GUIDE FOR THE WORK OF THE EUROPEAN PHARMACOPOEIA

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Guide for the work of the European Pharmacopoeia Commission

The Commission has prepared this Guide in order to build an efficient network for the activities of the European Pharmacopoeia Commission and those who participate in its work: delegates, experts, specialists, national secretariats, EDQM as secretariat, European organisations, industry, the universities and others.

The Guide describes the desired working methods that should be followed unless in exceptional and justified cases, there are good reasons for not doing so. It explicits and complements the Rules of Procedure of the European Pharmacopoeia Commission.

The work of the Commission and its Groups of Experts and Working Parties requires a certain commitment from the participants and a willingness to respect established procedures so that public health authorities and the public have an assurance that the human and scientific resources have been used in a timely and efficient manner.

1. EUROPEAN PHARMACOPOEIA COMMISSION

1.1 Activities

1.1.1 The legal framework for the use, elaboration and updating of the European Pharmacopoeia in close collaboration with its stakeholders is summarized in Annex 1.

1.1.2 A notification for suspected deficiencies in European Pharmacopoeia monographs to be used by the licensing authorities is given as Annex 2.

1.1.3 The Commission defines its Code of Practice.

1.1.4 The Commission elaborates detailed working procedures for the elaboration of monographs (See Annex 3)

1.1.5 The Commission establishes a list of basic documents that are to be provided to each appointed expert and specialist (see Annex 4).

1.2 Delegations

1.2.1 If a delegation intends to raise technical matters relating to an item on the agenda for a forthcoming session of the Commission it should notify in written in advance the Chair of the Commission, the Chair of the Group of Experts or Working Party concerned and the Secretariat. Appropriate steps should then be taken to resolve the points at issue before the item is discussed in session.

1.2.2 Delegations should submit in writing editorial comments on documents for adoption to the Chair of the Commission, the Chair of the Group of Experts or Working Party concerned and the Secretariat.

1.2.3 Delegations may propose Experts and Specialists for appointment to the Groups of Experts and Working Parties. When making proposals, the delegations should take into account whether the nominees have at their disposal the facilities necessary to contribute to the work of the Group of Experts or Working Party. The proposal should be accompanied by information on the relevant experience of the nominee (curriculum vitae). The curriculum vitae is held by the Secretariat and provided to the Presidium.

On request it might also be provided to Chairs of Groups of Experts or Working Parties.

1.2.4 When proposing an Expert or a Specialist for re-nomination, the delegation should consider the past contribution of the nominee and may consult the Chair of the Group of Experts or Working Party concerned, the Secretariat and the Presidium for advice on this.

1.2.5 Delegations should make every effort to send their comments or other contributions to matters to be treated by correspondence within the agreed deadlines. A delegation failing to observe a deadline should consider the disadvantages involved in delaying adoption of a text before asking the Commission to take a comment or contribution into consideration.

1.2.6 Delegations should send to the Chair of the Commission copies of all correspondence relevant to the work of the Commission.

2. GROUPS OF EXPERTS AND WORKING PARTIES

2.1 Activities

2.1.1 The procedures for elaboration of monographs and general chapters of the European Pharmacopoeia are described in Annex 3.

2.1.2 During the work, due consideration is taken of the relevant Technical Guide for the Elaboration of Monographs wherever applicable. Editorial style is taken care of by the Secretariat.

2.1.3 Where relevant, draft monographs, general chapters or other texts submitted by Experts and Specialists must be accompanied by validation reports relating to the methods proposed together with batch analysis for the full range of tests. Validation reports are archived at EDQM and are not released to third parties. The tests should be verified in at least a second laboratory. Specifications in monographs should be based on those for products approved in Member States.

2.1.4 Experts and Specialists should submit their monograph proposals together with a report including experimental results and summarising all available scientific information, including validation data.

2.1.5 Wherever possible work should proceed by correspondence between a limited number of Experts or Specialists (co-ordinator and co-workers). Copies of all relevant correspondence are sent to the Chair of the Group of Experts or Working Party and to the Secretariat. The aim of the preliminary exchange by correspondence between the co-ordinator and co-workers is to provide a good basis for the Group of Experts or Working Party to finalise the drafts as promptly as possible.

2.2 Chairs of Groups of Experts and Working Parties

2.2.1 Wherever possible, the Chair holds a preparatory meeting with the Secretariat prior to the meeting.

2.2.2 The Chair, with the support of the Secretariat, ensures that drafts are based on the Commission's relevant Technical Guides and are supported by the necessary documentation in the form of experimental results, reports of group meetings, validation data and an explanatory note, particularly for revision proposals.

The Chair ensures that scientific grounds are adequately reflected in the decisions of the Group of Experts or Working Party.

The Chair monitors, together with the Secretariat, that the present Guide for the Work is respected.

The Chair, with the support of the EDQM, follows up the appropriate work for establishing the reference standards.

2.2.3 The Chair decides, in consultation with the members, when a draft can be published in Pharmeuropa for comment.

2.2.4 Comments received after publication in Pharmeuropa are considered by the Group of Experts or Working Party concerned. The Chair ensures that the comments are considered according to their merits. Wherever a proposal for change is not accepted, the Chair ensures that the reasons are clearly formulated. When a substantial change is introduced in the light of the results of the enquiry, the text is published in Pharmeuropa again for comment.

2.2.5 The Chair decides, in consultation with the members, when a draft for a monograph, general chapter or other text can be submitted to the Commission for adoption. The Chair should be prepared, on behalf of the Group of Experts or Working Party, to resolve in session minor points raised by delegations of the Commission.

2.2.6 The Chair decides, in consultation with the Secretariat, the agenda for a meeting. Normally documents should be received by members a week in advance of the meeting.

2.2.7 The Chair ensures that only authorised persons are attending the meeting.

2.2.8 The Chair ensures that impartiality is maintained in case an interest is declared.

2.2.9 Where necessary, the Chair refers to the Commission in writing any question requiring a decision of principle prior to continuation of work on a given item.

2.2.10 Chairs report regularly to the Commission on progress with the work programme, highlighting items where the work has not advanced as expected and the reasons for this.

2.2.11 Chairs of Groups of Experts and Working Parties should be prepared to attend and play an active role in conferences organised by EDQM on subjects relevant for the activities of their Group of Experts or Working Party.

2.3 Experts and Specialists

2.3.1 Experts and Specialists should meet the selection criteria approved by the Commission. They contribute on a voluntary basis having fully understood the commitment involved.

2.3.2 Experts and Specialists receive the basic documents decided by the Commission (see Annex 4).

2.3.3 Each Expert or Specialist should make a fair contribution to the work of the Group of Experts or Working Party, including the provision of results of experimental work, where required, and respect the time limits set for assignments.

2.3.4 Experts and Specialists should maintain the correct degree of privacy concerning the work of the group.

2.3.5 An Expert or a Specialist should maintain proper communication with the National Pharmacopoeia Authority and the Secretariat, for example by making regular reports on the progress of work.

2.3.6 An Expert or a Specialist should inform the National Pharmacopoeia Authority and the Secretariat in good time if he/she is unable to attend a meeting.

2.3.7 A Specialist will attend meetings upon invitation by the Secretariat with the agreement of the Chair.

2.4 Meetings

2.4.1 Meetings should be held in Strasbourg. If it is proposed to hold a meeting elsewhere, the Chair should make a request in writing to the Director of EDQM providing justification for this in terms of the contribution to the advancement of the work of the Group. National Pharmacopoeia Authorities may be consulted.

2.5 Observers

2.5.1 Where so authorised by the Commission, observers may participate in the scientific and technical discussion and experimental work organised by the Group of Experts or Working Party, with a view to helping in its advancement.

2.5.2 An observer may contribute to the elaboration of a monograph, a general chapter or another text.

3. EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES AND HEALTH CARE

3.1 European Pharmacopoeia Department (EPD)

3.1.1 The Secretariat of the European Pharmacopoeia and its Groups of Experts and Working Parties is performed by the European Pharmacopoeia Department (EPD) of EDQM. The Head of this Department acts as scientific Secretary to the Commission.

3.1.2 The Secretariat arranges Sessions of the Commission and meetings of the Groups of Experts and Working Parties and any other meetings asked for by the Commission. Convocations, which should indicate the venue and duration of a session or a meeting are sent to the Delegates and/or Experts/Specialists, to Liaison Sections of the European Committee on Pharmaceuticals and Pharmaceutical Care and to central addresses of National Pharmacopoeia Authorities in adequate time, normally not less than 4 weeks before the meeting or session, to allow appropriate arrangements to be made.

3.1.3 For Sessions of the Commission, the Secretariat draws up a draft agenda, in consultation with the Chair. This draft agenda is sent to delegations so as to be available not less than 6 weeks before the Session. The agenda is drawn up taking into account comments received from delegations normally by the deadline indicated on the draft agenda. The agenda is sent to delegations such as to be available at least 3 weeks before the Session. An addendum to the agenda is prepared and provided to delegations at the beginning of the Session. The final agenda is adopted by the Commission at the beginning of the Session on the basis of the agenda and the addendum. If the addendum to the agenda contains an item submitted for adoption at the Session, this item may be deleted from the agenda on request of a delegation or adopted subject to confirmation by delegations following the Session.

3.1.4 For meetings of Groups of Experts and Working Parties, the Secretariat draws up a draft agenda, in consultation with the Chair of the Group of Experts or Working Party.

This draft agenda is sent to Experts and Specialists so as to be available not less than 3 weeks before the Meeting. The agenda is regularly updated based on the contributions of members. The final agenda is presented for adoption by the members at the beginning of the meeting.

3.1.5 Documents for adoption at a Session of the Commission are normally sent so as to be available not less than 14 days before the Session.

Documents submitted for adoption are posted on the DRT (Document Review Tool) of the EDQM to allow Delegations to enter their comments (if any). Comments are entered either in English or in French, in the English version of the text.

3.1.6 The Secretariat draws up an annual plan for the meetings of the Groups of Experts and Working Parties, in consultation with the Presidium. The Secretariat may propose, in consultation with the Presidium, to hold additional meetings if needed.

3.1.7 The Secretary to the Commission issues a summary of proceedings of each session within 14 days. The summary of the session shall briefly indicate for each item on the agenda the decision taken (adoption, adoption subject to confirmation by one, several or all delegations).

3.1.8 The Secretariat issues a summary of proceedings of a meeting within one week of the meeting. The summary of the meeting of a Group of Experts or Working Party shall briefly indicate for each item on the agenda the decision taken (discussion during the next meeting, Pharmeuropa, Commission) and any follow-up to be made.

3.1.9 The Secretary to the Commission issues the draft records of sessions of the Commission in the two official languages within 4 weeks. A deadline for comments on the draft record is set at not more than 6 weeks before the beginning of the next session. The record, amended if necessary, is issued promptly after the deadline.

3.1.10 The Secretariat issues the reports of Group meetings within 8 weeks unless otherwise agreed with the Chair. Each report shall indicate inter alia the names of the participants and the duration of the meeting; it shall have the summary of proceedings as a preface and the work programme of the group on new and revised texts, with the state of advancement, as an appendix. When a change proposed in writing by a National Pharmacopoeia Authority or by a manufacturer is not agreed, the Secretary clearly indicates the reasons for non-acceptance of the proposal in the report.

3.1.11 The Secretariat prepares new versions of working documents as necessary and sees to it that the correct editing style is used in draft monographs, general chapters and other texts of the Pharmacopoeia using the Style Guide.

3.1.12 Where a document is to be adopted by the Commission by correspondence, the Secretariat distributes the document to all delegations and to National Pharmacopoeia Authorities and indicates a deadline for adoption. If no delegation opposes adoption by the deadline, the Secretariat forwards the document for publication and informs the Commission at the next Session.

3.1.13 The Laboratory Department (DLAB) organises the adoption of reference standards.

Reference standards are adopted by correspondence. Reference standard establishment reports are approved by correspondence, unless an issue has arisen which makes the approval by the Experts/Specialists possible only after discussion in a meeting.

3.1.14 For adoption of reference standards by correspondence, the members of the relevant Group of Experts or Working Party are alerted by the DLAB and requested to approve the reference standard laboratory report within 3 weeks. In case of urgency this deadline might be shortened. The reference standard establishment report is considered approved by the Group of Experts/Working Party when no objection is received within the given deadline. The delegations are contacted after that by the DLAB for agreement of the adoption of the reference standard within 14 days, after which the reference standards are considered adopted and will be released. At each Session of the Commission, a document is presented which gives the detail of substances adopted, with the dates of approval by the Groups and adoption by the Commission.

3.1.15 The Secretariat, in consultation with the appropriate Chair, makes the necessary contacts with manufacturers or other suppliers in order to obtain samples of material needed for work on monographs, general chapters and other texts and for use as reference standards and to request proposals for specifications and validated methods to be included in monographs, general chapters or other texts.

3.1.16 The Secretariat submits to the Commission any proposals made in accordance with rules 20-23 of the Rules of Procedure for elaboration, revision or suppression of monographs, general chapters or other texts.

3.1.17 The Secretariat provides to the Commission, National Pharmacopoeia Authorities and delegations at regular intervals a document showing the state of advancement of all items (new and revised) on the work programme.

3.1.18 The Secretariat organises public conferences on subjects related to the work of the Commission where this is useful for achieving progress.

3.1.19 The Secretariat maintains suitable liaison with other parts of EDQM to ensure proper co-ordination of work.

3.1.20 Following the decision of the Commission to create a Group of Experts or Working Party, the Secretariat sends to National Pharmacopoeia Authorities and delegations an invitation to submit proposed nominations, indicating the terms of reference of the group and the profile expected for its members.

3.1.21 Not later than 6 months before the end of the term of office of Groups of Experts and Working Parties, the Secretariat sends to National Pharmacopoeia Authorities and delegations an invitation to submit proposed nominations, indicating the terms of reference of the group and the profile expected for its members.

3.1.22 Where a change to the work programme is proposed (addition or deletion of an item), the Secretariat sends a questionnaire to National Pharmacopoeia Authorities to determine whether they are in favour of the proposed change. Where deletion of an item is proposed because of lack of information on producers, if a National Pharmacopoeia Authority is in favour of maintaining the item on the work programme, the Authority shall endeavour to provide the information needed.

3.1.23 Where it is proposed to suppress a published monograph, a general chapter or another text, the Secretariat sends a questionnaire to National Pharmacopoeia Authorities to determine whether they are in favour of the proposed suppression.

3.1.24 The Secretariat organises an annual meeting of Secretaries of National Pharmacopoeia Authorities to facilitate and co-ordinate the activities of common interest and to provide a forum for exchange of information. This meeting is normally hosted by one of the Authorities on a rotation basis.

3.1.25 When needed, the Secretariat may organise hearings of relevant industry associations. Wherever possible, the Chair of the Commission and, where applicable, the Chair of the Group of Experts or Working Party concerned attend the meeting.

3.1.26 The Secretariat maintains the Knowledge database on the EDQM web site, providing supplementary information on monographs, general chapters and other texts for the assistance of users.

3.1.27 The Secretariat participates in the activities of the Pharmacopoeial Discussion Group together with representatives of the Japanese Pharmacopoeia and the United States Pharmacopeia and ensures that work is carried out with due respect for the Commission's established procedures. The secretariat makes liaison with the relevant groups of Experts and Working parties and informs the Commission of the state of work.

3.1.28 The Secretariat participates in the work of other bodies which have an impact on the work of the Commission, notably relevant committees of the European Medicines Agency (EMA), the Commission of the European Community, the World Health Organization and the Organisation Mondiale de la Santé Animale (OIE). Reports are made to the Commission on this participation.

3.2 Laboratory Department (DLAB)

3.2.1 The Laboratory contributes to the work on elaboration of monographs, general chapters and other texts at the request of the Commission or of a Group of Experts or Working Party.

3.2.2 A member of the scientific staff of the Laboratory should, wherever possible, attend the meetings of Groups to advise on aspects related to reference standards and for the discussion on work in which they have participated and on which they have reported to the group.

3.3 Reference standards

3.3.1 The Laboratory Department (DLAB) and the Department of the Biological Standardisation and OMCL (DBO) participate in the establishment and monitoring of reference standards.

3.3.2 The DLAB, in co-operation with the relevant Groups of Experts or Working Parties, undertakes work necessary for establishing reference standards. It carries out the establishment of reference standards and reports to the relevant Group of Experts or Working Party on work done.

3.3.3 The DBO, in co-operation with the relevant Groups of Experts or Working Parties, undertakes work necessary for establishing Biological Reference Preparations. It carries out the establishment of reference preparations and reports to the relevant Group of Experts or Working Party on work done.

3.3.4 The DLAB and the DBO ensure that the work for establishing any new reference standard is carried out so that the standard can be made available in good time for the entry into force of the monograph, preferably at the time of publication.

3.3.5 The DLAB and the DBO ensure that the work for establishing any replacement batch of reference standard is carried out so as to ensure continuous supply to users.

3.4 Publications and Multimedia Department (DPM)

3.4.1 The Publications and Multimedia Department (DPM) arranges for the publication in suitable form of monographs, general chapters and other texts adopted by the Commission.

3.4.2 The DPM arranges for publication of Pharmeuropa, which contains all texts issued for public enquiry and comment together with scientific notes, general information on the work of EDQM etc.

3.4.3 The DPM issues a definitive version of each text for publication adopted by the Commission. Corrections made to definitive texts before publication are notified to the interested parties, notably delegations and National Pharmacopoeia Authorities.

3.4.4 The DPM exercises general oversight for the drafting style of texts to be published and notifies the Secretary of the Group concerned of any problems.

3.4.5 The DPM prepares and updates the Style Guide.

3.5 Quality management system

3.5.1 The EDQM elaborates and implements a quality management system for its work in each of its departments according to an internationally acknowledged standard .

4. NATIONAL PHARMACOPOEIA AUTHORITIES

4.1 General role

The general role of the National Pharmacopoeia Authorities is outlined in Annex 1.

4.2 Activities

The National Pharmacopoeia Authority is the department within each Contracting Party, responsible for maintaining proper communication with the EDQM. By virtue of Rule 8.1 of the Rules of Procedure, each National Pharmacopoeia Authority must have (a) qualified person(s) (pharmacist or equivalent), responsible for implementation of the decisions of the Commission.

The necessary secretarial support is provided to the National Pharmacopoeia Authority to fulfil and assure the coordination of the following essential functions:

- preparation of and/or implementation of the European Pharmacopoeia and its supplements at national level;

- responding to questionnaires from EDQM on the work programme of the European Pharmacopoeia;

- provision of information on local manufacturers and other interested parties who wish to contribute to the work;

- inform their Expert Committees and local manufacturers, where necessary, on advanced drafts considering the necessary degree of confidentiality,

- forwarding to EDQM of national comments on Pharmeuropa drafts,

- briefing of Commission members before sessions;

- forwarding proposals for Experts and Specialists as members of Groups of Experts and Working Parties;

- provision of information on the European Pharmacopoeia to local users, in addition to the user support provided by EDQM (HelpDesk);

- attendance at annual meetings of National Pharmacopoeia Authorities to promote exchange on working methods etc. within Member States;

- notification of elaboration of national texts to the Commission.

4.3 Duties

4.3.1 National Pharmacopoeia Authorities are required to send their comments on a draft for a monograph or other text to the Secretariat within the indicated deadline. The deadline is usually 60 days from the deadline for public comment indicated in Pharmeuropa. If an amended draft is resubmitted for comment, no new matters can be raised in the comments. Comments are entered on the DRT (Document Review Tool) of the EDQM. Comments received after the deadline will be taken into account at the discretion of the Chair of the Group of Experts/Working Party and only where it is indispensable to do so.

4.3.2 Proposals for a fundamental change in a draft text should be well founded and should be supported, wherever necessary, by experimental evidence. Proposals that are not well founded or not supported by experimental evidence are considered but normally rejected on these grounds.

4.3.3 Any comment on a document should contain a substantiated proposal for its improvement or should clearly state the action expected and the reasons for this. Comments which do not fulfil these requirements will be considered but will normally be rejected on these grounds.

4.3.4 National Pharmacopoeia Authorities should maintain communication with the Experts and Specialists from their country whilst respecting their independent position as scientific advisers to the Commission.

5. OTHERS

5.1 Manufacturers and other interested parties from Member States of the Ph. Eur. Convention

5.1.1 Comments on Pharmeuropa texts should be submitted via the National Pharmacopoeia Authority.

5.1.2 Proposals for new items for the work programme or for revision of monographs or general chapters should be submitted via the National Pharmacopoeia Authority (according to the Rules of Procedures proposals from observers can be made via a delegation or via the Secretariat in Strasbourg).

5.1.3 Technical enquiries on monographs and other texts should be submitted, preferably in writing, either to the National Pharmacopoeia Authority or via the EDQM HelpDesk.

5.2 Manufacturers and other interested parties from non-Member States of the Ph. Eur. Convention or multinational interested parties:

5.2.1 Comments on Pharmeuropa texts should be submitted preferably via the National Pharmacopoeia Authority of the Member State where the product is authorised.

5.2.2 In case the Manufacturer or other interested party from non-Member States or multinational interested party selects the EDQM HelpDesk for submitting comments on Pharmeuropa texts(preferably as attachments to the enquiry form), it shall indicate the Member State(s) where the product is authorized.

5.2.3 Proposals for new items for the work programme or for revision of monographs or general chapters should be submitted to the Secretariat in Strasbourg.

5.2.4 Technical enquiries on monographs and other texts should be submitted via the EDQM HelpDesk.

5.3 International organisations

5.3.1 Communications should be made via the Secretariat in Strasbourg.

5.4 Industry associations or other associations

5.4.1 Communications should be made via the Secretariat in Strasbourg.

6. REVISION OF TEXTS

This chapter details the requirements and procedure for revisions of European Pharmacopeia monographs in accordance with Rule 21 of the Rules of procedure.

6.1 Technical revisions

6.1.1 Requests for revision should be submitted using the standard form (see Annex 5) for this purpose. The parts of the text to be revised should be clearly identified and where possible a concrete proposal should be formulated. The Group of Experts or Working Party may make a preliminary evaluation of the revision request before examination by the Commission if this is convenient taking account of meeting dates.

However, work on the revision should not start before the Commission has decided to add the item to the work programme.

6.1.2 Requests for revision should be accompanied by sufficient information to enable the Commission to decide whether revision is justified and necessary and to accord the appropriate priority. Where a request for revision does not fulfil the above criteria, after consultation with the Chair of the Group of Experts or Working Party and/or the Chair of the Commission, the Secretariat may refer the matter back to the originator with a substantiated request for further information.

6.2 Minor revisions

In the interest of simplification of working procedures, minor revisions may be submitted directly to the Commission where the Chair of the Group of Experts/Working Party or the Secretariat considers that prior publication in Pharmeuropa is not needed.

Submission of a minor revision implies that the change is not controversial and that the Commission will be able to decide simply on the basis of the briefing note to the monograph that the revision is justified and necessary. The briefing note is later posted in the “View History” field of the Knowledge database, after editorial adaptation where necessary, to inform users of the reasons for the change.

6.3 Corrections of errors

The Secretariat arranges for prompt republication of a text wherever notification of an error in the text or editorial style modification is received and informs the Commission and National Pharmacopoeia Authorities. Corrections that can be made with simple notification include: differences between the English and French texts where the correct version is evident; items that clearly do not correspond to the decision of the Group of Experts, the Working Party and/or the Commission.

ANNEX 1

USE, ELABORATION AND UP-DATING OF THE EUROPEAN PHARMACOPOEIA

INTRODUCTION

The European Pharmacopoeia is elaborated under an international convention of the Council of Europe. The Convention has been signed by 36 States and by the European Union. The signatories to the Convention undertake:

"to take the necessary measures to ensure that the monographs which … constitute the European Pharmacopoeia shall become the official standards applicable within their respective countries."

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

– facilitates the free movement of medicinal products in Europe;

– ensures the quality of medicinal products exported from Europe.

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

– regulatory authorities;

– those engaged in the control of quality;

– manufacturers of starting materials and medicinal products.

The European Pharmacopoeia can only fulfil its role properly when each of the interested parties participates actively in the process of elaboration and updating of standards. This note is intended to outline the elements of active participation.

EXCHANGES BETWEEN THE PHARMACOPOEIA AND STAKEHOLDERS

The Pharmacopoeia, an integral part of the regulatory control system for the quality of medicines, will remain useful only if it is promptly adapted to the needs of its users, notably the experts dealing with applications for marketing authorisation (assessed by the competent authorities and prepared by the manufacturers). Hence, the Pharmacopoeia has taken measures to respond promptly to requests from competent authorities.

First, the role of the Pharmacopoeia with respect to that of licensing authorities should be recalled:

Unlike licensing dossiers, which are prepared and assessed for an individual product, the Pharmacopoeia is the indispensable communication and standardisation tool that allows a

uniform standard to be applied; it should be maintained up-to-date to avoid duplication of work (and therefore increases in costs) and above all anarchy or differences in requirements; by providing harmonised, validated analytical methods, specifications and units, by establishing common reference standards for all European specialists, it acts as a reliable reference tool for communication, it links individuals, and it facilitates national and international administrative, commercial and scientific exchange between all the partners responsible for the design, manufacture and quality control of medicines, in both the public and private sectors.

This common tool continues to serve its users only if they wish and are able to make their opinions or needs for adaptation known.

Legally, the tripartite relationship between the Pharmacopoeia - Licensing Authorities – and Manufacturers is clarified by national legislation, notably EU directives (currently 2001/82, 2001/83 and subsequent amendments). They are summarized into the principles as follows:

Principle no 1: the European Pharmacopoeia and its standardised and validated specifications, adopted unanimously by the national delegations, are binding.

This was codified in Annex 1 to Commission Directive 2003/63/EC,

- Introduction and general principles, (5): “With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.”

- Chapter 3.2(5):“The monographs of the European Pharmacopoeia shall be applicable to all substances appearing in it...”

- “In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section “remark: of an application for a marketing authorization” by the appropriate detailed reference to the monograph(s) and general chapter(s).

Principle no 2: In exceptional cases , if it appears that the control of a product or specific preparation in a licensing dossier is inadequate, the licensing authority and the applicant for marketing authorisation must have additional tests.

“However, where a starting material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described...

In case where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the person responsible for placing the product on the market...”

Principle no 3: Where it has been found that a monograph is not sufficient to cover all products on the market , the licensing authority must inform the European Pharmacopoeia in general terms without breaking confidentiality and must ask the manufacturer to contact the Pharmacopoeia to up-date the monograph.

"...The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The person responsible for placing the product on the market shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied..."

Practically, the conditions for achieving these three principles merit clarification.

Regarding Principle no 1:

It is clear that application of principles 2 and 3 will be needed less if the texts of the European Pharmacopoeia are updated regularly. This means setting up a mechanism in the European Pharmacopoeia Commission allowing rapid up-dating and, outside the European Pharmacopoeia, the organisation of frequent, regular and effective communications with its different partners involved.

Within the European Directorate for the Quality of Medicines and HealthCare (Council of Europe, Strasbourg), the European Pharmacopoeia has a permanent Scientific Secretariat and a Laboratory dedicated to the elaboration and updating of monographs and general chapters.

The principles applied in elaboration of monographs are outlined in a series of Technical Guides, available for download from the EDQM web site (www.edqm.eu). The methods included are validated according to current guidelines. The monograph specifications are based on currently approved medicinal products in Member States. This applies in particular to impurity profiles and all specified impurities in monographs can be considered to be qualified at or above the level of the acceptance criterion.

In view of the above, it is essential that manufacturers respond to invitations from the Secretariat to participate in the work of elaboration and revision by providing samples and data. The Secretariat regularly sends out such invitations via industry associations and via individual pharmacopoeia liaison persons notified by manufacturers.

Different procedures are applied for elaboration of monographs but in all cases draft new monographs and drafts of revision proposals are published in Pharmeuropa for public consultation.

It is essential that competent authorities have in place a system for critical examination of Pharmeuropa drafts and generation of comments to be provided to the Secretariat. Similarly, manufacturers should have in place a system of alert for identification of drafts that are of interest and development of comments.

EDQM sends notifications to interested parties whenever an item is added to the work programme (new monograph or revision proposal). Interested parties are invited to contact EDQM and participate in the work, notably by providing data and samples of their product.

It is essential that interested parties have in place a system for identification of items of interest and that they contact EDQM in a timely manner. Appointment of a pharmacopoeia liaison within the company and notification of EDQM of the contact details is the most effective means.

Regarding Principle no 2:

A monograph may be incomplete and not cover an impurity present in a product manufactured by a new route of synthesis or of purification. When a marketing authorization is requested for a medicinal product containing such a substance for reasons of public health the applicant must submit additional information and the licensing authority must demand it.

The National Pharmacopoeia Authority is the most effective liaison for notification of suspected deficiencies in monographs. The form shown in the Annex 2 can be used for brief notification of a suspected deficiency in a monograph. The HelpDesk on the EDQM web site can also be used for communication of this type.

In the light of the international growth of trade, which is likely to make this situation more common, the demonstration that the reference to the Pharmacopoeia is suitable for a given source is requested by current guidelines of the Quality Working Party established under the Human Medicinal Products Committee and the Committee for Veterinary Medicinal Products (EMA)

To simplify the compilation of the marketing authorisation dossier and to make the reference to the Pharmacopoeia directly usable, the procedure for certification of suitability has been set up; this procedure allows the manufacturers to demonstrate the applicability of the monograph to their product whilst protecting the confidentiality of intellectual property. If the monograph does not provide adequate control, the certificate will be accompanied by additional requirements, pending revision of the monograph.

Regarding principle No 3:

As the Pharmacopoeia is the instrument shared by the three partners (two use it, one elaborates and up-dates it), the existing means of communication between them should be optimised to respond better to the specific needs of each partner whilst respecting its constraints.

Licensing authorities and manufacturers have similar needs:

•Reliable, accurate, transparent standards

•Up-to-date monographs

•Validated reference methods

Licensing authorities are constrained by the need for confidentiality of data submitted in licensing applications. Manufacturers can submit data to EDQM knowing that it will be treated in confidence if they so request, although the end result, a public standard will of course be freely available.

The Pharmacopoeia has its particular needs:

•Information on the market situation

•Information on the needs of licensing authorities in terms of general policy on safety and efficacy and public health policy

•Data and samples representative of approved products on the market. The main constraints for monograph development are:

•the work involved in development of validated and standardised methods that cover the range of available products;

•availability of substances needed to prepare reference standards.

Each partner should clearly understand the needs and constraints of the other two. For its part, EDQM, is committed to the following:

•Openness in monograph development based on the principles laid down in the relevant Technical Guide, available on the EDQM web site;

•Development of transparent monographs that can fully serve the needs of all users, with support from the Certification Procedure;

•Priority drafting of monographs and general chapters requested by licensing bodies, notably the Committees and Working Parties of EMA;

•Effective operation of the Certification Procedure to reduce the workload of assessors for the relevant part of an application;

•Publication of monographs on active substances at least 2 years before patent expiry so that a standard will be available when generic applications are made;

•Continuous development of the resources of the EDQM web site as a support for all aspects of the work;

•Organisation of hearings of interested parties at regular intervals or on request to promote exchange on all aspects related to our work

NATIONAL PHARMACOPOEIA AUTHORITIES

The process of monograph development is mainly undertaken at European level, with Member States contributing resources to this collaborative process rather than developing national standards. There is a consequent saving of resources and there is no subsequent need

to harmonise national positions. The role of national pharmacopoeia authorities has therefore evolved and they have become part of an active network functioning in different direction for:

•Provision of expertise for European monograph development;

•Provision of information on the local market situation for medicinal products;

•Relaying of information on the pharmacopoeia at the local level

•Liaison at local level between interested parties and EDQM

EDQM organises an annual meeting of Secretaries of National Pharmacopoeia Authorities, to facilitate and co-ordinate the activities of common interest and to provide a forum for exchange of information.

ANNEX 2

NOTIFICATION OF A SUSPECTED DEFICIENCY IN A MONOGRAPH OF THE EUROPEAN PHARMACOPOEIA

According to Directive 2003/63/EC a licensing authority should inform the Secretariat of the European Pharmacopoeia when, during the assessment of an application for marketing authorization, requirements in a monograph of the European Pharmacopoeia have to be supplemented in order to control sufficiently a raw material from a particular manufacturer.

Furthermore, the manufacturer has an obligation to cooperate with the European Pharmacopoeia Commission with a view to updating the monograph.

The licensing authorities cannot submit to the Secretariat of the European Pharmacopoeia any confidential information from a marketing authorisation application. Therefore, the information submitted to the Secretariat of the European Pharmacopoeia, if possible with the help of the National Pharmacopoeia Authorities, can be limited to a statement of the title of the monograph, the name of manufacturer, and the nature of deficiency in the monograph, etc. The Secretariat of the European Pharmacopoeia will then contact the manufacturer to obtain directly the more detailed information to allow initiation of the revision process.

When informing the Secretariat of the European Pharmacopoeia the following standard format may be used:

The information should be sent to:

European Pharmacopoeia Department

EDQM

Council of Europe

7, allée Kastner

CS 30026

F – 67081 STRASBOURG

France

Fax: (+33) 3.88.41.27.71

Name of monograph

Problem encountered (e.g. test for related substances, insufficient, additional testing needed, test replace due to malfunctioning etc.)

Name and address of manufacturer of finished product

Name and address of licensing authority and name of assessor

Name and address of the national Pharmacopoeia Authority

ANNEX 3

PROCEDURES FOR ELABORATION OF MONOGRAPHS FOR THE EUROPEAN PHARMACOPOEIA

The work programme is decided by the European Pharmacopoeia Commission. The Commission considers for addition to the work programme monographs on active substances, excipients and, for certain classes, medicinal products that are approved for use in Member States. In the interests of public health, the Commission may decide to elaborate monographs on articles that do not meet these criteria. At the time of addition to the work programme, a monograph or general chapter is allocated to a procedure and to a group of experts or working party.

PROCEDURE 1

ELABORATION BY A GROUP OF EXPERTS

1. INITIATION

1.1 Following addition of an item to the work programme, for items to be dealt with by Procedure 1, the Secretariat circulates information to the public via industry associations, pharmacopoeia liaison persons of manufacturers, the EDQM web site and Pharmeuropa Interested parties are invited to contact the Secretariat with a view to providing samples and data and participating in the work.

1.2 The Secretariat identifies the manufacturers of the substance from information provided by the National Pharmacopoeia Authorities and any other information it may have.

1.3 The Secretariat sends manufacturers/suppliers of the substance a standard letter informing them of the procedure and the programme to be followed and asking them to:

i) supply current production batches and small amounts of the known impurities;

ii) supply in-house specifications for period-of-use for all grades, as accepted by the licensing authorities, methods of analysis and analytical validation data;

iii) supply batch analysis data for stability batches;

iv) if possible, supply a batch which can be subsequently used as a chemical reference substance (CRS), if required.

2. PREPARATION OF THE DRAFT MONOGRAPH

2.1 Each substance is attributed to a co-ordinator and if necessary a co-worker within the Group.

2.2 After receiving the samples and documentation requested, the Secretariat sends copies of the documentation and portions of the samples to the co-ordinator and, if necessary, to the co-worker.

2.3 After receiving the samples and the data, the co-ordinator agrees target dates for completion of the laboratory work (preferably not more than 6 months) and initiates the work required, if necessary, in collaboration with the manufacturer and the coworker.

2.4 The co-worker or, in exceptional cases, the Ph. Eur. laboratory carries out the necessary verifications and sends comments to the co-ordinator who informs the Ph.Eur. Secretariat on progress.

2.5 The first draft, conforming to the relevant Technical Guide for the Elaboration of Monographs and the style guide is produced by the co-ordinator, ideally within 3 months after the completion of the laboratory work.

2.6 The draft is then submitted to the Secretariat in one of the official languages, the Secretariat is responsible for translation of the texts into the other official language and for final editorial verification of the texts.

3. APPROVAL FOR PUBLICATION IN PHARMEUROPA

3.1 The draft monograph and a report of the studies carried out are presented to the Group of Experts.

3.2 If the Group of Experts considers that further work is required, this should be undertaken by the co-ordinator or the co-worker and, if necessary, the Ph. Eur. Laboratory and preferably the results should be presented at the next meeting of the Group of Experts.

3.3 In general, the draft to be published in Pharmeuropa is approved by the group in not more than two meetings.

3.4 If there are any non-scientific difficulties or differences in conception, the problem is immediately submitted to the Commission.

4. PUBLICATION IN PHARMEUROPA

4.1 Once the Group of Experts has approved the draft monograph, the editorial amendments are made by the Secretariat, and the monograph is published in Pharmeuropa and simultaneously sent to the National Pharmacopoeia Authorities.

Whenever appropriate, the author of the monograph prepares an explanatory note to be published at the same time as the monograph. The deadline for comment by the public is set at 3 months from the publication date of Pharmeuropa.

5. EXAMINATION OF THE COMMENTS

5.1 The Secretariat uses an electronic "Document Review Tool" to prepare the compilation of the comments received which are made available to the co-ordinator/co-worker and to the group of experts for the next meeting of the Group of Experts.

5.2 The co-ordinator reviews the comments, tries to resolve the difficulties by carrying out, where relevant, any necessary laboratory work (the Ph. Eur. Laboratory may be asked to help) and submits proposals to the group.

5.3 The comments are considered by the Group of Experts and the monograph is then approved for adoption by the Commission. If necessary, to avoid delaying the publication of new texts, the group of experts submits a text for adoption by the Commission while proposing further work on an unresolved matter.

5.4 In cases where important modifications are foreseen in the light of the results of the enquiry (change of a method, significant change of specifications), either a second publication is envisaged or National Pharmacopoeia Authorities are consulted.

6. ADOPTION BY THE COMMISSION

6. 1 The Secretariat prepares the document for the Commission and submits it for adoption at the next Session.

PROCEDURE 2

ADAPTATION OF NATIONAL MONOGRAPHS

Procedure 2 is no longer used since the programme of adaptation of national monographs has been completed.

PROCEDURE 3

NATIONAL SECRETARIAT ACTING AS CO-ORDINATOR

This procedure has been integrated into the modified Procedure 4.

PROCEDURE 4

This procedure applies to substances for which a single interested party amongst manufacturers has been identified. It is usually applied to substances still under patent protection where there is potential for future production of generics. The aim of the procedure is to publish a monograph 5 years after the first approval in medicinal products in Europe, at latest 2 years or more before patent expiry. The work is co-ordinated by EDQM and overseen by the Group of Experts P4. Data provided by manufacturers is treated in confidence and

access is allowed only to EDQM staff and members of the Group of Experts P4, composed of representatives of national pharmacopoeia secretariats or regulatory authorities.

1. INITIATION

1.1 Following addition to the work programme, a co-ordinator in the Group of Experts P4 is appointed and responsible persons in the Secretariat and Laboratory. A National Pharmacopoeia Authority may act as a co-ordinator and nominate a contact who for the purpose of this monograph project becomes a member of the Group of Experts P4.

1.2 The Secretariat request data and samples from the manufacturer. Data are treated in confidence and are accessible only to the Group of Experts P4 and EDQM staff members involved in the P4 Procedure.

1.3 The Secretariat reviews the data and samples received. If the data and samples are complete and satisfactory, a first draft of the monograph is prepared by the responsible person within the Secretariat. If the data and samples appear to be incomplete the Secretariat requests further data/samples before proceeding with the preparation of a first draft.

2. PREPARATION OF A FIRST DRAFT

2.1 The first draft is reviewed by the co-ordinator, the Secretariat and the Laboratory and questions are compiled and forwarded to the manufacturer.

2.2 When all issues have been resolved with the manufacturer, the Laboratory tests one or more batches according to the draft. Where necessary to confirm results from the EDQM Laboratory, the tests are run in a second laboratory (of a national pharmacopoeia or OMCL).

If a National Pharmacopoeia Authority acts a co-ordinator, the draft is tested in its laboratories and the confirmatory testing is carried out by the EDQM laboratory.

2.3 Laboratory reports are sent to the manufacturer and further questions may be raised. The responsible person with the Secretariat endeavours to resolve with the manufacturer all points of difference, in collaboration with the co-ordinator and the responsible person in the Laboratory.

2.4 The amended draft, conforming to the relevant Technical Guide for the Elaboration of Monographs and the Style Guide, is produced by the Secretariat in collaboration with the co-ordinator, ideally within 3 months after the completion of the laboratory work.

2.5 The Secretariat is responsible for translation of the texts into the other official language and for final editorial verification of the texts.

PUBLICATION IN PHARMEUROPA

3.1 Once the Group of Experts P4 has confirmed the draft monograph, the necessary amendments are incorporated by the Secretariat. The monograph is published in Pharmeuropa and simultaneously sent to the National Pharmacopoeia Authorities.

Whenever necessary, the author of the monograph prepares an explanatory note to be published at the same time as the monograph. The deadline for comment by the public is set at 3 months from the publication date of Pharmeuropa.

4. CONSIDERATION OF COMMENTS

4.1 The Secretariat uses an electronic “Document Review Tool“ to prepare the compilation of the comments received, which are made available to the co-ordinator and to the Group of Experts P4.

4.2 The co-ordinator and the responsible person in the Secretariat study the comments and prepare a document showing the rationale for acceptance or non-acceptance of proposed changes.

4.3 A revised draft is prepared for confirmation by the Group of Experts P4 in the light of the rationale document. If necessary, to avoid delaying the publication of the new texts, the Group of Experts P4 submits a text for adoption by the Commission while proposing further work on an unresolved matter.

4.4 In cases where important modifications are foreseen in the light of the results of the enquiry (change of a method, significant change of specifications), either a second publication is envisaged or National Pharmacopoeia Authorities are consulted.

5. SUBMISSION TO THE COMMISSION

6. 1 The Secretariat prepares the document for the Commission and submits it for adoption at the next Session.

ANNEX 4

LIST OF BASIC DOCUMENTS PROVIDED TO THOSE INVOLVED IN THE WORK OF THE EUROPEAN PHARMACOPOEIA COMMISSION

1. Rules of procedure

2. Guide for the work of the European Pharmacopoeia

3. Code of Practice for the work of the European Pharmacopoeia

4. Technical guide (in the relevant field of work) for the elaboration of monographs

5. A document showing the composition of the Commission, Groups of Experts and Working Parties, together with details of Liaison Sections for the Partial Agreement, central addresses of Delegations and Secretaries of National Pharmacopoeia Authorities.

The Style Guide is made available on request.