



Health
Canada

Santé
Canada

May 29, 2015

Notice

Our file number: 15-106315-995

Adoption of International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) Guidance Document: Q4B Annex 14: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bacterial Endotoxins Test General Chapter

Health Canada is pleased to announce the adoption of the ICH guidance Q4B Annex 14: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bacterial Endotoxins Test 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.

.../2

Canada 

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

BPS Enquiries - Bureau of Pharmaceutical Sciences

E-mail: BPS_Enquiries@hc-sc.gc.ca

Telephone: 613-941-3184

Fax: 613-941-0571



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 Bacterial Endotoxins Test General Chapter

ICH Topic Q4B ANNEX 14(R1)

Published by the authority of the
Minister of Health

Date Adopted	2015/05/29
Effective Date	2015/05/29

Health Products and Food Branch

Canada 

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>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:</p> <ul style="list-style-type: none"> • 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. <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
--	---

© Ministre, Travaux publics et services gouvernementaux Canada 2015

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'essai des endotoxines bactériennes, Annexe 14(R1) 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.

Table of Contents

1. INTRODUCTION.....	1
2. Q4B OUTCOME.....	1
2.1 Analytical Procedures	1
2.2 Acceptance Criteria	1
3. TIMING OF ANNEX IMPLEMENTATION.....	1
4. CONSIDERATIONS FOR IMPLEMENTATION	2
4.1 General Consideration.....	2
4.2 United States Food and Drug Administration (FDA) Consideration.....	2
4.3 European Union (EU) Consideration	2
4.4 MHLW Consideration.....	2
4.5 Health Canada Consideration.....	2
5. REFERENCES USED FOR THE Q4B EVALUATION	2

1. INTRODUCTION

This annex is the result of the Q4B process for the Bacterial Endotoxins Test 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 analytical procedures described in the official pharmacopoeial texts, European Pharmacopoeia (Ph. Eur.) 2.6.14. Bacterial Endotoxins, Japanese Pharmacopoeia (JP) 4.01 Bacterial Endotoxins Test, and United States Pharmacopoeia (USP) General Chapter <85> Bacterial Endotoxins Test, can be used as interchangeable in the ICH regions subject to the following conditions:

- 2.1.1 Any of the three techniques can be used for the test. In the event of doubt or dispute, the gel-clot limit test should be used to make the final decision on compliance for the product being tested.
- 2.1.2 The USP, JP, and Ph.Eur. reference standards are considered interchangeable as they have been suitably calibrated against the WHO (World Health Organization) International Standard for Endotoxin.
- 2.1.3 In the section *Photometric quantitative techniques, Preparatory testing, Test for interfering factors*, the user should perform the test on solutions A, B, C, and D on at least 2 replicates using the optimal conditions as recommended by the lysate manufacturer.

2.2 Acceptance Criteria

The evaluated texts did not contain acceptance criteria. Endotoxin limits should be specified in the application dossier unless otherwise specified in an individual monograph.

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.

4.3 European Union (EU) Consideration

For the European Union, 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 2.6.14. 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 (Rev. 1 - Correction 1): *Japanese Pharmacopoeial Forum*, Volume 18, number 4 (December 2009).

5.2 The pharmacopoeial references for the Bacterial Endotoxins Test General Chapter for this annex are:

- 5.2.1** *European Pharmacopoeia* (Ph. Eur.): Supplement 6.6 (official January 1, 2010), Bacterial Endotoxins (reference 01/2010:20614);
- 5.2.2** *Japanese Pharmacopoeia* (JP): General Test 4.01 Bacterial Endotoxins Test as it appears in the JP Sixteenth Edition (March 24, 2011, The Ministry of Health, Labour and Welfare Ministerial Notification No.65);
- 5.2.3** *United States Pharmacopeia* (USP): Text for <85> Bacterial Endotoxins Test, USP 33 Reissue (published April 2010 and official October 1, 2010).