
Guidance for Industry

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

Annex 6 Uniformity of Dosage Units General Chapter

**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)**

**June 2014
ICH**

Revision 1

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Annex 6
Uniformity of Dosage Units General Chapter

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)²

This annex is one in a series of guidance documents that describe the evaluations and recommendations 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. Implementation of the Q4B annexes is intended to avoid redundant testing by industry. For general information on the Q4B process, the reader is referred to the core guidance *Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions*.³ This annex revises annex 6 on uniformity of dosage units general chapter that issued on June 16, 2014. This revision changes section II.B (2.2) of this annex to correctly state that the acceptance criteria are harmonized between the three pharmacopoeias.

This annex is the result of the Q4B process for the Uniformity of Dosage Units General Chapter.

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 2013. 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 2013.

³We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or the FDA Biologics guidance page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

The proposed texts were submitted by the Pharmacopoeial Discussion Group (PDG).

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.

II. Q4B OUTCOME (2)

A. Analytical Procedures (2.1)

The ICH Steering Committee, based on the evaluation by the Q4B Expert Working Group (EWG), recommends that the official pharmacopoeial texts, Ph. Eur. 2.9.40. Uniformity of Dosage Units, JP 6.02 Uniformity of Dosage Units, and USP General Chapter <905> Uniformity of Dosage Units, can be used as interchangeable in the ICH regions subject to the following conditions:

1. (2.1.1) Unless the 25 milligrams (mg)/25% threshold limit is met, the use of the Mass/Weight Variation test as an alternative test for Content Uniformity is not considered interchangeable in all ICH regions.
2. (2.1.2) For specific dosage forms that appear in local text in the pharmacopoeias by enclosing the text in black diamond symbols, application of the Uniformity of Dosage Units test is not considered interchangeable in all ICH regions.
3. (2.1.3) If a correction factor is called for when different procedures are used for assay of the preparation and for the Content Uniformity Test, the correction factor should be specified and justified in the application dossier.

B. Acceptance Criteria (2.2)

The acceptance criteria are harmonized between the three pharmacopoeias.

III. TIMING OF ANNEX IMPLEMENTATION (3)

When this annex is implemented (incorporated into the regulatory process at ICH Step 5) in a region, it can be used in that region. Timing might differ for each region.

IV. CONSIDERATIONS FOR IMPLEMENTATION (4)

A. General Consideration (4.1)

When sponsors or manufacturers change their existing methods to the implemented Q4B-evaluated pharmacopoeial texts that are referenced in section II.A (2.1) of this annex, any change

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notification, variation, and/or prior approval procedures should be handled in accordance with established regional regulatory mechanisms pertaining to compendial changes.

B. FDA Consideration (4.2)

Based on the recommendation above, and with reference to the conditions set forth in this annex, the pharmacopoeial texts referenced in section II.A (2.1) of this 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.

FDA finds unsuitable for regulatory purposes the not more than (NMT) 2% relative standard deviation (RSD) exception to the 25 mg/25% threshold that appears in the JP and the Ph. Eur. Therefore, in accordance with the official text in the USP, for those items below the 25 mg/25% threshold, testing by Content Uniformity should be performed.

C. European Union Consideration (4.3)

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.A (2.1), in accordance with the conditions set out in this annex, as fulfilling the requirements for compliance with the Ph. Eur. Chapter 2.9.40. on the basis of the declaration of interchangeability made above.

D. MHLW Consideration (4.4)

The pharmacopoeial texts referenced in section II.A (2.1) of this annex can be used as interchangeable in accordance with the conditions set out in this annex. Details of implementation requirements will be provided in the notification by MHLW when this annex is implemented.

E. Health Canada Consideration (4.5)

In Canada any of the pharmacopoeial texts cited in Section 2.1 of this annex and used in accordance with the conditions set out in this annex can be considered interchangeable.

V. REFERENCES USED FOR THE Q4B EVALUATION (5)

A. (5.1) The PDG Stage 5B sign-off document: *Japanese Pharmacopoeial Forum*, Volume 13, number 2 (May 2004).

B. (5.2) The pharmacopoeial references for Uniformity of Dosage Units for this annex are:

1. (5.2.1) *European Pharmacopoeia* (Ph. Eur.):

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Supplement 6.1 (official April 2008) Uniformity of Dosage Units (reference 04/2008:20940). Further changes to the official text were made in Supplement 7.4, official April 1, 2012.

2. (5.2.2) *Japanese Pharmacopoeia (JP)*:
6.02 Uniformity of Dosage Units, as it appears in the JP Fifteenth Edition (March 31, 2006, The Ministry of Health, Labour and Welfare Ministerial Notification No. 285), officially updated by errata published by MHLW at http://www.pmda.go.jp/english/pharmacopoeia/pdf/jpdata/H201105_jp15_errata.pdf on November 5, 2008. Further changes were implemented via MHLW Ministerial Notification No. 190 on May 31, 2013 (see <http://www.pmda.go.jp/english/pharmacopoeia/pdf/jpdata/JP16-1en.pdf>).

3. (5.2.3) *United States Pharmacopeia (USP)*:
<905> Uniformity of Dosage Units, Pharmacopeial Forum, Volume 35, Number 3, official in USP 33-Reissue (October 2010). USP provided notification on February 25, 2011, (see <http://www.usp.org/usp-nf/harmonization/stage-6/uniformity-dosage-units>) to implement requirements set forth in the 2nd paragraph of section IV.B (4.2) of this annex and other changes. These changes made official on December 1, 2011, concurrent with USP 34 – NF 29, 2nd Supplement.