Health Canada Santé Canada

May 29, 2015

Notice

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Adoption of ICH[1] Guidance Document: Q4B Annex 6: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Uniformity of Dosage Units General Chapter

Health Canada is pleased to announce the adoption of the ICH guidance Q4B Annex 6: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Uniformity of Dosage Units General Chapter.

This guidance 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. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

In adopting this ICH guidance, Health Canada endorses the principles and practices described therein. This document should be read in conjunction with this accompanying notice and with the relevant sections of other applicable Health Canada guidances.

It is recognized that the scope and subject matter of current Health Canada guidances may not be entirely consistent with those of the ICH guidances that are being introduced as part of our commitment to international harmonization and the ICH Process. In such circumstances, Health Canada adopted ICH guidances take precedence.

Health Canada is committed to eliminating such discrepancies through the implementation of a phased-in work plan that will examine the impact associated with the adoption of ICH guidances. This will result in the amendment or, depending on the extent of revisions required, withdrawal of some Health Canada guidances.

This and other Guidance documents are available on the Health Canada website.

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[1] *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use*

Canada

Should you have any questions or comments regarding the content of the guidance, please contact:

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Health Canada Santé Canada

GUIDANCE DOCUMENT

Evaluation and Recommendation of Pharmacopoeial Texts for Use in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Regions on Uniformity of Dosage Units General Chapter

ICH Topic Q4B ANNEX 6(R1)

Published by the authority of the
Minister of Health

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food branch; and • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : Ligne directrice : Évaluation et recommandation de textes de pharmacopée pour usage dans les régions de l'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (l’ICH) sur le chapitre général relatif à l'uniformité des préparations unidoses, Annexe 6 de la directive Q4B

FOREWORD

This guidance 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. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and the United States of America.

In adopting this ICH guidance, Health Canada endorses the principles and practices described therein. This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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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, European Pharmacopoeia (Ph. Eur.) 2.9.40. Uniformity of Dosage Units, Japanese Pharmacopoeia (JP) 6.02 Uniformity of Dosage Units, and United States Pharmacopeia (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 2.2.1 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 United States Food and Drug Administration (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 European Union 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 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 2nd 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, 2nd Supplement.