specified impurities' is used for impurities that have defined individual acceptance criteria. A revision of the general monograph *Substances for pharmaceutical use (2034)* was also presented in the 5th Edition to implement the threshold values of the revised ICH guideline Q3A (R) for reporting, identification and qualification of organic impurities in active substances. For the 5th Edition a new chapter, *5.10. Control of impurities in substances for pharmaceutical use*, was developed with great assistance from 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 was the revision of monographs to ensure that they contain related substances tests and lists of specified and other detectable impurities. Monographs containing a related substances test based on TLC are being revised and the work will thus proceed during the coming years. Hopefully, these revisions can be completed during the publication of the 6th Edition. In the meantime, users of the Pharmacopoeia must consult the new general 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 Knowledge database.

The aim of the revisions is to ensure that the related substances tests and impurity lists reflect the purity of pharmaceutical substances 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 CHMP/CVMP Quality Working Party has been established, which has contributed to ensuring the validity of monographs. The Certification of Suitability of Monographs of the European Pharmacopoeia can also 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 agrees to provide the relevant Group of Experts with the information required for updating.

Since the 5th Edition of the European Pharmacopoeia, a number of excipient monographs have contained a non-mandatory section on functionality-related characteristics (FRCs). The aim of this section 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 development is in line 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.

Over the last three years the European Pharmacopoeia Commission has developed this work by drafting sections on FRCs in monographs on excipients available in more than one physical grade. Introduction of the concept of FRCs presupposes that the relevant general methods are available in the Pharmacopoeia. The European Pharmacopoeia Commission has therefore established a Working Party on FRCs to investigate the need for general methods for controlling these properties and to collaborate with the Working Party on powder-characterisation methods. The provision of the necessary general methods, for example in the field of powder characterisation, has also been included in international harmonisation among the pharmacopoeias.

Furthermore, a general chapter on FRCs has been developed and published in *Pharmeuropa* for incorporation into the 6th Edition.

A general chapter on viral safety has been published by the European Pharmacopoeia, intending to reinforce the need for all substances of human or animal origin to demonstrate freedom from the possibility of contamination by viruses by careful control of starting materials and manufacturing process conditions. In completing the work on the preparation of this general chapter, the EDQM greatly appreciates the input of the European Medicines Agency (EMEA) in its very substantial contribution. This general chapter (*5.1.7*) was published in the final supplement to the 5th Edition and emphasises the importance of carrying out a risk assessment on viral safety of materials of human or animal origin. In turn, a number of general monographs covering allergens, extracts, immunosera, monoclonal antibodies, products of recombinant DNA technology, vaccines and substances for pharmaceutical use generally are cross-referring to this chapter on viral safety to re-emphasise the importance of this attribute.

During 2005, the EDQM held a very useful symposium on traditional Chinese (and other ethnic) medicines, which was set up to consider the possibility of preparing quality standards to deal with such substances and to develop a new role for the European Pharmacopoeia in this area. Based on some very useful suggestions from the seminar, it was agreed that the two herbal medicinal products Groups of Experts (Groups 13A and 13B) would be asked to prepare draft monographs based on the information that was already available in some Member States where national monographs on such substances were available or under preparation, and also taking into consideration the very useful collaboration that had been established with the Chinese Pharmacopoeia authorities. The first of these TCM monographs are published in the 6th Edition, and it is hoped that many more will follow to supplement the growing importance of regulation of such substances and their products on the European market.

Work on homoeopathic medicinal products also progressed well during the last three years, and in particular an agreement to incorporate into the Pharmacopoeia specific chapters dealing with homoeopathic manufacturing methods based on information available in existing Homoeopathic Pharmacopoeias within Europe. As a result of this progress, a new Working Party on homoeopathic manufacturing methods has been established and will work very closely with the existing Homoeopathic Products Working Party in a renewed effort at developing meaningful standards for such products. Once again, the Pharmacopoeia has worked closely with the Regulatory Authorities within the EU in attempting to achieve these goals.

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 of their time and expertise to participate in 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 also totally 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 online electronic version is possible only because of professionalism, dedication and hard work by the staff of the EDQM Secretariat.

Along with the growing size 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 continue to appear in the Pharmacopoeia during the publication of the 6th Edition as a result of the international harmonisation efforts and because the European Pharmacopoeia Commission has agreed on the elaboration of other chapters for information. During the past few 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 website is another valuable source of information on the work programme and other activities of the Commission, its Groups and the EDQM, with both the Knowledge Database and the HelpDesk, which provides a question and answer service.

During the past three years I have had the honour and privilege to serve the European Pharmacopoeia Commission as its elected Chair. The task has been challenging and extremely rewarding because of the insight it has given me into the many elements of the work that go into the drafting of the quality standards that are provided by the texts of the Pharmacopoeia. The close relationship that binds regulatory processes in Europe with the standards provided by the Pharmacopoeia is essential in maintaining public health.

I wish to thank all members of the European Pharmacopoeia Commission for their support and the collaborative spirit they have displayed within and between the Sessions of the Commission. Together with the excellent work of the two vice-chairs of the Commission and the Director and the Secretary to the Pharmacopoeia we have collaborated very effectively as the Presidium to guide the work of the Commission. I sincerely thank the Presidium for their wisdom and support during my time as Chair. The staff of the EDQM have been extremely supportive and it is clear that this work could not have been accomplished without their patience, hard work and professionalism and I owe them all a debt for the collaboration and friendship they have shown to me, especially in my tenure in the Chair.

Finally, I wish to express my sincere thanks to the Director of the EDQM, Dr Agnes Artiges, and her deputy as Secretary to the European Pharmacopoeia Commission, Mr Peter Castle. I have long appreciated our collaboration but especially during the last 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.

Dr J. Michael Morris

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, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, 'the former Yugoslav Republic of Macedonia', Turkey, United Kingdom, and by 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 Procedures. Observers are at present admitted from: Albania, Algeria, Australia, Belarus, Brazil, Canada, China, Georgia, Israel, Kazakhstan, Madagascar, Malaysia, Morocco, Russian Federation, Senegal, Syria, Tunisia, Ukraine, United States of America and the World Health Organisation.

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 relations 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 relations by facilitating regulatory partnerships and the exchange of information and working documents.

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 healthcare professionals and others concerned with the quality of medicines. Such standards are to be appropriate 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 and their components imported into or 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 of medicinal products and their consitutents;
- 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 all 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 European Pharmacopoeia.

EUROPEAN PHARMACOPOEIA HEADQUARTERS

The headquarters of the European Pharmacopoeia are situated in Strasbourg with a Scientific Secretariat, a Publications and Multimedia Department and a Laboratory, the latter being charged, among other duties, with the establishment and monitoring of the reference standards needed for the monographs of the Pharmacopoeia. These departments are parts of the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe.

GENERAL PRINCIPLES

General rules for interpretation of the texts of the European 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 available on the EDQM website. The principles applied are revised from time to time without complete retrospective application so that monographs already published may not always follow the latest recommendations, but wherever an issue with an impact on public health is identified, monographs are revised.

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 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 are represented by general and individual 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. From the 4th Edition, the scope of general monographs was extended, except where otherwise stated, to cover products where there is no individual monograph. It is now usually necessary to apply one or more general monographs along with any

individual monograph. Where a substance 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 the general monograph.

Since it is not practically possible to include in each individual monograph a cross-reference to applicable or potentially 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 an individual 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 pharmacopoeial testing, and encourages those associated with its work to seek alternative procedures. An animal test is included in a monograph only if it has clearly been demonstrated that it is necessary to achieve satisfactory control for pharmacopoeial purposes.

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 general monograph *Substances for pharmaceutical use (2034)* and general chapter *5.9. Polymorphism* should also be consulted.

Specificity of assays. For the elaboration of monographs on chemical active substances, the approach generally preferred by the Commission is to provide control of impurities (process-related impurities and degradation products) via a well-designed Tests section, with stability-indicating methods, 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 throughout its period of use.

Impurities. Following a review of policy on control of impurities, a new general chapter *5.10. Control of impurities in substances for pharmaceutical use* was included in the 5th Edition. Together with the general monograph *Substances for pharmaceutical use (2034)*, it describes the policy of controlling impurities in individual monographs and provides explanations on how the limits in the related substances test should be understood.

The current general policy of the Commission is to include quantitative tests for impurities in monographs. Older monographs elaborated before the establishment of this policy are the subject of a special revision programme to introduce quantitative methods. Where a monograph does not conform to the general policy, compliance with the general monograph *Substances for pharmaceutical use (2034)* will usually imply that the individual monograph requirements need to be supplemented accordingly.

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

Chromatographic columns. As an aid to users, information is made available via the website (see also Knowledge database, 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 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 general monograph *Substances for pharmaceutical use (2034)* and general chapter *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.

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 the deletion of some monographs on specific types of sutures in favour of a more general approach.

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 then the monograph in the main body of the European Pharmacopoeia applies.

Functionality-related characteristics. Following a policy decision of the Commission, increased attention is being given to functionality-related characteristics of excipients. A new information section has been created in the monographs. The contents of this section do not constitute mandatory requirements but the characteristics may be relevant for a particular use of an excipient. The characteristics may be presented in different ways:

- citing the name only;
- citing the name and a suitable test method, preferably one included in the European Pharmacopoeia;
- citing the name, a suitable test method and typical values or tolerances on the stated value; these values or tolerances are used to define a suitable grade of an excipient for a particular use.

In all cases, the method and acceptance criteria are not mandatory requirements but are given for guidance. The decision to control a functionality-related characteristic of an excipient remains with the pharmaceutical manufacturer and is taken with knowledge of the formulation of the product in which it is to be used; the method of determination, acceptance criteria and tolerances are determined on a contractual basis by the user and the supplier of the excipient.

The Commission's aim is to highlight the need for attention to functionality-related characteristics and to foster harmonisation of methods for their evaluation.

Editorial revision of monographs. During the course of the 3rd Edition, a new, improved editorial style was adopted, particularly for monographs on organic chemicals. New and extensively revised monographs were generally published in the new style for the 4th and 5th Editions. During the 5th Edition, a new, improved editorial style was adopted for monographs on veterinary vaccines. For the 6th Edition, a large number of monographs published in the old style for the 5th Edition have been converted to the new style so that there is greater uniformity in editorial presentation. Conversion to the new style does not affect the technical content of the monographs. Since the editorial revision does not affect the technical content, the changes are not tracked by the use of lines in the margin.

Patents. The description in the European 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.

Chemical Abstracts Service (CAS) registry number. In the 6th Edition, CAS registry numbers have been included for information in monographs, where applicable, to provide convenient access to useful information for users. Previously these numbers were given only for reagents, where they are of use in locating suppliers. CAS Registry Number® is a Registered Trademark of the American Chemical Society.

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.

MONOGRAPHS ON PHARMACEUTICAL PREPARATIONS

According to the current policy of the Commission, monographs on pharmaceutical preparations are not elaborated, with the exception of those on immunosera for human use, immunosera for veterinary use, some biological preparations such as insulin preparations, radiopharmaceutical preparations, vaccines for human use and vaccines for veterinary use. This policy has been established since:

- the specifications for a given preparation are approved by the competent authority in light of data from pharmaceutical development work and stability studies; a unique specification for the dosage form of a given active substance would therefore be inappropriate in most instances;
- specifications for a pharmaceutical preparation depend on factors related to the particular formulation and a mandatory quality standard could hamper innovation and improvement by setting acceptance criteria that are contingent rather than essential.

Harmonisation and standardisation for pharmaceutical preparations have so far been dealt with via the drafting of general dosage form monographs setting out elements common to all preparations within the scope of the monograph, and via the development of standard test methods used for testing of finished products. The inclusion of these general monographs and methods in the European Pharmacopoeia gives a common basis for competent authorities and manufacturers in the preparation and evaluation of applications for marketing authorisation.

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 one of the three annual sessions. In general, whenever two 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. Interested parties are invited to contact the Secretariat for any items where they wish to be involved in the work.

CERTIFICATION PROCEDURE

A procedure for the certification of suitability of monographs of the Pharmacopoeia with respect to control of the quality 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 the EDQM and on its website] 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 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 of the operation of this scheme are available from the Secretariat and on the EDQM website. A daily updated list of 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, in the form of a book with 3 supplements per year, and in electronic form (online and CD-ROM). An electronic version in Spanish has been available since July 2006 for the convenience of Spanish-speaking users.

Pharmeuropa, the European Pharmacopoeia Forum, is published 4 times per year as an aid for the elaboration of monographs and as a vehicle for information on pharmacopoeial and related matters. *Pharmeuropa Bio*, a publication indexed by bibliographic services, includes papers mainly related to the establishment of biological reference preparations and validation of biological methods within the Biological Standardisation Programme of the EDQM. *Pharmeuropa Scientific Notes*, a publication indexed by bibliographic services, presents scientific papers on all aspects of pharmaceutical analysis and other subjects relevant to the Pharmacopoeia.

Website. Information on activities and many other aspects of the European Pharmacopoeia is to be found on the EDQM website.

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

- chromatography columns used in monograph development;
- suppliers of reagents and equipment that may be difficult to find for some users;
- the status of monographs (in development, adopted, published, under revision);
- revisions of the monographs on a historical basis, beginning from the 5th Edition;
- other useful information.

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 of the European Pharmacopoeia. The HelpDesk has a section of Frequently Asked Questions that should be consulted by users before submission of an enquiry.

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 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 Public Health Committee 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.

Revision programme. Monographs and other texts of the European Pharmacopoeia are revised as necessary following a decision of the Commission. Revision proposals are published in *Pharmeuropa*. Proposals to revise monographs may be submitted by a delegation, by the Chair of the Commission or by the chair of a group of experts. Requests for revision from other parties should be submitted via the national pharmacopoeia authority of a Member State or, where this is not possible, to the EDQM, preferably via the HelpDesk. Proposals to revise monographs must be accompanied by sufficient data to justify the need for revision.

COMBISTATS

Certain tests 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

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 general chapter *5.8. Pharmacopoeial harmonisation* and on the PDG page of the EDQM website. 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 2006

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