
Guidance for Industry

Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**February 2008
ICH**

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Guidance for Industry¹

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1, 1.1, 1.3)²

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 favorable 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.

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 harmonization proposals are being developed and could also be considered for Q4B evaluation.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2007. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

² Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2007.

II. BACKGROUND (1.2)

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 guidances would depend on the successful harmonization of pharmacopoeial procedures and encouraged the work of the Pharmacopoeial Discussion Group (PDG).

A. The Pharmacopoeial Discussion Group (PDG) (1.2.1)

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 Pharmacopeial Convention, Inc. (USP). The PDG produces harmonized pharmacopoeial texts through independent public comment and consultation. The PDG reports on the status of its harmonization efforts at ICH meetings as appropriate.

B. The Q4B Expert Working Group (EWG) (1.2.2)

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 harmonization effort for a specific pharmacopoeial text. In such a case, the Q4B EWG can accept proposals from one or two PDG pharmacopoeias.

III. GENERAL PRINCIPLES (1.4)

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 favorably evaluated, the Q4B EWG intends to develop a topic-specific annex to the Q4B guidance 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 guidance.

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.

IV. GUIDANCE (2)

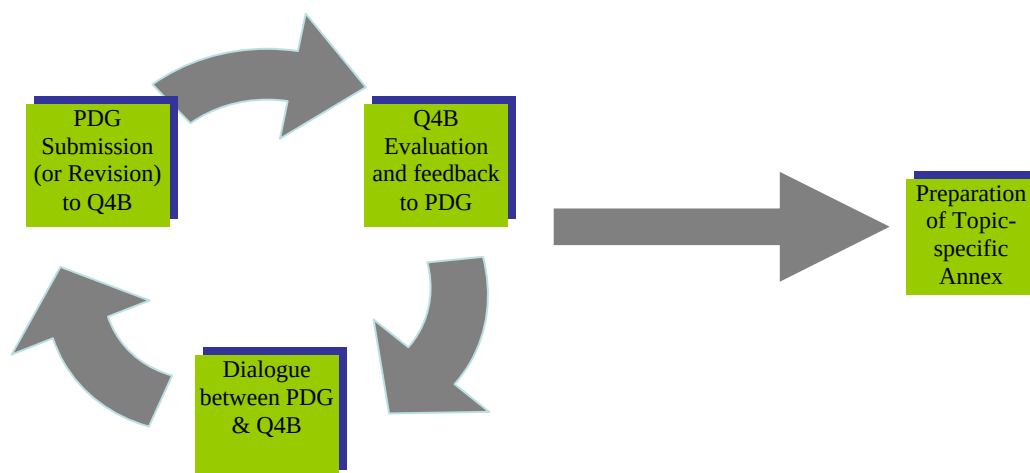
A. Q4B Evaluation Process (2.1)

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.

1. Step 1 (2.1.1)

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. Step 2 (2.1.2)

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.

Contains Nonbinding Recommendations

3. Step 3 (2.1.3)

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.

4. Step 4 (2.1.4)

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

5. Step 5 (2.1.5)

The annex moves to the regional regulatory implementation step.

B. Annex Contents (2.2)

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

C. Use of the Pharmacopoeial Text (2.3)

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 IV (4) *Considerations for Implementation*. The basic information will be as provided below:

• Considerations for Implementation (2.3.1)

General consideration: When sponsors or manufacturers change their existing methods to the implemented Q4B-evaluated pharmacopoeial texts that are referenced in section II (2) of the annex, any change notification, variation, and/or prior approval procedures should be

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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 II (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 authorization application, renewal or variation application citing the use of the corresponding text from another pharmacopoeia as referenced in section II (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 II (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.

GLOSSARY (3)

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 pharmacopeia 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 Pharmacopeial 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 favorable evaluation.

ATTACHMENT I

General Chapters Discussed During ICH Q6A Development

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

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 Q4B guidance) 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-harmonized 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 harmonization;
 - 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 harmonization. Therefore, the revised information chapter on harmonization 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.