

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  
ON  
UNIFORMITY OF DOSAGE UNITS GENERAL CHAPTER  
Q4B ANNEX 6**

Current *Step 4* version  
dated 13 November 2013

*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 Annex 6**  
**Document History**

Code	History	Date
Q4B Annex 6	Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.	13 November 2008
Q4B Annex 6(R1)	Integration into <i>Step 2</i> of the Health Canada Interchangeability Statement under Section 4.5 after approval by the Steering Committee.	27 September 2010

**Current *Step 4* version**

Q4B Annex 6	Approval by the Steering Committee under <i>Step 4</i> and recommendation for adoption to the three ICH regulatory bodies. The R was removed from the name of the document as this is the first version of the Annex 6 <i>Step 4</i> .	13 November 2013
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**ICH Harmonised Tripartite Guideline**

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 13 November 2013, this guideline is recommended for adoption to the three regulatory parties to ICH.

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## **1. INTRODUCTION**

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

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

## **2. Q4B OUTCOME**

### **2.1 Analytical Procedures**

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:

- 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.
- 2.1.2** 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.
- 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.

### **2.2 Acceptance Criteria**

The acceptance criteria are harmonized between the three pharmacopoeias.

## **3. TIMING OF ANNEX IMPLEMENTATION**

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.

## **4. CONSIDERATIONS FOR IMPLEMENTATION**

### **4.1 General Consideration**

When sponsors or manufacturers change their existing methods to the implemented Q4B-evaluated pharmacopoeial texts that are referenced in Section 2.1 of this annex, any change notification, variation, and/or prior approval procedures should be handled in accordance with established regional regulatory mechanisms pertaining to compendial changes.

### **4.2 FDA Consideration**

Based on the recommendation above, and with reference to the conditions set forth in this annex, the pharmacopoeial texts referenced in Section 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 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.

#### **4.3 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 2.1, 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.

#### **4.4 MHLW Consideration**

The pharmacopoeial texts referenced in Section 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.

#### **4.5 Health Canada Consideration**

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.

### **5. REFERENCES USED FOR THE Q4B EVALUATION**

- 5.1** The PDG Stage 5B sign-off document: *Japanese Pharmacopoeial Forum*, Volume 13, number 2 (May 2004).
- 5.2** The pharmacopoeial references for Uniformity of Dosage Units for this annex are:
  - 5.2.1** *European Pharmacopoeia* (Ph. Eur.): 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.
  - 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](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>).
  - 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 2<sup>nd</sup> paragraph of Section 4.2 of this Annex and other changes. These changes made official on December 1, 2011, concurrent with USP 34 – NF 29, 2<sup>nd</sup> Supplement.