

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  
BACTERIAL ENDOTOXINS TEST  
GENERAL CHAPTER  
Q4B ANNEX 14**

Current *Step 4* version  
dated 18 October 2012

*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 14  
Document History**

Code	History	Date
Q4B Annex 14	Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.	10 June 2010

**Current *Step 4* version**

Q4B Annex 14	Approval by the Steering Committee under <i>Step 4</i> and recommendation for adoption to the three ICH regulatory bodies.	18 October 2012
--------------	--	-----------------

**EVALUATION AND RECOMMENDATION OF  
PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS  
ON  
BACTERIAL ENDOTOXINS TEST  
GENERAL CHAPTER  
Q4B ANNEX 14**

**ICH Harmonised Tripartite Guideline**

Having reached *Step 4* of the ICH Process, this guideline is recommended for adoption to the three regulatory parties to ICH.

**TABLE OF CONTENTS**

<b>1. INTRODUCTION.....</b>	<b>1</b>
<b>2. Q4B OUTCOME .....</b>	<b>1</b>
<b>2.1 Analytical Procedures.....</b>	<b>1</b>
<b>2.2 Acceptance Criteria .....</b>	<b>1</b>
<b>3. TIMING OF ANNEX IMPLEMENTATION .....</b>	<b>1</b>
<b>4. CONSIDERATIONS FOR IMPLEMENTATION.....</b>	<b>2</b>
<b>4.1 General Consideration .....</b>	<b>2</b>
<b>4.2 FDA Consideration.....</b>	<b>2</b>
<b>4.3 European Union Consideration.....</b>	<b>2</b>
<b>4.4 MHLW Consideration .....</b>	<b>2</b>
<b>4.5 Health Canada Consideration.....</b>	<b>2</b>
<b>5. REFERENCES USED FOR THE Q4B EVALUATION .....</b>	<b>2</b>

**EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL  
TEXTS FOR USE IN THE ICH REGIONS  
ON  
BACTERIAL ENDOTOXINS TEST  
GENERAL CHAPTER  
Q4B ANNEX 14**

**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, Ph.Eur. 2.6.14. Bacterial Endotoxins, JP 4.01 Bacterial Endotoxins Test, and 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 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 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).