

Frequently Asked Questions

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

The Q4B Expert Working Group developed a set of frequently asked questions to help users of the Q4B Guideline and Annexes to understand the use and implication of these documents

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1. What is PDG?

The Pharmacopoeial Discussion Group (PDG) was formed in 1989 with representatives from the European Directorate for the Quality of Medicines (EDQM)/European Pharmacopoeia (Ph. Eur.), United States Pharmacopoeia (USP), and Japanese Pharmacopoeia (JP) to work on harmonising excipient monographs and general chapters in the pharmacopoeias. In 2001, the PDG welcomed the World Health Organization (WHO) as an observer. While not part of ICH, the PDG typically met in conjunction with the ICH and provides the ICH Steering Committee with reports of its harmonisation progress.

The PDG considers proposals made by national and regional associations of manufacturers of pharmaceutical products and excipients in order to select general methods of analysis and excipient monographs for addition to its harmonisation work programme. To promote these exchanges and synergy, since 2001, the PDG has organised, upon request, hearings for representatives of the pharmaceutical and excipient industries. At all times, PDG works to maintain an optimal level of science consistent with protection of the public health.

Each pharmacopoeia is responsible for a programme of international harmonisation. Each text drafted by the three co-ordinating pharmacopoeias is published for public comment at PDG Stage 4 in each of their respective forums. Please refer to the Working Procedures of the PDG, for further information. See the pertinent pharmacopoeial website.

2. What is Q4B?

Q4B is an ICH Expert Working Group (EWG) established in November 2003. As with all of the ICH EWGs, it is composed of regulators and industry representatives of the three ICH regions, with some observers. The subject of Q4B is "Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions". The texts evaluated by Q4B are primarily the result of harmonisation by the Pharmacopoeial Discussion Group (PDG). The aim of Q4B is to recommend that the texts published in the three pharmacopoeias (Ph. Eur., JP and USP) can be used as interchangeable. Texts determined to be interchangeable, can be used by industry and accepted by the regulators of the three regions. The recommendation of interchangeability is provided in a series of topic-specific "Annexes" as published on the ICH website (www.ich.org).

The initial scope, as approved by the ICH Steering Committee, was composed of the 10 general chapters mentioned in the ICH Guideline Q6A on specifications, subsequently expanded with 5 additional chapters. The scope does not include any excipient, drug substance, or drug product monographs.

The overall process of Pharmacopoeial Harmonisation (Q4A: PDG) associated with the process for evaluation of interchangeability (Q4B EWG) defines the current framework of ICH Q4.

3. Why is Q4B necessary?

One of the ultimate goals for the pharmaceutical industry is the ability to generate analytical data by a single test method which is acceptable in each region. This goal of interchangeable test methods has not been achieved, and companies have been forced to perform multiple tests due to lack of harmonisation among the pharmacopoeias. One of the approaches taken to address this issue is the effort by the Pharmacopoeial Discussion Group (PDG) for the harmonisation of JP, Ph. Eur., and USP. The PDG-harmonised text would be interchangeable if implemented without change in each pharmacopoeia. In reality, some modifications are usually made to the harmonised text as it is incorporated into each pharmacopoeia, due to regional requirements. Therefore, it is crucial for pharmaceutical companies to assess the acceptability of data obtained per a particular pharmacopoeia in the other regions, or determine the necessity of repeating the test per the regional pharmacopoeia requirement.

If the Q4B process were not in place, pharmaceutical companies would have to investigate the similarity or differences among the pharmacopoeias and judge the interchangeability of the data by themselves. The acceptability to the regulatory agencies of such judgment by the companies is not clear until the submission is made, and hence the companies take on a larger workload and potential regulatory risks.

Q4B compares the PDG-harmonised text with each pharmacopoeial text as officially published and evaluates the interchangeability based on a review of any differences from the PDG-harmonised text. As an outcome of Q4B evaluation, each topic-specific Annex indicates whether and how the regulatory authorities will accept the chapters as interchangeable when the Annex is implemented in each region. The Annex also states the conditions for interchangeability, which helps the pharmaceutical companies to understand the points to be noted during drug development, at the time of submission, and for compliance during product lifecycle.

In addition, Q4B comments facilitate PDG in revisiting local requirements or non-harmonised attributes, with the possibility of eliminating these residual differences.

4. How does industry use the Q4B Annexes?

Implementation of the Q4B Annexes is intended to avoid redundant testing by industry. A pharmaceutical manufacturer who follows the conditions (if any) detailed in Section 2 of a particular Q4B Annex is assured that the pharmacopoeial chapters listed in the Annex may be used as interchangeable to ensure compliance with pharmacopoeial and regulatory requirements in the countries/regions listed in Section 4 of the Annex. A status of "interchangeable" in the Q4B Annex means that any of the official texts from JP, Ph. Eur., 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 Pharmacopoeial Discussion Group (PDG) pharmacopoeia is used.

The Q4B Annexes give guidance to industry for registration and implementation of the harmonised pharmacopoeial chapters. Section 2 of the Annexes contains the Q4B recommendation of interchangeability, and may include specific considerations regarding the

pharmacopoeial chapters. If there are no considerations listed in Section 2 of the Annex, then the interchangeability of the chapters is without condition. It should be noted that any conditions contained in Section 2 of the Annexes do not introduce additional requirements beyond the details already contained in the harmonised chapters. Rather, the conditions in Section 2 provide guidance on details that must be included in drug product registrations, as well as information needed by testing laboratories to enable use of the harmonised chapters, as a result of non-harmonised sections of the pharmacopoeial text and/or details not covered in the text.

For example, in Q4B Annex 1 (Residue on Ignition/Sulphated Ash General Chapter), one of the conditions in Section 2.1 indicates that the appropriate sample weight should be justified and the sample weight and acceptance criteria should be specified in the application dossier, unless otherwise specified in a monograph. A second condition states that the muffle furnace should be appropriately calibrated to ensure compliance with regional GMP requirements. The first condition is necessary in the Q4B Annex due to the absence of information in the harmonised general chapters (sample weight and acceptance criteria). The second condition addresses residual differences that remain after publication of the harmonised chapters in each of the individual pharmacopoeias (calibration of the muffle furnace).

Similarly, the conditions listed in Q4B Annex 5 (Disintegration Test General Chapter) are necessary to provide regulatory clarification regarding non-harmonised sections in the chapters for specific dosage forms, along with a statement of information that must be included in the application dossier to enable use of the chapters.

Section 4 of the Q4B Annexes contains important information regarding regulatory considerations (both general and region-specific) for implementation of the harmonised chapters. For existing product registrations, 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. For new product registrations, sponsors or manufacturers should ensure that the Q4B-evaluated pharmacopoeial text is appropriately referenced in the application dossier to enable use of the interchangeable chapters.

It should also be noted that the pharmacopoeial references listed in Section 5 are only intended to provide historical context for the Q4B evaluation of the harmonised chapters. The most current version of the appropriate pharmacopoeial chapters listed in Section 2 should always be used to ensure ongoing compliance.

5. How do regulators use the Q4B Annexes?

Regulators consider texts listed in Section 2 of the Q4B Annexes to be interchangeable such that any of the official texts from JP, Ph. Eur., or USP chapters that have been designated as "interchangeable" with an annex can be referenced in dossiers and compliance testing, and will be considered to be equivalent to each other, subject to any conditions detailed in the Annex. Any specific considerations necessary for implementation in an ICH region are detailed in Section 4 of the Annex. For example, for the U.S., 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.

For existing products, when making a change to reference another interchangeable pharmacopoeial method, any change notification, variation, and/or prior approval procedures should be handled in accordance with established regional regulatory mechanisms pertaining to compendial changes.

- For FDA: Notification in Annual Report
- For EU: Notification in Annual Report
- For MHLW: Notification to the Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division (PFSB/ELD)

6. When can Q4B Annexes be used?

When an Annex has been implemented (incorporated into the regulatory process at the regional regulatory implementation, ICH *Step 5*) following the Q4B evaluation, it means that the Q4B evaluation process has resulted in a conclusion and recommendation that the pharmacopeial text can be used as interchangeable in the ICH regions. At that time, a topic-specific Q4B Annex will be issued and published on the official ICH website, with general considerations on implementation timing provided in Section 3 of the Annex. Timing of implementation timelines might differ for each region.

On the official ICH website, for each Annex, the date for implementation in each region is given by the following references:

- EU: references to the adoption date by CHMP and date for coming into operation.
- MHLW: reference to the adoption date by PFSB/ELD.
- FDA: date of publication as a final *Guidance for Industry* in the Federal Register.

These implementation timelines indicate when stakeholders can begin using the pharmacopoeial text as interchangeable.

As an example, the implementation timelines for Q4B Annex 1 (Residue on Ignition/Sulphated Ash General Chapter) are provided below:

- EU: Adopted by CHMP December 2007, issued as [EMEA/CHMP/ICH/222063/2006](#). Date for coming into operation: June 2008.
- MHLW: Adopted 26 May 2009, Notification PFSB/ELD N° 052 6002
- FDA: Published in the Federal Register, Vol. 73, N° 35, pages 9576-9577, 21 February 2008.

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.

7. Can harmonised pharmacopoeial text be considered interchangeable in countries/regions outside of ICH?

ICH Guidelines can be used by industry and regulators in ICH and non-ICH countries. ICH Guidelines have already been adopted and implemented in a number of non-ICH countries. Before using an ICH Guideline all stakeholders should verify the status of the guideline with the regulatory authority in the country where they intend to file.

Similarly, the ICH Q4B Guideline and Annexes are being adopted/implemented in non-ICH countries as exemplified by the adoption of the Q4B Guideline and Annexes in Canada (with revised Annexes published on the ICH website to reflect adoption by Health Canada). For more information on the acceptability of Q4B Annexes in a non-ICH region and their implementation, the regulatory authorities should be contacted directly.