PHARMACOPOEIAL DISCUSSION GROUP

SIGN-OFF DOCUMENT

WORKING PROCEDURE OF THE

PHARMACOPOEIAL DISCUSSION GROUP (PDG)

Revised version (June 2010)

European Pharmacopoeia

Signature	Name	Date
	WEITEL	9/6/10

Japanese Pharmacopoeia

Signature	Name	Date
	Toru KAWANISHI	June 9, 2010

for Masatoshi Narita

United States Pharmacopeia

Signature	Name	Date
	ANTHONY J DESTEFANO	09-JUN-2010

WORKING PROCEDURES OF THE PHARMACOPOEIAL DISCUSSION GROUP (PDG)
Revised version (June 2010)

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 occurs 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 are held to identify potential solutions to resolve difficult problems.

The specific stages of the PDG Procedure (Process) involved in harmonisation are:

Stage 1: Identification

Based on inquiry among its users, the PDG identifies subjects to be harmonised among PDG pharmacopoeias and nominates a coordinating pharmacopoeia for each subject.

The PDG distributes the work by consensus amongst the three pharmacopoeias. The PDG strives for a balance in the distribution of coordinating pharmacopoeia assignments.

Stage 2: Investigation

The coordinating pharmacopoeia for a subject to be harmonised retrospectively collects the information on the existing specifications in the three pharmacopoeias, on the grades of products marketed and on the potential analytical methods.

The coordinating pharmacopoeia prepares a draft monograph or chapter, accompanied by a report giving the rationale for the proposal with validation data.

Stage 2 ends with the proposal draft, which is mentioned in this procedure as "stage 3 draft". The Stage 3 draft, accompanied by supporting comments or data that explain the reasons for each test method or limit proposed, is sent by the coordinating pharmacopoeia to the secretariats of the other two PDG pharmacopoeias.

Stage 3: Proposal for Expert Committee Review

The three pharmacopoeias forward the Stage 3 draft to their expert committee (meeting or consultation by correspondence).

Comments by the experts resulting from this preliminary survey are sent to their respective pharmacopoeial secretariat, preferably within 2 months. The comment period should, however, not exceed 4 months. Within 2 months of receipt of the comments, the

Pharmacopeial Secretariat should consolidate them and forward them to the coordinating pharmacopeia.

The coordinating pharmacopoeia reviews the comments received and prepares a harmonised document (Stage 4 draft) accompanied by a commentary discussing comments received regarding the previous text and providing reasons for action taken in response to those comments.

The Stage 4 draft, as far as possible in "global style," together with the commentary 1 is sent to the secretariats of the other pharmacopoeias (end of Stage 3).

Stage 4: Official Inquiry

The Stage 4 draft and the commentary are published in the forum of each pharmacopoeia in a section entitled International Harmonisation. The draft is published in its entirety. 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. The style may be adapted to that of the pharmacopoeia concerned or the "global style" may be used. The three pharmacopoeias endeavour to publish the drafts simultaneously or as closely as possible.

Comments regarding this draft are sent by readers of the forum to their respective Pharmacopoeial secretariat, preferably within 4 months and at most within 6 months of publication in the forum.

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

The coordinating pharmacopoeia reviews the comments received and prepares a draft harmonised document (Stage 5A 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 5A draft may include a draft of the sign-off cover sheet.

The Stage 5A draft together with the commentary is sent to the secretariats of the other two PDG pharmacopoeias.

Stage 5. Consensus

A. Provisional

The stage 5A draft is reviewed and commented on by the other two PDG pharmacopoeias within 4 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 coordinating pharmacopoeia prepares a revised version (Stage 5A/2), taking relevant substantiated comments on the Stage 5A document from the two other pharmacopoeias into consideration. The revised document (Stage 5A/2) together with the commentary is sent to the secretariats of the other two PDG pharmacopoeias. The revised document is reviewed and commented by the other two PDG

pharmacopoeias preferably within 2 months of receipt. This review/comment and revision process of the 5A document is repeated (Stage 5A/n) until the three PDG pharmacopoeias reach a consensus or until the co-ordinating pharmacopoeia considers that harmonisation by attribute/provision should be applied.

If the co-ordinating pharmacopoeia considers that certain attributes in the monograph or certain provisions in a general chapter (especially for retroactive harmonisation) are such that it will not be possible to harmonise within a reasonable time period, then harmonisation by attributes/provisions will be applied. If harmonisation by attributes/provisions is applied, a special sign-off cover ~~page~~ 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 ~~attributes/ provisions~~ 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 ~~attribute~~ requirement'.

The co-ordinating pharmacopoeia 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.

If the stage 5A draft is substantially different from the stage 4 draft, the PDG may decide that it should be published again in the forums; the draft then reverts technically to stage 4 revised.

B. Draft sign-off

When full agreement is reached, the 5B draft is sent by the coordinating pharmacopoeia to the other pharmacopoeias not later than 4 weeks before a PDG meeting for final confirmation. The document is then presented for sign-off at the PDG meeting.

Stage 6: Regional adoption and implementation

Stage 6 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.

W T.K AD

Adopted texts are published by the three pharmacopoeias in the Supplements or, where applicable, in a new edition.

If a pharmacopoeia includes a local requirement after the sign-off of a text, it will submit the PDG with a proposed revision of the sign-off cover sheet.

~~If necessary, the Stage 5B draft may be adopted with some amendments (local requirements) corresponding to a general policy in the national or regional (European) area. If a pharmacopoeia includes a local attribute after the sign-off of a text, it will inform PDG.~~

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. EP and USP reference the corresponding text of the other PDG pharmacopoeias. JP references the harmonised text. In case of residual differences, these are indicated by ~~a~~ 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.

Harmonisation is achieved when all pharmacopoeias have highlighted harmonisation and any residual differences, based on a general policy in the national or regional area.

Concurrent to Stages 6A, B and C, a dialogue is opened between PDG and ICH Q4B Expert Working Group for the purpose of obtaining regulatory acceptance of the harmonised text. The co-ordinating pharmacopoeia provides documents to ICH Q4B EWG as defined in the ICH Q4B Guideline.

Stage 7: Inter-regional acceptance

Following Q4B evaluation process, a formal notification of regulatory acceptance is posted by ICH.

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.

C W T.K AD

A pharmacopoeia requesting the revision of a monograph or chapter shall apply the following criteria for justification of revision:

- 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.

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 PDG as a whole has to agree to initiate the revision. A coordinating pharmacopoeia will be nominated.

The coordinating pharmacopoeia, on the basis of data provided by the pharmacopoeia requesting the revision, will prepare a Stage 3 draft (tracked-changed and clean versions).

The Working Procedure of the PDG will then be followed. The revisions of a sign-off document prepared for this or other reasons are indicated as revision 1, 2, 3, etc.

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 5A as opposed to Stage 3. 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 coordinating pharmacopoeia may proceed directly with the elaboration of a stage 5A draft.

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

Correction

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.

Addition or revision of a local requirement

Any pharmacopoeia which has identified a need for addition of a new local requirement or a revision of a local requirement 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/revised local requirements or with the published local text, if available. A revised cover sheet (see Appendix 4) is prepared by the pharmacopoeia requesting the revision. 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/revised local requirement. After agreement by PDG that this is a local requirement, only the revised 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 Pharmacopeia

Signature Name Date

c/w T.K. ATD

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 Pharmacopeia

Appendix 3

PHARMACOPOEIAL DISCUSSION GROUP

CORRECTION

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

Item to be corrected : ...

European Pharmacopoeia

Signature	Name	Date

Japanese Pharmacopoeia

Signature	Name	Date

United States Pharmacopeia

Signature	Name	Date

Appendix 4

PHARMACOPOEIAL DISCUSSION GROUP

REVISION OF SIGN-OFF COVER SHEET

CODE: ... **(General Chapter or Monograph)**

NAME: ... (General Chapter or Monograph)

(Revision of the sign-off cover sheet ... signed on ...)

Item to be revised: ...

European Pharmacopoeia

Signature _____ Name _____ Date _____

Japanese Pharmacopoeia

Signature _____ Name _____ Date _____

United States Pharmacopeia

Signature _____ Name _____ Date _____