BRIEFING NOTE:

- Due to the launch of the EDQM DoI for experts database the declaration of interests (DoI) has been disconnected from the Nomination form and CV (ref/ 179th EPC session)

GUIDE FOR THE WORK OF THE EUROPEAN PHARMACOPOEIA

The purpose of this Guide is to build an efficient network for the activities of the European Pharmacopoeia Commission and all those who participate in its work, including delegates, experts, *ad hoc* specialists, national secretariats, the EDQM (Secretariat), European professional organisations, industry, academia and other stakeholders.

The present Guide is a technical document intended to explain the provisions of the Rules of Procedure of the European Pharmacopoeia Commission. It should also be read in conjunction with both the *Code of Practice for the Work of the European Pharmacopoeia* and the *Privacy statement of the European Pharmacopoeia.*

The work of the European Pharmacopoeia Commission and its groups of experts and working parties requires a certain commitment from participants and a willingness to respect established procedures, so that public health authorities and the public can be confident that the human and scientific resources involved have been used in a timely and efficient manner.

The Guide describes:

- the roles of the main actors involved in the elaboration of the European Pharmacopoeia (namely the European Pharmacopoeia Commission and its groups of experts and working parties), the National Pharmacopoeia Authorities and entities of the European Directorate for the Quality of Medicines & HealthCare;
- the working methods and procedures to be followed with the exception of justified cases in which there are good reasons for not doing so.

Hereinafter, European Pharmacopoeia shall be written 'Ph. Eur.', European Pharmacopoeia Commission shall be written 'EPC', and 'groups' shall be used indifferently to refer Ph. Eur. groups of experts and working parties or both. "EDQM" stands for the European Directorate for the Quality of Medicines & HealthCare and "NPAs" for National Pharmacopoeia Authorities. The term 'text' covers monographs, general chapters and other texts to be published in the Ph. Eur.

All references to functions, titles or positions are understood as applying equally to men and women. For ease of reading, the masculine pronouns will be used throughout.

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ANNEXES:

1. EUROPEAN PHARMACOPOEIA COMMISSION

1.1 Activities

1.1.1 The legal framework for the use, elaboration and updating of the Ph. Eur. in close collaboration with its stakeholders is summarised in Annex 1.

1.1.2 The functions of the EPC are described in article 6 of the *Convention on the Elaboration of a European Pharmacopoeia* and in the *Rules of Procedure of the European Pharmacopoeia Commission*. In this context, the EPC:

- prepares a notification for suspected deficiencies in Ph. Eur. monographs to be used by the licensing authorities (see Annex 2),
- defines its *Code of Practice for the Work of the European Pharmacopoeia*,
- develops detailed working procedures for the elaboration of monographs (see Annex 3),
- establishes a list of basic documents that are to be provided to each appointed expert and, if deemed appropriate, to *ad hoc* specialists (see Annex 4).

1.2 Delegations

1.2.1 Delegations should notify technical matters relating to an item on the agenda for a forthcoming session of the EPC, in writing and in advance, , e.g. by submitting a comment in the Document Review Tool (DRT) or via correspondence to the Chair of the EPC, the Chair of the group 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, e.g. by submitting a comment in the DRT or via correspondence to the Chair of the EPC, the Chair of the group concerned and the Secretariat.

1.2.3 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 EPC to take a comment or contribution into consideration.

1.2.4 Delegations should send copies of all correspondence relevant to the work of the EPC to the Chair of the EPC.

2 GROUPS OF EXPERTS AND WORKING PARTIES

2.1 Activities

2.1.1 The procedures for elaboration of texts are described in Annex 3.

2.1.2 During the work, the relevant technical guide(s) for the elaboration of monographs are taken into consideration wherever applicable. The Secretariat is responsible for ensuring that the

agreed editorial style is applied in Ph. Eur. texts.

2.1.3 Where relevant, new text proposals submitted must include a draft text and related scientific information, such as analytical procedures, specifications, validation reports relating to the analytical procedures proposed and batch analysis data for the full range of tests. Validation reports and batch analysis data are archived at the EDQM and handled confidentially, in accordance with the rules set out in the Code of Practice. The tests should be verified in at least a second laboratory. Any deviation from this rule should be assessed by the group and made transparent to the NPAs (e.g. via the group meeting report).

2.1.4 Specifications in monographs should be based on those for products approved by member states unless otherwise agreed by the EPC (e.g. in the case of unlicensed medicinal products).

2.1.5 Wherever possible, work should proceed by correspondence between a limited number of experts and *ad hoc* specialists (e.g. rapporteur and co-rapporteur(s)). Copies of all relevant correspondence are sent to the Chair of the group and to the Secretariat. The aim of the preliminary exchange by correspondence is to provide a good basis for the group to finalise the draft texts as promptly as possible.

2.1.6 A member of the Secretariat shall attend each meeting of a group. The member of the Secretariat in attendance may contribute to the work of the group at any time.

2.2 Chairs

2.2.1 Applications should be submitted not later than 28 days before the beginning of the session at which the appointment is to be made. The Secretariat should notify the delegations in writing of applications received, not later than 21 days before the beginning of the session.

2.2.2 In the event that no applications or no suitable applications have been received, different approaches may be explored to ensure that, as far as possible, the work of the group is not put on hold. These include:

- appointment by the group of an acting Chair from amongst its experts proposed by Contracting Parties, as a temporary solution;
- Secretariat to act as Chair.

In all cases, the proposed approach shall be submitted for approval by the EPC.

2.2.3 The Chair, in collaboration with the Secretariat, is responsible for the progress of the work allocated to the group and monitors the work plan, including adherence to the timetable.

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

2.2.5 The Chair, in collaboration with the Secretariat, ensures a sound decision-making process within the group, in particular that scientific grounds are adequately reflected in the draft text and that any decision of the group is based on technical and scientific considerations.

2.2.6 The Chair decides, in consultation with the group members, when a draft text can be published in *Pharmeuropa* for comment.

2.2.7 Comments received during the public consultation in *Pharmeuropa* are considered by the group concerned. The Chair, in collaboration with the Secretariat ensures that the comments are considered according to their merits. Wherever a proposal for change is not accepted, the Chair, in collaboration with the Secretariat, ensures that the reasons are clearly expressed. When a substantial change is introduced in the light of the results of the enquiry, the text is again published in *Pharmeuropa* for comment.

2.2.8 The Chair decides, in consultation with the group members, when a draft text can be submitted to the EPC for adoption. The Chair, in collaboration with the Secretariat, should be prepared, on behalf of the group, to resolve in session minor points raised by delegations of the EPC.

2.2.9 The Chair approves the agenda for a meeting. Typically, documents should be received by members a week in advance of the meeting.

2.2.10 The Chair, in collaboration with the Secretariat, ensures that impartiality is maintained if an interest is declared during the meeting.

2.2.11 Where necessary, the Chair or the Secretariat refers to the EPC in writing any questions requiring a decision of principle prior to continuing work on a given item.

2.2.12 Chairs (except those of "dormant" working parties), who are not part of EPC delegations, are welcome to attend a session of the EPC. The Chair, in collaboration with the Secretariat, reports to the EPC on progress with the work programme when and if deemed appropriate, for example to highlight items special successes / achievements or where the work has not advanced as expected.

2.2.13 Chairs should be prepared to attend and play an active role in conferences organised by the EDQM on subjects relevant for the activities of their group.

2.2.14 Chairs may be convened to special meetings subject to the approval of the EPC, which shall also determine the date and agenda of such meetings.

2.2.15 Any Chair attending and playing an active role in conferences organised by third parties on subjects relevant to the activities of the EPC shall keep the Chair of the EPC and the Secretariat informed prior to the conference.

2.2.16 In the absence of the Chair, the group shall appoint an acting Chair from amongst its experts proposed by Contracting Parties.

2.3 Experts

2.3.1 Applications should be submitted not later than 28 days before the beginning of the session

at which the appointment is to be made. For possible re-appointments, the Secretariat should send the list of current experts to NPAs ideally 6 months before the end of the term of office of the group. NPAs should inform the Secretariat of the names of the experts who will or will not be re-appointed not later than 28 days before the beginning of the session at which the appointment is to be made.

2.3.2 Experts should meet the selection criteria approved by the EPC. They contribute on a voluntary basis having fully understood the commitment involved.

2.3.3 Experts shall be appointed by the EPC, by consensus, for their personal competence and if applicable, have at their disposal the facilities necessary to contribute to the group. They shall be allocated to groups on the proposal of the Presidium according to the selection criteria approved by the EPC. For each group, the Secretariat shall provide the EPC with the geographical distribution of the members already appointed (if applicable) and proposed. Based on this information, the EPC shall ensure a fair and appropriate balance of the geographical distribution between the experts proposed by Contracting Parties but also between these experts and the experts proposed by the Secretariat.

2.3.4 At the end of the term of office, the appointment of each expert may be renewed. The term of office of an expert appointed during the three-year period shall end at the same time as that of other members. At a time sufficiently before the end of the term of office, the EPC shall review the Terms of Reference and the need to reappoint groups for a new period. Based on the results of this review, the Secretariat of the EPC shall update the Terms of Reference and ask each Contracting Party for its proposals, in writing, for the appointment of experts.

2.3.5 Experts shall receive the basic documents decided by the EPC (see Annex 4).

2.3.6 Each expert should make a fair contribution to the work of the group, including an active participation in meetings or the provision of results of experimental work, where required, and shall respect the time limits set for assignments.

2.3.7 Experts receive all documents and other written communications that are to be studied by the group. The received data or information must be handled in compliance with the rules set out in the *Code of Practice*.

2.3.8 Experts should maintain proper communication either with the NPA if they are proposed by a Contracting Party or otherwise with the Secretariat, for example by giving regular reports on the progress of work.

2.3.9 Experts should attend all meetings of the group to which they are appointed. Experts proposed by a Contracting Party should inform the NPA and the Secretariat in good time if they are unable to attend a meeting. Experts proposed by the Secretariat should inform the Secretariat in good time if they are unable to attend a meeting

2.3.10 If an expert fails to contribute according to section 2.3.6 in this Guide, the Chair of the group and the Secretariat may decide to stop sending documents and other written communications to him. The NPA concerned must be consulted beforehand in the case of experts proposed by a Contracting Party.

2.3.11 Experts may involve other persons in their work for the Ph. Eur. only where this is useful for its advancement. They are responsible for ensuring that these persons are aware of the confidential nature of any information or data provided and that the results of the work shall only be used by the Ph. Eur. Please refer to the *Code of Practice* for more information.

2.3.12 Any experts attending and playing an active role in conferences organised by third parties on subjects relevant to the activities of the EPC shall keep the Chair of the EPC and the Secretariat informed prior to the conference.

2.4 *Ad hoc* specialists

2.4.1 *Ad hoc* specialists with expertise on a specific topic may be invited. The term of office of an *ad hoc* specialist is therefore limited and ends with the conclusion of the discussions on the specific topic. Ideally, applications for the approval of *ad hoc* specialists should be submitted not less than 28 days before the beginning of the meeting of the group concerned.

2.4.2 Subject to the prior approval of the Chair of the group and of the Secretariat, *ad hoc* specialists with current scientific and/or technical expertise that is considered useful for the advancement of the work may assist a group.

2.4.3 *Ad hoc* specialists should meet the selection criteria approved by the EPC. Where considered useful for the advancement of the work of the group, *ad hoc* specialists with specific expertise on a given topic not covered in the Terms of Reference and Profile for Members document may also be invited. *Ad hoc* specialists contribute on a voluntary basis having fully understood the commitment involved.

2.4.4 *Ad hoc* specialists receive part or all of the basic document package decided by the EPC (see Annex 4) as considered appropriate by the Chair of the group and by the Secretariat.

2.4.5 *Ad hoc* specialists do not have access to other documents that are to be studied by the group unless so decided, on a case-by-case basis, by the Chair of the group and by the Secretariat, i.e. if considered necessary for the *ad hoc* specialist to fulfil his role.

2.4.6 The Secretariat provides all documents and other written communication intended to be studied by the *ad hoc* specialist at the relevant meeting.

2.4.7 The data or information received must be handled in compliance with the rules set out in the *Code of Practice*.

2.4.8 *Ad hoc* specialists will be invited to attend meetings where their expertise is relevant and

needed. *Ad hoc* specialists may then attend the whole meeting.

2.4.9 An *ad hoc* specialist should inform the NPA and the Secretariat in good time if he is unable to attend a meeting.

2.4.10 At each EPC session, a list of *ad hoc* specialists having participated in the work of the groups since the previous session will be provided to the EPC.

2.4.11 *Ad hoc* specialists may involve other persons in their work for the Ph. Eur. only where this is useful for the advancement of the work of the Ph. Eur. In such cases, they are responsible for ensuring that these persons are aware of the confidential nature of the information and data provided and that the results of the work shall only be used by the Ph. Eur. Please refer to the *Code of Practice* for more information.

2.4.12 When an *ad hoc* specialist attends and plays an active role in conferences organised by third parties on subjects relevant to the activities of the EPC, he shall inform the Chair of the EPC and the Secretariat prior to the conference.

2.5 Substitutes

2.5.1 A substitute should have similar knowledge and expertise to those of the appointed expert or *ad hoc* specialist. His *curriculum vitae* should be sent by the Contracting Party to the Secretariat. The declaration of interests is managed as described in the Code of Practice for the Work of the European Pharmacopoeia and in the Privacy Statement of the European Pharmacopoeia.

2.5.2 The Contracting Party provides all documents and other written communication intended to be studied by the substitute at the relevant meeting.

3 EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE

3.1 European Pharmacopoeia Department (EPD)

3.1.1 The Secretariat of the EPC and its groups is provided by the EDQM's European Pharmacopoeia Department (EPD). The Head of this Department acts as scientific Secretary to the EPC. In exceptional cases, and if agreed by the EPC, the Secretariat may act as Chair of a group.

3.1.2 The Secretariat supports and assists the EPC and the Chairs of groups in carrying out their duties as described in sections 1 and 2.2. of this Guide. The Secretariat may also make presentations, statements or recommendations to the EPC on behalf of the Chair or the group (after consultation of and validation by the Chair).

3.1.3 The Secretariat monitors compliance with the present Guide. In case of doubt or issue, the Secretariat consults the Chair of the EPC or of the group concerned.

3.1.4 The Secretariat arranges sessions of the EPC and meetings of groups and any other meetings requested by the EPC. Invitations are provided to the participants in adequate time, typically not less than four weeks before the session or meeting, to allow appropriate arrangements to be made. A copy of the invitations is provided to Liaison Sections of the European Committee on Pharmaceuticals and Pharmaceutical Care and to the central addresses of NPAs.

3.1.5 The Secretariat ensures that only authorised persons attend a session of the EPC or a meeting of a group. If there are any doubts or questions in this regard, the Secretariat will consult the Chair of the EPC or of the group concerned.

3.1.6 Agendas:

- The Secretariat draws up a draft agenda for each session of the EPC, in consultation with the Chair of the EPC. This draft agenda is provided to delegations and NPAs at least four weeks before the opening of the session. Changes to the draft agenda are then highlighted and provided to delegations and NPAs. Changes made to the lists are dated. The final agenda is adopted by the delegations at the beginning of the session. Documents for adoption at a session of the EPC are usually provided not less than 14 days before the session. Documents submitted for adoption are posted on the EDQM's electronic Document Review Tool to allow the delegations to enter their comments (if any). Comments can be entered either in English or in French, in the English version of the text. If an item has been added to the agenda after the deadline, this item may be deleted from the agenda at the request of a delegation or can be adopted subject to confirmation by the delegations following the session.

- The Secretariat draws up a draft agenda for each group meeting, in consultation with the Chair of the group. This draft agenda is provided to experts, *ad hoc* specialists and NPAs at least three weeks before the meeting. Changes to the draft agenda are highlighted and provided to experts, *ad hoc* specialists and NPAs. The final agenda is adopted by the group at the beginning of the meeting.

3.1.7 The Secretariat draws up an annual schedule of group meetings, where necessary in consultation with the Presidium

3.1.8 Summary of decisions:

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

- The Secretariat of a group issues a summary of decisions within one week of the meeting. The summary of decisions of a group shall briefly indicate, for each item on the agenda, the decision taken (e.g. discussion during the next meeting, *Pharmeuropa*, EPC) and any follow-up to be made. If the most important information is included in the summary of decisions and only some additional information or details such as a reference to DEC documents are to be provided, a short

report may be issued within two weeks of the meeting. This document then replaces the classic summary of decisions and the report (see 3.1.9).

3.1.9 Reports and short reports:

- The Secretary of the EPC issues the draft records of a session of the EPC in the two official languages, ideally within four weeks. The deadline for comments on the draft record is not later than six weeks before the beginning of the next session. The record, amended if necessary, is issued promptly after the deadline.

- The Secretariat to a group issues the group meeting reports within eight weeks unless otherwise agreed with the Chair, or a short report (see 3.1.8). Each report or short report shall indicate *inter alia* the names of the participants and the duration of the meeting and include the work programme of the group on new and revised texts, with the state of advancement, as an appendix. A report has the summary of decisions as a preface. When a change proposed in writing by an NPA or by a manufacturer is not agreed, the Secretariat clearly indicates the reasons for non-acceptance of the proposal in the report and in the "DEC" document.

3.1.10 Drafting of texts:

- The Secretariat exercises general oversight for the drafting style of texts to be published. To this end, the Secretariat prepares and updates the *Style Guide*.

- The Secretariat verifies that draft texts are based on the EPC's relevant technical guides and are supported by the necessary documentation in the form of experimental results, reports of group meetings, validation data and a briefing note, particularly in the case of revision proposals. In case of doubt or issue, the Secretariat consults the Chair of the EPC or of group concerned to decide on the next steps.

- The Secretariat prepares new versions of documents as necessary and sees to it that the correct drafting style is used in draft texts of the Ph. Eur., using the *Style Guide*.

3.1.11 Adoption of texts and other urgent decisions to be taken by correspondence. Where a text is to be adopted or an urgent decision is to be taken by the EPC by correspondence, the Secretariat distributes the supporting document(s) to all delegations and to NPAs and indicates a deadline for adoption/decision. Any delegation that is not in favour of the adoption/decision proposed informs the Secretariat at the latest by the deadline, failing which the text will be considered adopted or the decision confirmed. If no opposition is received by the Secretariat at the latest by the deadline (meaning that no delegation opposes adoption or decision), the Secretariat proceeds as decided and informs the EPC and NPAs, promptly after the adoption/decision.

3.1.12 Corrections made to final texts before publication are notified to the interested parties, i.e. delegations and NPAs.

3.1.13 Stakeholder engagement:

- The Secretariat arranges for publication of relevant information to stakeholders, e.g. texts issued for public enquiry and comment, scientific notes, general information on the work of EDQM, etc.

- The Secretariat organises an annual meeting of Secretaries of NPAs to facilitate and co-ordinate the activities of common interest and to provide a forum for exchanges of information. This meeting is normally hosted by one of the NPAs on a rotating basis. Additional meetings may also be organised during the year; these meetings would usually take place virtually.

- The Secretariat, in consultation with the appropriate Chair, contacts manufacturers or other suppliers as necessary in order to obtain samples of materials needed for work on texts and for use as reference standards; proposals for specifications and validated analytical procedures to be included in these texts are requested at this time.

- The Secretariat organises public conferences on subjects related to the work of the EPC where this helps drive progress.

- When needed, the Secretariat may organise hearings of relevant industry associations. Wherever possible, the Chair of the EPC and, where applicable, the Chair of the group concerned attend the meeting.

- The Secretariat maintains the Knowledge database on the EDQM website, providing supplementary information on texts for the assistance of users.

3.1.14 Work programme:

- The Secretariat submits to the EPC any proposals made in accordance with Rule 18 of *the Rules of Procedure* for introduction, revision, suspension or suppression of texts.

- At regular intervals, the Secretariat provides to the EPC and NPAs a document showing the state of advancement of all items (new and revised) on the work programme.

- The Secretariat draws up the plan for the work allocated to the group. This plan shall indicate, inter alia, the distribution of work as decided in consultation with the members of the group and the time limits set for assignments. The Secretariat, in collaboration with the Chair of the group, monitors the progress of the work, including adherence to the timetable.

- The Secretariat provides statistics to the EPC on a yearly basis. The Secretariat assists the Chair of the group in reporting to the EPC on the progress of the work programme when and if deemed appropriate, for example to highlight special successes / achievements or where the work has not advanced as expected.

3.1.15 Creation of groups and nominations:

- When the EPC decides to create a group, the Secretariat sends the NPAs and delegations an invitation to submit proposed nominations, indicating the Terms of Reference of the group and the profile expected for its members.

- Ideally six months before the end of the term of office of the groups, the Secretariat sends the NPAs and delegations an invitation to confirm the re-appointment of relevant experts and to submit new nominations, indicating the Terms of Reference of the group and the profile expected for its members.

- The nomination form, curriculum vitae and the declaration of interests of all individual taken part in the work of the Ph. Eur. are held by the Secretariat. The nomination form and curriculum vitae are shared with the Presidium. The declarations of interests are managed as described in the Code of Practice for the Work of the European Pharmacopoeia and in the Privacy Statement of the European Pharmacopoeia.

- When proposing an expert, the Secretariat should consider the past contribution of the nominee and may consult the Chair of the group concerned and the Presidium for advice on this.

3.1.16 The Secretariat participates in the activities of the Pharmacopoeial Discussion Group and ensures that work is carried out with due respect for the EPC's established procedures. The Secretariat liaises with the relevant groups and informs the EPC of the state of work.

3.1.17 The Secretariat participates in the work of other bodies that have an impact on the work of the EPC, notably relevant committees of the European Medicines Agency (EMA), the Commission of the European Union (EU), the World Health Organization (WHO) and the World Organisation for Animal Health (OIE). Reports are made to the EPC on this participation.

3.2 Laboratory Department (DLAB)

3.2.1 DLAB contributes to the work on elaboration of texts at the request of the EPC or of a group.

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

3.3 Reference standards

3.3.1 EDQM is responsible for establishing and monitoring reference standards.

3.3.2 As far as is technically feasible and economically reasonable, the EDQM, in co-operation with the relevant groups, undertakes the work required to establish reference standards and Biological Reference Preparations. It establishes reference standards and preparations and reports to the relevant groups on work done.

3.3.3 Provided suitable candidate material is available, the EDQM ensures 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.

3.3.4 The EDQM ensures that the work for establishing any replacement batch of a reference standard is carried out in order to ensure a continuous supply to users.

3.3.5 When a reference standard is to be adopted, the members of the relevant group are alerted by the EDQM and requested to approve the reference standard laboratory report within 14 days. In an emergency, this deadline may be shortened. The reference standard establishment report is considered approved by correspondence unless an issue has arisen which makes approval by the experts possible only after discussion in a meeting. Once approved by the relevant Group, the Reference standards are adopted by the EPC by correspondence following the same process as described in 3.1.11. At each session of the EPC, a document is presented which gives the details of substances adopted, with the dates of approval by the groups and adoption by the EPC.

3.4 IT and Publications Division (ITPD)

ITPD arranges for the publication, in suitable form, of texts adopted by the EPC.

3.5 Certification of Substances Department (DCEP)

3.5.1 DCEP runs the Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) procedure which is intended to be used for substances for which a monograph (general monograph and/or individual monograph) has been adopted by the EPC (organic or inorganic substances [active or excipients], manufactured or extracted; substances produced by fermentation as indirect gene products; herbal drugs or herbal drug preparations and products with risk of transmitting agents of animal spongiform encephalopathies).

3.5.2 The CEP ensures that by applying the relevant monographs of the Ph. Eur., if necessary with additional tests appended in an annex to the corresponding CEP, it is possible to control fully all possible impurities and contamination from the particular route of manufacture (including source materials) for which the CEP has been granted.

3.5.3 If, during assessment of the quality dossier submitted by the applicant, a need to update the monograph due to impurities that are not adequately controlled by the current version of the monograph has been identified, DCEP may propose a revision of the monograph in question. This may be the case for new impurities generated by a route of synthesis not considered during the elaboration of the monograph or when the monograph does not describe a quantitative method for the control of related substances. The proposal for revision contains the information that the relevant Ph. Eur. group needs to consider when deciding whether to update the monograph that has been shown to be inadequate or improvable. It is prepared so as not to divulge the confidential information contained in the dossier.

3.6 Quality management system

The EDQM maintains a quality management system for its work in each of its departments according to an internationally recognised standard.

4 NATIONAL PHARMACOPOEIA AUTHORITIES

4.1 General role

The general role of the NPAs is outlined in Annex 1.

4.2 Activities

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

4.2.2 The necessary secretarial support is provided to the NPA to fulfil and assure the co-ordination of the following essential functions:

- preparing and/or implementing the Ph. Eur. and its supplements at national level;
- responding to questionnaires from the EDQM on the work programme of the Ph. Eur.;
- providing information on local manufacturers and other interested parties who wish to contribute to the work;
- submitting requests for revision of texts – when needed in close co-operation with National Competent Authorities (NCAs) and other stakeholders;
- informing their national expert committees and local manufacturers, where necessary, about advanced draft texts while respecting the level of confidentiality of the information in question;
- forwarding national comments on *Pharmeuropa* draft texts to the EDQM;
- briefing EPC members before sessions;
- forwarding proposals for experts and *ad hoc* specialists to join Ph. Eur. groups;
- providing information on the Ph. Eur. to local users, in addition to the user support provided by the EDQM (HelpDesk);
- attending annual NPA meetings to promote exchanges on working methods, etc., within member states;
- notifying the EPC of the elaboration of national texts.

4.3 Duties

4.3.1 NPAs are required to provide their comments on draft texts to the Secretariat within the indicated deadline. The deadline is usually 60 days after the deadline for public comment indicated in *Pharmeuropa*. New issues on a modified draft text that has been resubmitted for comment after an initial commenting period should be avoided and only be raised if well justified. Comments are entered via the EDQM's Document Review Tool. Comments received after the deadline will be taken into account at the discretion of the Chair of the group 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 will be 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 give the reasons for this. Comments that do not fulfil these requirements will be considered but will usually be rejected on these grounds.

4.3.4 NPAs should send copies of all correspondence relevant to the work of the EPC to the Chair of the EPC. They should make every effort to send their comments or other contributions to matters to be treated by correspondence within the agreed deadlines. A NPA failing to observe a deadline should consider the disadvantages involved in delaying e.g. adoption of a text before asking the EPC to take a comment or contribution into consideration.

4.3.5 NPAs should ensure that nominations of Chairs, experts and/or *ad hoc* specialists for appointment to the groups are sent to the Secretariat. Applications should be accompanied by information on the relevant experience of the nominee (*curriculum vitae*). In the event of a re-nomination, the NPAs will check, with the expert or *ad hoc* specialist, that the *curriculum vitae* that was submitted to the Secretariat at the time of nomination is still up-to-date and, if applicable, that an updated version will be sent to the Secretariat. The declarations of interests are managed as described in the Code of Practice for the Work of the European Pharmacopoeia and in the Privacy Statement of the European Pharmacopoeia.

4.3.6 When proposing an expert or an *ad hoc* specialist for re-nomination, NPAs should consider the past contribution of the nominee and may consult the Chair of the group concerned, the Secretariat and the Presidium for advice on this.

4.3.7 NPAs should maintain communication with the experts and *ad hoc* specialists from their country while respecting their independent position as scientific advisers to the EPC.

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 NPA.

5.1.2 Proposals for new items for the work programme or for revision of texts should be submitted via the NPA.

5.1.3 Technical enquiries on texts should be submitted, preferably in writing, either to the NPA 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 NPA of one of the member states in which the product is authorised.

5.2.2 The member state(s) in which the product is authorised should be indicated for any comments on *Pharmeuropa* texts (preferably as attachments to the enquiry form) submitted via the EDQM HelpDesk.

5.2.3 Proposals for new items for the work programme or for revision of texts should be submitted to the Secretariat, according to the *Rules of Procedure* (§18.1).

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

5.3 International organisations

Communication should go via the Secretariat.

5.4 Industry associations or other associations

Communication should go via the Secretariat.

6 INTRODUCTION OF TEXTS

6.1.1 When a new text is proposed for addition to the work programme, the Secretariat sends a questionnaire to NPAs to determine whether they are in favour of the proposed addition. Any NPA that is not in favour of the addition must provide a substantiated justification.

6.1.2 If at least two NPAs are in favour of adding the text to the work programme and none is opposed to it, the text is proposed for addition to the EPC. The EPC will decide which group to assign the text to and also on the procedure to be applied (see Annex 3).

6.1.3 If it is perceived that the introduction of a new text could have a major impact on the Ph. Eur. or if the EPC wishes to receive more information before taking a decision, a pilot phase might be considered. The main aim of the pilot phase will be to gain practical experience, to check feasibility and/or to collect additional information in order to allow the EPC to take a well-informed decision. *See Annex 5.*

6.1.4 Work on a new text should not start before the EPC has decided to add it to the work

programme.

6.1.5 When the deletion of a new text from the work programme is proposed (for example, because of a lack of information on producers or products), the Secretariat sends a questionnaire to the NPAs to determine whether they are in favour of the proposed deletion. If an NPA is in favour of maintaining the text on the work programme, the Authority shall endeavour to provide the information needed. Otherwise, the text is deleted from the work programme.

7 REVISION OF TEXTS

7.1 Technical revisions

7.1.1 Technical revisions of the texts of the Ph. Eur. shall be carried out as follows:

(a) a delegation or the Chair of the EPC or of a group, an NPA or the Secretariat, having noted the need for revision, shall present a reasoned request for the revision of a text;

(b) the group concerned may be consulted to provide a preliminary evaluation of the revision request (see 7.1.2) before submission of the request to the EPC; however, work on the revision should not start before the EPC has decided to add the request to the work programme;

(c) the EPC will decide on the priority to be accorded to the proposed revision and the Secretariat will inform the group concerned;

(d) the usual working procedure shall then be followed and the revised text shall be published after adoption by the EPC.

7.1.2 Requests for revision should be submitted using the standard form (see form to request the revision of a monograph or general chapter). The parts of the text to be revised should be clearly identified and where possible a concrete proposal should be formulated. The group may make a preliminary evaluation of the revision request before examination by the EPC.

7.1.3 Requests for revision should be accompanied by sufficient information to enable the EPC to decide whether revision is justified and necessary and on the level of priority to be accorded to the work. Where a request for revision does not fulfil the aforementioned criteria, after consultation with the Chair of the group and/or the Chair of the EPC, the Secretariat may refer the matter back to the originator with a substantiated request for further information.

7.1.4 Once approved by the group, the draft texts are published in *Pharmeuropa* for comment.

7.1.5 Texts that have been revised are accompanied by a briefing note that summarises the revision, when submitted to the EPC. 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 changes and of the changes themselves.

7.1.6 If it is perceived that a request for revision could have a major impact on the Ph. Eur. (for example, making a substantial change to a concept or procedure) or if the EPC wishes to receive more information before taking a decision, a pilot phase might be considered. The main aim of the pilot phase will be to gain practical experience, to check feasibility and/or to collect additional information in order to allow the EPC to take a well-informed decision. *See Annex 5.*

7.1.7 When it is proposed to delete a request for revision because of a lack of information on producers, if an NPA is in favour of maintaining the item on the work programme, the Authority shall endeavour to provide the information needed.

7.1.8 If a revision cannot take place, the EPC should also decide whether it is still appropriate to keep the unrevised text in the Ph. Eur. or if the unrevised text should be suppressed or suspended from the Ph. Eur. according to sections 9 and 7.4, respectively.

7.2 Minor revisions

7.2.1 In the interest of simplification of working procedures, minor revisions may be submitted directly to the EPC if the Chair of the group or the Secretariat considers that prior publication in *Pharmeuropa* is not needed.

7.2.2 Submission of a minor revision implies that the change is not controversial and that the EPC will be able to decide simply on the basis of the briefing note to the text that the revision is justified and necessary. Therefore, no request for revision is necessary to start the work on a minor revision however, the briefing note should explain why the revision can be treated as minor revision.

7.2.3 The briefing note mentioned above 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.

7.3 Rapid revision

The procedure for rapid revision of a Ph. Eur. text is as follows:

(a) a delegation or the Chair of the EPC or of a group, an NPA or the Secretariat, having noted the need for rapid revision, shall present a reasoned proposal for the revised text and, where appropriate, data supporting the proposed revision;

(b) the Secretariat shall inform the EPC and the group concerned. The group shall be consulted promptly in writing and, if necessary, be convened as soon as possible and shall take the necessary action concerning the problem. The Secretariat shall prepare all necessary documents and send them to the delegations (including a draft briefing note to be later posted in the “View History” field of the Knowledge database, after editorial adaptation where necessary, to inform users of the reasons for the changes and the rapid

revision);

(c) the EPC shall take a decision at its next session or by correspondence; unless otherwise decided by the EPC, the draft text is usually not published in *Pharmeuropa* for comment;

(d) if the EPC decides that the revised text is to be published and implemented rapidly, outside the normal publication cycle of the Ph. Eur., the text is published in the form of a *Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care*.

7.4 Suspension of all or part of a text

The procedure for suspending all or part of a Ph. Eur. text is as follows:

(a) a delegation or the Chair of the EPC or of group, an NPA or the Secretariat, having noted the need to suspend all or part of a text, shall present:

a. a reasoned proposal, accompanied by data supporting the suspension where appropriate;

b. an assessment of the impact of the suspension from the user perspective (including the regulatory implications);

c. a recommendation as to how all or part of the text could be reinstated, by submitting a reasoned request for revision;

(b) the Secretariat shall inform the EPC and the group concerned. The latter shall be consulted promptly in writing and, if necessary, be convened as soon as possible. The group concerned analyses the information transmitted and prepares a reasoned opinion for the EPC, including the technical feasibility of the actions to be taken to reinstate the text. The Secretariat compiles all available and relevant documents and sends them to the delegations;

(c) the EPC shall take a decision at its next session or by correspondence, including whether publication in *Pharmeuropa* for comment is deemed appropriate. If the EPC decides that all or part of a text is to be suspended and the decision implemented rapidly, outside the normal publication cycle of the Ph. Eur., this decision is published in the form of a *Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care* with a view to its rapid implementation;

(d) The group concerned shall take the necessary action concerning the problem, to the satisfaction of the EPC.

8 CORRECTION OF ERRORS

The Secretariat may correct errors or make editorial (stylistic) changes to texts without prior discussion with the EPC. Corrections that can be made with simple notification include differences between the English and French texts when it is evident which version is correct; orthotypographical errors; items

that clearly do not correspond to the recommendation of the group and/or to the decision of the EPC.

However, the EPC and NPAs shall be informed promptly of the correction of errors or style modifications made and the date on which these corrections become effective (the date of publication).

9 SUPPRESSION OF THE TEXTS OF THE EUROPEAN PHARMACOPOEIA

The procedure for suppression of a text of the Ph. Eur. is as follows:

(a) a delegation or the Chair of the EPC or of a group, an NPA or the Secretariat, having noted the need to suppress a Ph. Eur. text, shall present a reasoned proposal;

(b) the Secretariat sends a questionnaire to the NPAs (together with draft briefing note to be later posted in the "View History" field of the Knowledge database, after editorial adaptation where necessary, to inform users of the reasons for the suppression) to determine whether they are in favour of the proposed suppression. Any NPA that is not in favour of suppression shall provide substantiated justification;

(c) the Secretariat transmits the responses to the questionnaire to all the delegations;

(d) the EPC shall decide whether the text shall be suppressed;

(e) if the EPC decides that the text shall be suppressed, this decision is published in the form of a *Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care* with the date on which the suppression shall take effect.

10 CONFIDENTIALITY

The Ph. Eur. is committed to finding a balance between transparency and confidentiality. While it strives to ensure transparent processes and decisions, it is also constrained by the need for confidentiality of data and information submitted by stakeholders, be they regulators, manufacturers or others.

Stakeholders can therefore submit data and information to the EDQM knowing that it will be handled confidentially, in accordance with the rules set out in the *Code of Practice*.

Individuals taking part in the work of the Ph. Eur. (see section 5 of the *Code of Practice*) have been appointed on the basis of their expertise. They must be able to freely share their knowledge and express their views and opinions without fear of reprisal. Thus, neither details on the decision-making process nor detailed data and information provided to the Ph. Eur. can be disclosed to third parties.

For more information on the confidentiality and use of data and information please refer to sections 12-16 of the *Code of Practice*.

ANNEX 1

USE, ELABORATION AND UPDATING OF THE EUROPEAN PHARMACOPOEIA

INTRODUCTION

The European Pharmacopoeia (Ph. Eur.) is elaborated under an international convention of the Council of Europe. The signatories to this 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 Ph. Eur. promotes public health by providing recognised common quality standards for medicines and their ingredients, for use by healthcare professionals and other stakeholders in the medicinal product supply chain. The requirements laid down in these standards help ensure that medicinal products can be used safely by patients. Their existence:

– facilitates the free movement of medicinal products in Europe;

– ensures the quality of medicinal products exported from Europe.

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

– regulatory authorities;

– those engaged in quality control;

– manufacturers of starting materials and medicinal products.

The Ph. Eur. can only fulfil its role properly when each of the interested parties participates actively in the process of elaboration and updating of standards. The aim of this document is to define and describe what is understood by active participation.

EXCHANGES BETWEEN THE PHARMACOPOEIA AND STAKEHOLDERS

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

First, the role of the Ph. Eur. with respect to that of licensing authorities should be recalled:

Unlike licensing dossiers, which are prepared and assessed for an individual product, the Ph. Eur. 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 and validated analytical procedures, specifications and units, by establishing common reference standards for all users in

Europe and beyond. It acts as a reliable reference tool for communication, linking individuals and facilitating national and international administrative, commercial and scientific exchanges amongst 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.

The tripartite relationship linking the Ph. Eur., the licensing authorities and manufacturers may be clarified by national or supranational legislation. EU directive 2001/83/EC (including its subsequent amendments) and EU regulation 2019/6 (including its subsequent amendments) summarise the principles for example as follows:

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

This was codified in Annex 1 to Commission Directive 2001/83/EC as amended,

- 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 marketing authorisation applicant must carry out additional tests.

“However, where a 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 cases 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 Ph. Eur. in general terms without breaking confidentiality and must ask the manufacturer to contact the Ph. Eur. to update 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 recourse to principles 2 and 3 would be required less frequently if the texts of the Ph. Eur. were updated regularly. This means setting up a rapid update mechanism within the EPC and, outside the Ph. Eur., maintaining frequent, regular and effective communication with its different stakeholders.

Within the EDQM (Council of Europe, Strasbourg), the Ph. Eur. has a permanent Scientific Secretariat and a Laboratory (DLAB) dedicated to the elaboration and revision of monographs and other texts.

The principles applied during elaboration of monographs are outlined in a series of technical guides, available for download from the EDQM website (www.edqm.eu). The analytical procedures included are validated according to current guidelines. The monograph specifications are based on those of medicinal products currently approved by member states unless otherwise agreed by the EPC (e.g. in the case of unlicensed medicinal products). In particular, impurity profiles are based on those of medicinal products currently approved by member states 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 liaisons appointed 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 for Competent Authorities to dispose of a system for the critical examination of *Pharmeuropa* drafts and generation of comments to be provided to the Secretariat. Similarly, manufacturers should also have an alert system to identify drafts that are of interest and development of comments.

The 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 the 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 the identification of items of interest and that they contact EDQM in a timely manner. This can be achieved most effectively by appointing a pharmacopoeia liaison within the company whose contact details can then be sent to the EDQM.

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 authorisation is requested for a medicinal product containing such a substance, for reasons of public health, the licensing authority must demand and the applicant submit additional information.

The NPA is the liaison point of choice when reporting suspected deficiencies in monographs. The form shown in Annex 2 can be used to submit a brief notification of a suspected deficiency in a monograph. The HelpDesk on the EDQM website can also be used for communication of this type.

With the increasingly global nature of trade liable to make this situation more common, the demonstration that the reference to the Ph. Eur. is suitable for a given source is requested by current guidelines of the Quality Working Party established under the Committee for Medicinal Products for Human Use and the Committee for Veterinary Medicinal Products (EMA).

The Certification of Suitability procedure was set up to make compilation of the marketing authorisation dossier easier and to make the reference to the Ph. Eur. directly usable; this procedure allows manufacturers to demonstrate the applicability of the monograph to their product while 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 Ph. Eur. is the instrument shared by the three partners (two use it, one elaborates and updates it), the existing means of communication between them should be optimised to respond better to the specific needs of each partner while respecting its constraints.

Licensing authorities and manufacturers have similar needs:

- Reliable, accurate, transparent standards
- Up-to-date monographs
- Validated reference analytical procedures

When sharing documents that include the data and information necessary to update monographs, licensing authorities are constrained by the confidentiality rules applying to documents submitted in licensing applications, whereas documents submitted to the EDQM are treated according to the rules laid down in the *Code of Practice*..

The Ph. Eur. 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 analytical procedures 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. The 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 website;
- development of transparent monographs that fully serve the needs of all users, with support from the certification procedure;
- giving priority to the drafting of monographs and general chapters requested by licensing bodies, notably the Committees and Working Parties of EMA;
- effective deployment 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 is available when generic applications are made;
- continuous development of the resources of the EDQM website as a support for all aspects of the work;
- organisation of hearings of interested parties at regular intervals or on request to promote dialogue on all aspects related to our work.

NATIONAL PHARMACOPOEIA AUTHORITIES (NPAs)

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. This results in considerable resource savings, with no subsequent need to harmonise national positions. The role of NPAs has therefore evolved and they have become part of an active network 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.

The EDQM organises an annual meeting of NPA Secretaries to facilitate and co-ordinate the activities of common interest and to provide a forum for exchanges of information.

ANNEX 2

NOTIFICATION CONCERNING A MONOGRAPH OF THE EUROPEAN PHARMACOPOEIA

According to Directive 2001/83/EC as amended, a licensing authority should inform the Secretariat of the European Pharmacopoeia (Ph. Eur.) when, during the assessment of an application for marketing authorisation, requirements in a monograph of the Ph. Eur. must be supplemented to enable sufficient control of a raw material from a particular manufacturer.

According to this Guide, specifications in monographs are based on those for products approved by member states (*unless otherwise agreed by the EPC*). However, in exceptional cases, based on scientific, technical and regulatory considerations, a licensing authority might consider, during the assessment of an application for marketing authorisation, that different specifications (e.g. wide limits) than those provided in a monograph of the Ph. Eur. can be approved.

In such cases, the licensing authority shall bring this to the attention of the EPC for review of the monograph and the manufacturer is under obligation to co-operate with the EPC with a view to updating the monograph.

The licensing authorities cannot submit any confidential information from a marketing authorisation application to the Secretariat of the Ph. Eur. Therefore, the information submitted to the Secretariat, if possible with the help of the NPAs, can be limited to a statement of the title of the monograph, the name of the manufacturer, and the nature of the requested change in the monograph, etc. The Ph. Eur. Secretariat will then contact the manufacturer to obtain the most detailed information directly to allow initiation of the revision process.

When informing the Secretariat, information should be sent to:

E-mail address:

epd@edqm.eu

Postal address:

European Pharmacopoeia Department
EDQM - Council of Europe
7, allée Kastner
CS 30026
F – 67081 STRASBOURG
France

The following standard format may be used:

Name of monograph

Change requested (e.g. limit or test for related substances, insufficient, additional testing needed, test replace due to malfunctioning etc.)

1 Name and address of manufacturer of medicinal product

2 Name and address of licensing authority, together with the competent department and – if
3 possible - name of the assessor

4 Name and address of the National Pharmacopoeia Authority

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ANNEX 3

PROCEDURES FOR ELABORATION OF MONOGRAPHS FOR THE EUROPEAN PHARMACOPOEIA

The work programme is decided by the EPC. The EPC 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 EPC 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.

PROCEDURE 1

ELABORATION BY A GROUP

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, manufacturers' pharmacopoeia liaisons, the EDQM website 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 NPAs 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 shelf life specifications for all grades, as accepted by the licensing authorities, analytical procedures and analytical validation data;

iii) supply batch analysis data for stability batches;

iv) if possible, supply a batch that 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 rapporteur and if necessary a co-rapporteur 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 rapporteur and, if necessary, to the co-rapporteur.

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

2.4 The co- rapporteur or, in exceptional cases, the EDQM Laboratory carries out the necessary verifications and sends comments to the rapporteur 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 Ph. Eur. *Style Guide*, is produced by the rapporteur, 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.

3.2 If the group considers that further work is required, this should be undertaken by the rapporteur or the co- rapporteur and, if necessary, the EDQM Laboratory and preferably the results should be presented at the next meeting of the group.

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 EPC.

4. PUBLICATION IN *PHARMEUROPA*

4.1 Once the group has approved the draft monograph, any editorial changes are made by the Secretariat, and the monograph is published in *Pharmeuropa* and simultaneously sent to the NPAs.

4.2 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 three months from the publication date in *Pharmeuropa*.

5. EXAMINATION OF COMMENTS

5.1 The Secretariat uses the electronic Document Review Tool to compile the comments received and that are made available to the rapporteur /co- rapporteur and to the group in time for its next meeting.

Comments should contain a substantiated proposal or should clearly state the action expected and the reasons for it. If the information provided appears to be incomplete, the Secretariat may request further information either directly from the commenter or via the NPA. Comments that are incomplete and/or unclear will be considered but are typically rejected on these grounds.

5.2 The rapporteur 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 and the monograph is then approved for adoption by the EPC. If necessary, to avoid delaying the publication of new texts, the group submits a text for adoption by the EPC while proposing further work on an unresolved matter.

5.4 In cases where major modifications are foreseen in the light of the results of the enquiry (change in analytical procedure, significant change in specifications), either a second publication is envisaged or the NPAs are consulted.

6. ADOPTION BY THE EPC

6. 1 The Secretariat prepares the document for the EPC 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 RAPPORTEUR

This procedure has been integrated into 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 five years after the first approval in medicinal products in Europe, at the latest two years or more before patent expiry. The work is co-ordinated by EDQM and overseen by Group of Experts P4. Data provided by manufacturers is treated in confidence and access is allowed only to EDQM staff and members of Group of Experts P4, composed of representatives of Competent Authorities (NPAs, regulatory authorities or OMCLs). Further information on the management of confidentiality by the Ph. Eur. is provided in its *Code of Practice*.

1. INITIATION

1.1 Following addition to the work programme, a rapporteur in Group P4 is appointed together with responsible persons in the Secretariat and Laboratory. Any member of the P4 group may act as a

rapporteur and nominate a contact within the Competent Authority who, for the purpose of this draft monograph, becomes a member of Group P4.

1.2 The Secretariat requests data and samples from the manufacturer. Data are treated in confidence and are accessible only to Group P4 and EDQM staff members involved in Procedure 4.

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 rapporteur, 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 NPA acts as rapporteur, 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 within the Secretariat endeavours to resolve with the manufacturer all points of difference, in collaboration with the rapporteur 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 Ph. Eur. *Style Guide*, is produced by the Secretariat in collaboration with the rapporteur, 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.

3. PUBLICATION IN *PHARMEUROPA*

3.1 Once Group 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 NPAs.

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 three months from the publication date in *Pharmeuropa*.

4. CONSIDERATION OF COMMENTS

4.1 The Secretariat uses the electronic Document Review Tool to compile the comments received and that are made available to the rapporteur and to Group P4.

Comments should contain a substantiated proposal or should clearly state the action expected and the reasons for it. If the information provided appears to be incomplete, the Secretariat may request further information either directly from the commenter or via the NPA. Comments that are incomplete and/or unclear will be considered but are typically rejected on these grounds.

4.2 The rapporteur 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 Group P4 in the light of the rationale document. If necessary, to avoid delaying the publication of the new texts, Group P4 submits a text for adoption by the EPC 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 an analytical procedure, significant change of specifications), either a second publication is envisaged or the NPAs are consulted.

5. SUBMISSION TO THE EPC

The Secretariat prepares the document for the EPC and submits it for adoption at the next session.

PROCEDURE 5

This procedure is used for the elaboration of monographs that are applicable in all the member states that have signed the European Pharmacopoeia (Ph. Eur.) Convention and that are useful for the evaluation of the quality of raw materials and stocks for Homoeopathic preparations , in particular in the context of mutual recognition.

Where several official national monographs exist, they can be adapted to produce a Ph. Eur. monograph with harmonised requirements. As part of this procedure, tests can be introduced in the European monograph if they help guarantee the quality of the substance, whether or not they are present in any of the existing national monographs, provided that this is justified and supported by scientific data.

Cultural differences in the area of homoeopathy in Europe sometimes make harmonisation difficult, but a European system can only be established on a common foundation while taking into consideration aspects specific to each country. It is evident that efforts must be made at national level to overcome these difficulties. It is to be borne in mind that the final goal is the quality of raw materials and stocks for homoeopathic preparations and that it is not the purpose of Ph. Eur. monographs to exclude substances from the market.

1. INITIATION OF WORK

1.1 Survey of national authorities to draw up a list of high priority monographs on a national basis.

1.2. Examination of the list of substances by the HOM Working Party to identify those substances for which national monographs already exist.

1.3. Circular letter to be sent by the Secretariat to the NPAs indicating the substances/monographs to be treated by this procedure and asking for the most recent versions of national monographs, their English translations (if they exist), the report(s) of any studies performed in their drafting, the validation and/or the performance data for the described methods, any information about manufacturers/suppliers relevant for the elaboration of a monograph, details of problems that have been reported, and whether the monograph is under revision at national level.

1.4. 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) comment on the existing monographs(s);

ii) supply current production batches;

iii) supply internal specifications as accepted by the Competent Authority, methods of analysis and validation data;

iv) supply batch analysis data for stability batches;

v) if possible, supply a batch that can be used subsequently as a reference standard (CRS/HRS), if required.

2. PREPARATION OF THE FIRST DRAFT MONOGRAPH

2.1 Each substance is assigned to a rapporteur and if necessary a co-rapporteur within the HOM Working Party. The rapporteur and the co-rapporteur should have a laboratory at their disposal to check the proposed analytical procedures, compare existing procedures and if necessary develop tests.

2.2 Where several national monographs exist, the rapporteur makes sure that they have the same scope. If not, a scope is proposed for the European monograph. In general, it is proposed that the scope of the European monograph should cover the various scopes of the national monographs so that no product will be excluded from the European market if its quality complies with Ph. Eur. requirements. When a common definition cannot be given (closely related starting materials), more than one monograph of the same quality standard (same methods) may be elaborated.

2. 3 After receiving the requested samples and documentation, the Secretariat sends copies of the documentation and portions of the samples to the rapporteur and, if necessary, to the co-rapporteur.

2. 4 If necessary, the EDQM Laboratory examines batches, using the analytical procedures in the national monograph(s), and gives its opinion on these procedures.

2. 5 After receiving the samples and the data, the rapporteur agrees target dates for completion of the laboratory work (preferably not later than six months) and initiates the work required, if necessary, with the manufacturer and the co-rapporteur.

2. 6 The co-rapporteur or, in exceptional cases, the EDQM Laboratory carries out the necessary verifications and sends comments to the rapporteur who informs the Secretariat on progress.

2.7 The first draft, conforming to the relevant technical guide for the elaboration of monographs and the Ph. Eur. *Style Guide*, is produced by the rapporteur, ideally within three months after the completion of the laboratory work. This first draft is based on the national monograph(s) and takes account of the results obtained by the laboratory(ies). Where appropriate, CRS/HRS strategy for the monograph is fixed with EDQM Laboratory. Products currently on the European market should *a priori* comply with the prescribed requirements.

2.8 The homoeopathic production methods mentioned in the general monograph *Methods of preparation of homoeopathic stocks and potentisation (2371)* or in an official national pharmacopoeia are mentioned in the draft European monograph, and the specifications and characteristics of the product are given separately for each production method.

If a production method mentioned in a national monograph is required, it is described in full in the draft European monograph.

2.9 Where a test is prescribed in one national monograph and not in another, the HOM Working Party initiates a discussion on whether or not it is necessary to keep the test, taking the following into consideration:

i) the test is included in the first draft of the European monograph if justified for reasons related to the quality of the substance and if supported by scientific data, as described in the relevant guide for the elaboration of monographs on homoeopathic preparations,

ii) the test is not included if it does not provide an additional guarantee of the quality of the substance,

iii) in the event of differences of opinion, information and data are collected to check whether all European products comply with the requirements in the draft Ph. Eur. monograph and to provide a basis for adjusting the specifications and reaching an agreement,

iv) if differences of opinion persist after information and data have been collected, when there are non-scientific difficulties or differences in concept, the problem is submitted to the EPC.

2.10 When several national analytical procedures exist for the same test, the EDQM Laboratory or an expert from the HOM Working Party carries out a comparative study of the procedures and submits his or her recommendations, with appropriate arguments and justifications, to the HOM Working Party, which will take its decision based on these recommendations.

2.11 If a new test (not part of a national monograph) is proposed, the HOM Working Party discusses the need to include this test in the European draft to guarantee the quality of the substance in Europe

based on the scientific data provided by the requestor. In this regard, it is proposed that only tests that are justified because they guarantee the quality of the substance and that are based on scientific data can be introduced into the European draft.

2.12 The first 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 laboratory studies carried out are presented to the HOM Working Party. If there are no difficulties, this draft is simultaneously published in *Pharmeuropa* and submitted for comment to the NPAs.

3.2 If the Working Party considers that further work is required, this should be undertaken by the rapporteur or the co-rapporteur and, if necessary, the EDQM Laboratory; wherever possible, the results should be presented at the next meeting of the HOM Working Party.

3.3 In general, the draft to be published in *Pharmeuropa* is approved by the HOM Working Party 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 EPC.

4. PUBLICATION IN *PHARMEUROPA*

4.1 Once the HOM Working Party has approved the draft monograph, any amendments are made by the Secretariat, and the monograph is published in *Pharmeuropa* and simultaneously sent to the NPAs and industry associations and published on the EDQM web site and the HMA web sites.

4.2 Whenever appropriate, the author of the monograph or the Secretariat prepares an explanatory note to be published at the same time as the monograph. This note contains information that may be useful to the reader, for example, explanations of the modifications made to the national monographs, and where applicable, explanations on the introduction of new tests or the introduction of a transition period.

4.3 The deadline for comment by the public is set at three months from the publication date in *Pharmeuropa*.

5. EXAMINATION OF COMMENTS

5.1 The Secretariat uses the electronic Document Review Tool to compile the comments received and that are made available to the rapporteur/co-rapporteur and to the HOM Working Party for its next meeting.

5.2 The rapporteur reviews the comments, tries to resolve any difficulties by carrying out, where relevant, any necessary laboratory work (the EDQM Laboratory may be asked to help), and submits proposals to the Working Party.

5.3 The HOM Working Party examines the comments received from the national authorities and in the light of these comments decides to:

— ask the Secretariat to prepare the COM document for submission to the EPC for adoption, in the absence of any major objections by the NPAs;

— in cases where major changes are foreseen on the strength of the results of further work or the public enquiry (change of an analytical procedure, significant change in specifications), either envisage a second publication or consult the NPAs;

— send the monograph describing the test for which a fundamental objection had been received to the HOM Working Party for examination. If there are any non-scientific difficulties or differences in conception, the problem is immediately submitted to the EPC.

6. ADOPTION BY THE EPC

6.1 The Secretariat prepares the document for the EPC for adoption at the next session.

ANNEX 4

LIST OF BASIC DOCUMENTS FOR WHICH A LINK IS 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. *Privacy Statement of the European Pharmacopoeia*
5. *Technical guide(s) (in the relevant field of work) for the elaboration of monographs*
6. *Style Guide*

ANNEX 5

PILOT PHASE: BEST PRACTICE RECOMMENDATIONS

These best practices are intended to provide assistance with the preparation of meaningful proposals for pilot phases that would allow the EPC to take an informed decision.

How to decide whether a pilot phase should be carried out

A pilot phase can be considered for any new or revised item (for example, a European Pharmacopoeia [Ph. Eur.] text, a procedure, a concept or an idea):

- that may have a **considerable impact** (for example, on the principles or portfolio of the Ph. Eur.);
- that may require substantial investment of resources (human or financial) to develop the new text/concept/idea
- when there is **doubt** as to whether it will **work in practice**;
- when the EPC is **not in a position to take a decision** without access to more information and data.

The following questions should be considered in order to determine whether to carry out a pilot phase:

- How will it benefit patients and public health?
- What future policy or practice is planned? What is the aim of the proposal?
- What would be the changes required and potential consequences for the Ph. Eur. and potentially for its stakeholders (positive or negative)?
- What information would be needed/desired to be able to take a decision?
- What improvements could the Ph. Eur. expect from the pilot phase?

The answers to such questions should allow the EPC to decide whether or not a pilot phase is the best approach or whether other means (for example, stakeholder consultations/enquiries/surveys) or a combination of the two, would be more appropriate.

How to plan and carry out a pilot phase

The following questions could be helpful to describe how to best plan and carry out a pilot phase*:*

- What are the aims of the pilot phase?
- What are the success criteria?
  (what criteria must be met so that a new activity/proposal can be implemented?)
- What criteria define the end of the pilot phase?
  (clear distinction between pilot phases/projects and business as usual; the criteria that define the end of a pilot project should be clearly determined when the initial plans for the pilot

project are first drawn up. If not, endless discussions could take place without a clear final decision)

- What possibilities exist if it becomes necessary to adapt the approved form of the pilot phase?
  (for example, requests for changes that allow the EPC to approve them, thus ensuring the necessary flexibility when performing pilot phases)
- How and when to provide updates to the EPC on the progress of the pilot phase?

The question of whether a public or other stakeholder consultation is to be launched and if so, in what format, should be considered during the pilot phase on a case-by-case basis:

- after provisional agreement has been reached on the development of the pilot project
  (a pilot phase is only a first attempt and it may turn out that the original idea is not feasible)
- IF specific questions need to be answered
  (*Not for routine consultations – well-established tools such as questionnaires on the work programme or enquiries on draft texts via Pharmeuropa should be continued*)

The following options for stakeholder consultations/enquiries/surveys could be considered:

- public surveys
  (mainly for general issues with a high impact on stakeholders/the public; they can be used to investigate the needs of users or how concepts are perceived)
- meetings/symposiums
  (*mainly for technical questions or feasibility aspects*)
- if considered appropriate, stakeholders could be invited to participate in the project.

The parts in italics are just examples (recommendations). The final decision to select any of the options proposed above should be taken on a case-by-case basis.

How to conclude a pilot phase

Once it is believed that the necessary criteria to end the pilot phase have been met, the outcome of the pilot phase should be appropriately documented in a report together with the outcomes of consultations, if undertaken, and the proposed recommendations for submission to the EPC, which will review them and make a final decision. This will enable the EPC to discuss the recommendations or, if it considers further work is required, to advise on what further information is needed to allow a decision to be made.

If the EPC does not support the final recommendation made and rejects it, a rationale should be provided to all involved parties especially the Chair and experts.