

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL
TEXTS FOR USE IN THE ICH REGIONS**

Q4B

Current *Step 4* version
dated 1 November 2007

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q4B
Document History

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Current *Step 4* version

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* *Code as per the new codification system adopted by the ICH Steering Committee in November 2007*

**EVALUATION AND RECOMMENDATION OF
PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS**

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting
on 1 November 2007, this guideline is recommended for
adoption to the three regulatory parties to ICH

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EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS

1. INTRODUCTION

1.1 Objective(s) of the Guideline

This document describes a process for the evaluation and recommendation by the Q4B Expert Working Group (EWG) of selected pharmacopoeial texts to facilitate their recognition by regulatory authorities for use as interchangeable in the ICH regions. Following favourable evaluations, ICH will issue topic-specific annexes with information about these texts and their implementation (the Q4B Outcomes). Implementation of the Q4B annexes is intended to avoid redundant testing by industry.

1.2 Background

When issuing *Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, and *Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*, ICH recognized that full use and value of both ICH Guidelines would depend on the successful harmonisation of pharmacopoeial procedures and encouraged the work of the Pharmacopoeial Discussion Group (PDG).

1.2.1 *The Pharmacopoeial Discussion Group (PDG)*

The PDG, founded in 1990, consists of representatives from the European Directorate for the Quality of Medicines (EDQM) in the Council of Europe; the Ministry of Health, Labour and Welfare (MHLW) of Japan; and the United States Pharmacopoeial Convention, Inc (USP). The PDG produces harmonised pharmacopoeial texts through independent public comment and consultation. The PDG reports on the status of its harmonisation efforts at ICH meetings as appropriate.

1.2.2 *The Q4B Expert Working Group (EWG)*

In November 2003, ICH established the Q4B EWG to evaluate and recommend pharmacopoeial texts that are proposed for use in the three ICH regions. The Q4B EWG anticipates that the PDG will be the principal source of pharmacopoeial text proposals. There might be an occasion where not all three parties of the PDG participate in a harmonisation effort for a specific pharmacopoeial text. In such a case, the Q4B EWG can accept proposals from one or two PDG pharmacopoeias.

1.3 Scope of the Guideline

Initially, the Q4B process will focus on evaluating the 11 General Test Chapters discussed during the development of ICH Q6A (refer to Attachment I). Many other pharmacopoeial harmonisation proposals are being developed and could also be considered for Q4B evaluation.

1.4 General Principles

The EWG will evaluate pharmacopoeial text proposals and assess the regulatory impact of the proposals. The Q4B EWG will continue its dialogue with the PDG as necessary during the Q4B process. Following its evaluation, the Q4B EWG will reach a conclusion and make a recommendation on the use of the text in the ICH regions which will be conveyed to the ICH Steering Committee. For each proposal that is

favourably evaluated, the Q4B EWG intends to develop a topic-specific annex to the Q4B Guideline following the ICH step process. The annex will provide information on how the pharmacopoeial texts can be used in the ICH regions. Each annex will be issued as a stand-alone companion document to the Q4B guideline.

To preserve transparency, the Q4B EWG should be notified of any revisions to a pharmacopoeial text that has been submitted to the Q4B evaluation process. Any change to pharmacopoeial text that has been proposed to, or recommended through, the Q4B evaluation process will prompt a Q4B EWG review to assess both the merit of the change and the appropriateness of any subsequent Q4B activity related to that text.

2. GUIDELINES

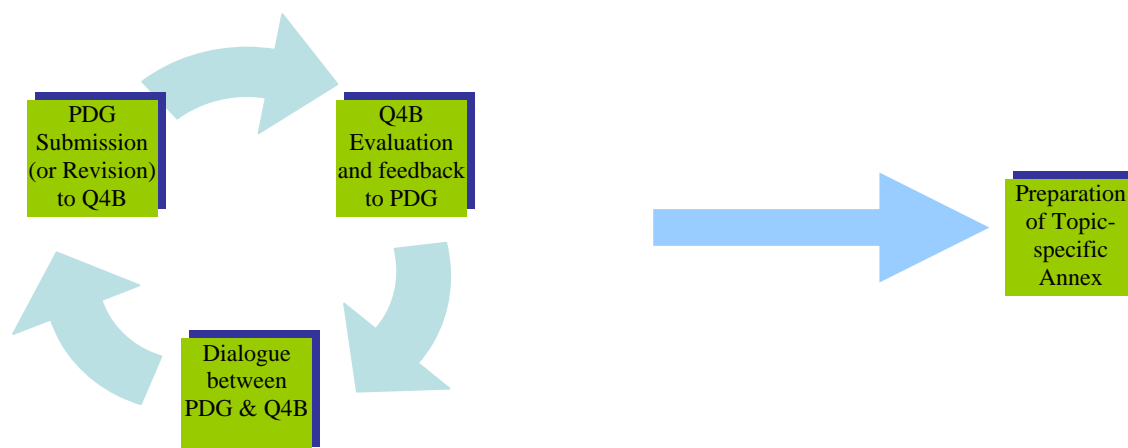
2.1 Q4B Evaluation Process

The process begins with a document submission to the Q4B EWG. For PDG proposed pharmacopoeial text, the document submission should be provided as soon as possible after PDG Stage 5B sign-off (refer to Attachment II). The document submission should outline any issues for resolution and should contain any appropriate supporting data.

When the Q4B evaluation process results in a conclusion and recommendation that the pharmacopoeial text can be used as interchangeable in the ICH regions, a topic-specific Q4B annex will be issued following the steps in the ICH process as detailed below.

2.1.1 Step 1

Each Q4B party independently evaluates the documents for regulatory impact. Additional discussion within the Q4B EWG, and/or communication/dialogue with the submitting party (e.g., the PDG), might be warranted to resolve any issues that surfaced during the evaluation (see example in the figure below).



When the Q4B evaluation process results in a recommendation that the pharmacopoeial text can be used as interchangeable in the ICH regions, the Q4B EWG prepares and signs off on a draft Q4B annex, which is submitted to the Steering Committee for adoption at *Step 2*.

2.1.2 Step 2

The Steering Committee agrees, based on the report of the Q4B EWG, that there is sufficient scientific consensus on the technical issues for the draft annex to proceed to *Step 3* regulatory consultation and discussion.

2.1.3 Step 3

The draft Q4B annex is made available for regulatory consultation in the three regions (generally for 3 months). The regulatory consultation and discussion should focus on the Q4B Outcome in the annex. The Q4B EWG can revise the annex based on comments received and submits a final draft of the annex to the ICH Steering Committee.

2.1.4 Step 4

The ICH Steering Committee adopts the annex and issues it as a stand-alone companion document to the ICH Q4B guideline.

2.1.5 Step 5

The annex moves to the regional regulatory implementation step.

2.2 Annex Contents

The Q4B annexes will contain the following information at a minimum. Other information might be incorporated on a case-by-case basis.

- Topic title;
- Introduction;
- Q4B Outcome;
- As appropriate, statements that will assist in the use of the referenced pharmacopoeial text by stakeholders;
- Implementation timelines indicating regulators' advice on when stakeholders can begin using the pharmacopoeial text as interchangeable;
- References to methods and acceptance criteria, as appropriate.

2.3 Use of the Pharmacopoeial Text

After a regulatory ICH region has implemented the Q4B annex, the official pharmacopoeial texts referenced in the annex can be used as interchangeable in that region. Any general and/or specific implementation recommendations for a regulatory region will be provided in the Q4B topic specific annex as part of Section 4. *Considerations for Implementation*. The basic information will be as provided below:

2.3.1 Considerations for Implementation

General consideration: When sponsors or manufacturers change their existing methods to the implemented Q4B-evaluated pharmacopoeial texts that are referenced in Section 2 of the annex, any change notification, variation, and/or prior approval procedures should be handled in accordance with established regional regulatory mechanisms pertaining to compendial changes.

In addition to these general considerations, specific information for each regulatory region can assist the implementation in that region. Each regulatory region will provide such notification to its stakeholders in conjunction with regional implementation of the annex.

FDA consideration: Based on the recommendation above, and in accordance with the conditions set forth in the annex, the pharmacopoeial texts as referenced in Section 2 of the annex can be considered interchangeable. However, FDA might request that a company demonstrate that the chosen method is acceptable and suitable for a specific material or product, irrespective of the origin of the method.

EU consideration: For the European Union, the monographs of the Ph. Eur. have mandatory applicability. Regulatory authorities can accept the reference in a marketing authorisation application, renewal or variation application citing the use of the corresponding text from another pharmacopoeia as referenced in Section 2 of the annex, in accordance with the conditions set out in the annex, as fulfilling the requirements for compliance with the Ph. Eur. Chapter [*chapter name and Ph. Eur. Reference*], on the basis of the declaration of interchangeability made above.

MHLW consideration: The pharmacopoeial texts as referenced in Section 2 of the annex can be used as interchangeable in accordance with the conditions set out in the annex. Details of implementation requirements will be provided in the notification by MHLW when the specific annex is implemented.

3. GLOSSARY

Document Submission

The working documents received from the PDG or one or more pharmacopoeial sources (USP, Ph. Eur., or JP) that contain the proposed pharmacopoeial text and any other support documents provided for Q4B evaluation.

Interchangeable

Where such status is indicated, any of the official texts from JP, EP, or USP can be substituted one for the other (appropriately referenced) in the ICH regions for purposes of the pharmaceutical registration/approval process. Using any of the interchangeable methods, an analyst will reach the same accept or reject decisions irrespective of which PDG pharmacopoeia is used.

PDG

The three-party Pharmacopoeial Discussion Group consisting of representatives from the European Directorate for the Quality of Medicines (EDQM) in the Council of Europe; the Ministry of Health, Labour and Welfare (MHLW) of Japan, and the United States Pharmacopoeial Convention, Inc (USP).

Pharmacopoeial text

The pharmacopoeial monographs, general test chapters, and analytical methods emanating from the three regional pharmacopoeias.

Q4B Outcome

Produced by the Q4B evaluation process; information concerning how the evaluated pharmacopoeial text can be used. The Q4B Outcome is included as part of the topic-specific Q4B annex developed as a result of each favourable evaluation.

ATTACHMENT I

General Chapters Discussed During ICH Q6A Development

| | |
|--------------------------------------|--|
| Dissolution | |
| Disintegration | |
| Uniformity of Content | Harmonised to Uniformity of Dosage Units |
| Uniformity of Mass | |
| Extractable Volume | |
| Particulate Matter | |
| Sterility | |
| Microbiological Quality | |
| Bacterial Endotoxins | |
| Residue on Ignition/Sulphated Ash | |
| Colour | |

ATTACHMENT II

PDG Document Submission Provided for ICH Q4B EWG Evaluation

This is an example of a document submission from the PDG:

The Coordinating Pharmacopoeia, on behalf of PDG, is asked to provide, as soon as possible after PDG Stage 5B sign-off and usually within six months, the following texts and information (termed the "document submission" as defined in the *Guideline*) to the Q4B EWG, via the ICH secretariat, with a copy to the Q4B EWG Rapporteur (for awareness):

- 1) The PDG sign-off document containing the PDG-harmonised text (PDG Stage 5B).
- 2) A Briefing Note dealing in particular with:
 - a. Residual differences between one or more of the pharmacopoeias, to include a commentary on any difference from the point of view of harmonisation;
 - b. Any specific issues relating to publication;
 - c. If any equivalency study was conducted, a summary of the outcome;
 - d. The projected publication and implementation schedule in each pharmacopoeia; and
 - e. Any additional information not covered above.
- 3) The texts as intended for adoption and publication in each pharmacopoeia together with a statement of any local differences with respect to the sign-off text.
- 4) Additional clarifying information is incorporated by one or more of the PDG pharmacopoeias in their respective information chapters on pharmacopoeial harmonisation. Therefore, the revised information chapter on harmonisation from each pharmacopoeia incorporating such information (in draft form where this is available) should accompany the provided documents.

If any changes occur or additional differences are discovered after submission to Q4B for evaluation, the Q4B EWG should be informed promptly by the pharmacopoeia concerned.