WORKING PROCEDURES OF THE PHARMACOPOEIAL DISCUSSION GROUP (PDG)

Revised version (September 2017)

General

Harmonisation may be carried out retrospectively for existing monographs or chapters or prospectively for new monographs or chapters.

The three pharmacopoeias have a commitment to respecting the agreed working procedures and the associated time deadlines as an essential part of the harmonisation procedure.

Harmonisation of pharmacopoeial documents in the PDG occur based on decisions of the expert bodies of each pharmacopoeia. The PDG works transparently in many ways, including, principally, the public notice and comment procedures of each pharmacopoeia.

Where necessary, meetings of experts including technical telecons/webex meetings are held to identify potential solutions to resolve difficult problems.

Sign-off can occur either electronically via email, by mail, or during the PDG meeting.The specific stages of the Pre-PDG and PDG Procedure (Process) involved in harmonisation are:

Pre-PDG

PDG identifies subjects to be harmonised among PDG pharmacopoeias and nominates a coordinating pharmacopoeia (CP) for each subject. The subject can include potential new topics, as well as revisions to existing topics to the PDG workplan. The Pre-PDG step provides a pipeline of potential topics/request for revisions to the PDG Work Plan.

- New topic: for a subject to be harmonised the CP develops a clear concept written document, scientific rationale, including Stakeholder input, impact and perspective. The CP will coordinate with the other PDG pharmacopoeias, determine impact of local requirements and barriers to harmonization and utilize technical teleconferences if needed (limited to 3 experts per pharmacopoeia). PDG decides on an approve/disapprove decision whether to add a new topic to the PDG workplan and on the agreed upon timeframe. Subject should be considered for removal after 12 months if no agreement is reached.

- Requests for revision: following coordination with the Experts from the three pharmacopoeias, PDG decides on an approve/disapprove decision whether to add a revision to the PDG workplan. Subject should be considered for removal after 12 months if no agreement is reached.

PDG approval

Once a topic/request for revision is added to the PDG workplan, the three PDG pharmacopoeias strive not to revise their national (regional) text unilaterally, with the understanding that each pharmacopoeia would notify PDG of any required changes to local or regional text stemming from regulations and policy that will have impact on the harmonised text moving forward.

Stage 1: Preparation of first draft

Upon PDG approval to add the topic/request for revision to the workplan, the CP prepares and forwards the Stage 1 draft and supporting data to PDG for pharmacopoeial expert committee review/comment within the timeframe as proposed in the Concept Paper. The Stage 1 draft explains the reasons for each test method or limit proposed.

Each Pharmacopoeia shall provide feedback or rationale through consultation with experts or governing body within 3 months. The comment period should, however, not exceed 4 months. Each pharmacopoeia should consolidate their comments and forward to the CP.

The CP reviews the comments received and makes an initial go/no go decision on whether the proposed harmonised draft document can move on for public comment / inquiry (Stage 2 draft). If the initial CP decision is “go”, the Stage 2 draft is prepared as close as possible to “global style,” together with the commentary and sent to the secretariats of the other pharmacopoeias.

The other pharmacopoeia’s commit to providing a response within one month whether they can agree to publish the draft for public comment/inquiry. If all three pharmacopoeias agree the decision is a “go,” the draft moves forward for public comment/inquiry.

If the decision by one or more pharmacopoeias is “no go”, additional teleconferences may be held (limited to 3 experts per pharmacopoeia) to resolve “sticking points.” Ideally, these teleconferences will be held within 1-2 months of the decision to “no go”. The goal of these teleconferences will be to either successfully commit to publish a Stage 2 draft, determine necessary next steps to reach Stage 2 (e.g. obtaining sponsor data, development and validation of analytical methods, etc.), or remove the topic from the PDG workplan.

Stage 2: Official Inquiry

The Stage 2 draft and the commentary are published in the respective fora of each pharmacopoeia. The draft proposal is published in its entirety. The style may be adapted to that of the individual pharmacopoeia concerned or the “global style” may be used. The three pharmacopoeias commit to publish the drafts simultaneously or as closely as possible.

The corresponding secretariats may have to add information needed for the understanding of implementation of the texts, e.g., the addition of the description of an analytical procedure or of reagents that do not exist in the pharmacopoeia and a translation is added by the European and Japanese Pharmacopoeias.

Each pharmacopoeia analyses the comments received and submits its consolidated comments to the CP within 2 months of the end of the review/comment period.

The CP reviews the comments received. If the comments received during the public comment/inquiry stage are significant enough to preclude a reasonable chance to reach consensus at Stage 3, the CP will determine the appropriate course of action, with consultation of the other PDG pharmacopoeias. Otherwise, the CP prepares a draft harmonised document (Stage 3A draft) accompanied by a commentary discussing comments received regarding the previous text and providing reasons for action taken in response to those comments. When residual differences are anticipated for sign-off, the stage 3A draft includes a draft of the sign-off cover sheet (see below).

The Stage 3A draft together with the commentary is sent to the other two PDG pharmacopoeias.

Stage 3: Consensus

A. Provisional

The stage 3A draft is reviewed and commented on by the other two PDG pharmacopoeias within 2 months of receipt. The three pharmacopoeias shall do their utmost to reach full agreement already at this stage with a view to reaching a final consensus document.

If a consensus has not been reached, the CP prepares a pharmacopoeia teleconference within 2 months to discuss remaining residual differences brought up through the public comment/inquiry period. The purpose of the pharmacopoeia teleconference is to make decisions on the remaining differences and whether they can be resolved, assigned as non-harmonised attributes or local requirements, if re-publication is necessary at Stage 2, or in extreme circumstances, remove from the workplan.

If harmonisation by attributes/provisions is applied, a special sign-off cover sheet (see Appendixes 1 and 2) indicating harmonisation is included with the draft. The text contains only harmonised attributes/provisions; non-harmonised attributes/provisions and local requirements are not included. The table is prepared as follows:

- 3 pharmacopoeias agree on the attribute/provision: '+' in all columns

- 2 pharmacopoeias agree that the attribute/provision should be included and have agreed on the method and limit: '+' in the column for those two pharmacopoeias, '–' in the column for the pharmacopoeia that will not stipulate the test

- 3 pharmacopoeias agree that the attribute/provision should be included but have not come to an agreement on the method and/or limit: state attribute/provision under 'Non-harmonised attributes/provisions'

- 1 pharmacopoeia only will include an attribute/provision: state under 'local requirement'.

The CP collects information about needs for amendments (local requirements) corresponding to a general policy in the national or regional (European) area. Local requirements, if needed, will be listed on the sign-off cover sheet.

B. Draft sign-off

When full agreement is reached, the stage 3B draft is sent by the CP to the other pharmacopoeias no later than 4 weeks before a PDG meeting for final confirmation. Sign-off on stage 3B can occur either electronically via email, by mail, or during the PDG meeting.

Stage 4: Regional adoption and implementation

Stage 4 takes place individually according to the procedures established by each pharmacopoeial organisation.

A. Adoption and publication

The document is submitted for adoption to the organisation responsible for each pharmacopoeia. Each pharmacopoeia incorporates the harmonised draft according to its own procedure.

If a pharmacopoeia needs to include a local requirement after the sign-off of a text, it will submit a proposed revision of the sign-off cover sheet to PDG. This can be done electronically or at the PDG meeting.

B. Implementation

The pharmacopoeias will inform each other of the date of implementation in the particular region.

The date of implementation of a harmonised document varies in the three PDG regions depending on their legal requirements, need of translation, and publication schedules. Each pharmacopoeia generally allows some period of time after publication for implementation, to allow manufacturers and other users to achieve conformity.

C. Indication of harmonisation

Each pharmacopoeia will introduce a statement indicating the harmonisation status according to the policy of the pharmacopoeia. In case of residual differences, these are indicated by specific symbols (black diamonds indicate non-harmonised attributes/provisions, white diamonds indicate local requirements). The residual differences all correspond to differences that have been agreed upon by PDG, via the sign-off cover sheet.

Stage 5: Inter-regional acceptance (for chapters previously evaluated by ICH Q4B for Regulatory Interchangeability)

16 chapters were evaluated by the ICH Q4B Expert Working Group. Following the Q4B evaluation process, a formal notification of regulatory acceptance was posted on the ICH website.

A topic-specific annex to Q4B guideline for each monograph or chapter concerned is processed for publishing and implementation by each regional authority.

Revision

Procedure for the revision of harmonised monographs and chapters

The Pharmacopoeias participating in PDG have agreed not to revise unilaterally any harmonised document (monograph or chapter) after sign-off or after publication.

Criteria for justification of revision may include but is not limited to:

- Public health and safety reasons.
- Insufficient supply of pharmacopoeial quality product on the market.
- Specified analytical reagents or equipment are not available

- New methods of preparation of product/reagent are not covered by the current monograph

- Analytical methods can be replaced by more appropriate/accurate/precise methods.

- New technologies that are suitable to be included in the pharmacopoeias.

A pharmacopoeia requesting the revision of a monograph or chapter shall provide PDG with a formal request including a rationale for revision and appropriate supportive data.

The process for revisions will follow the Working Procedure of the PDG as described above under “Pre-PDG”.. The revisions of a sign-off document prepared for this or other reasons are indicated as revision 1, 2, 3, etc., for the sake of consistency

Whenever agreed by the PDG, an expedited procedure may be applied. In certain circumstances where appropriately justified, the expedited procedure would result in a revision reverting to Stage 3A as opposed to Stage 1. In these instances, a pharmacopoeia requesting the revision of a monograph or chapter using the expedited procedure will submit a formal request for revision, including, in addition to the information supplied in the normal revision process, a justification for recommending the expedited procedure. Agreement by PDG to the expedited procedure will be handled on a case-by-case basis. After agreement by PDG to proceed with the revision, the CP may proceed directly with the elaboration of a stage 3A draft.

The PDG as a whole instead of a pharmacopoeia may also request a revision.

Revisions to already harmonised chapters can be introduced as national text if, after consultation with all the parties, there is no consensus for the revision. An assessment of the harmonisation status is conducted which may result in suppression in the workplan.

Correction of a sign-off text

Any pharmacopoeia which has identified an error in a sign-off text may submit a request for correction to PDG together with appropriate justification. A cover sheet (see Appendix 3) is prepared by the pharmacopoeia requesting the correction, together with appropriate justification. The cover sheet includes the name and code of the general chapter or monograph, the date of the sign-off and the description of the correction. After confirmation by PDG, the cover sheet is signed-off at the PDG meeting. When needed for clarity purposes, a full text including the correction is to be signed-off together with the cover sheet.

Correction of a sign-off cover sheet

Any pharmacopoeia which has identified a need for addition of a new local requirement or a correction of a local requirement/non-harmonised attribute already included in a previously signed-off cover sheet will inform PDG accordingly, together with appropriate justification. When needed for clarity purposes, the pharmacopoeia provides PDG with a full text including the new/corrected local requirement/non-harmonised attribute or with the published local text, if available. A corrected cover sheet (see Appendix 4) is prepared by the pharmacopoeia requesting the correction. The cover sheet includes the name and code of the general chapter or monograph, the date of the sign-off and the description of the new/corrected local requirement/non-harmonised attribute with tracked changes. After agreement by PDG that this is a local requirement/non-harmonised attribute, only the corrected cover sheet is signed-off at the PDG meeting.

Appendix 1

PHARMACOPOEIAL DISCUSSION GROUP

SIGN-OFF DOCUMENT
CODE: ...(General chapter)
NAME: … (General chapter)

It is understood that sign-off covers the technical content of the draft and each party will adapt it as necessary to conform to the usual presentation of the pharmacopoeia in question; such adaptation includes stipulation of the particular pharmacopoeia's reference materials and general chapters.

Harmonised provisions:

Provision	**EP**	**JP**	**USP**
Introduction	+	+	+
...	+	+	+
…	+	+	+
…	+	-	+

Non-harmonised provisions:

1)

2)

Local requirement

EP	**JP**	**USP**

European Pharmacopoeia

Signature Name Date

Japanese Pharmacopoeia

Signature Name Date

United States Pharmacopoeia

Signature Name Date

Appendix 2

PHARMACOPOEIAL DISCUSSION GROUP

SIGN-OFF DOCUMENT
CODE: ... (Monograph)
NAME: …(Monograph)

-Harmonised Attributes

Attribute	EP	JP	USP
Definition	+	+	+
Identification	+	+	+
…	+	+	+
…	+	-	+
…	+	+	+
…	+	+	+
…	+	-	+
…	+	+	+
…	+	+	+

Legend
+: will adopt and implement
–: will not stipulate

Non-harmonised attributes
…

Local requirements

EP	JP	USP

Reagents and reference materials

Each pharmacopoeia will adapt the text to take account of local reference materials and reagent specifications.

Date: Signatures:

European Pharmacopoeia Japanese Pharmacopoeia United States Pharmacopoeia

Appendix 3

PHARMACOPOEIAL DISCUSSION GROUP

CORRECTION

CODE: ... (General Chapter or Monograph)
NAME: …(General Chapter or Monograph)
(Correction of the sign-off document ... signed on ...)

Item to be corrected : ...

European Pharmacopoeia

Signature Name Date

Japanese Pharmacopoeia

Signature Name Date

United States Pharmacopoeia

Signature Name Date

Appendix 4

PHARMACOPOEIAL DISCUSSION GROUP

CORRECTION OF SIGN-OFF COVER SHEET

CODE: ... (General Chapter or Monograph)
NAME: … (General Chapter or Monograph)
(Correction of the sign-off cover sheet ... signed on …)

Item to be corrected: …

European Pharmacopoeia

Signature Name Date

Japanese Pharmacopoeia

Signature Name Date

United States Pharmacopoeia

Signature Name Date