

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

Annex 6: Uniformity of Dosage Units General Chapter

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

For questions regarding this draft document contact (CDER) Robert King 301-796-1242, or (CBER) Christopher Joneckis 301-827-0373.

Final STEP 2 signoff - Annex 6 Uniformity of Dosage Units (UDU) Nov. 13, 2008
[For Brussels November 2008] Corrected 12-18-08

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS 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 2* Version
dated 13 November 2008

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

Final STEP 2 signoff - Annex 6 Uniformity of Dosage Units (UDU) Nov. 13, 2008
[For Brussels November 2008] Corrected 12-18-08

39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54

**Q4B Annex 6
Document History**

Current *Step 2* version

Code	History	Date
Q4B Annex 6	Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.	13 November 2008

55
56

57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93

**EVALUATION AND RECOMMENDATION OF
PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS
ON
UNIFORMITY OF DOSAGE UNITS GENERAL CHAPTER
Q4B Annex 6**

Draft ICH Consensus Guideline
Released for Consultation on 13 November 2008, at *Step 2* of the ICH Process

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.....2
4. CONSIDERATIONS FOR IMPLEMENTATION.....2
4.1 General Consideration.....2
4.2 FDA Consideration.....2
4.3 EU Consideration.....2
4.4 MHLW Consideration.....2
5. REFERENCES USED FOR THE Q4B EVALUATION.....2

94

95

96

EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS

97

ON

98

UNIFORMITY OF DOSAGE UNITS GENERAL CHAPTER

99

Q4B Annex 6

100

101

102

103

104

105

106

107

108

109

110

111

112

113

114

115

116

117

118

119

120

121

122

123

124

125

126

127

128

129

130

131

132

133

134

135

136

137

138

139

140

141

1. INTRODUCTION

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

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 The Uniformity of Dosage Unit test is not considered to be interchangeable in the three regions unless the target test sample amount at time of manufacture (T) is 100% (i.e., T=100%).

2.1.2 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.

2.1.3 For specific dosage forms which have been indicated in local text in the pharmacopoeias by enclosing the text within the black diamond symbols, application of the Uniformity of Dosage Units test is not considered interchangeable in all ICH regions.

2.1.4 For Mass/Weight Variation, the PDG-harmonised definition for 'W Bar' should be used.

2.1.5 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.

142
143
144
145
146 **3. TIMING OF ANNEX IMPLEMENTATION**
147

148 When this annex is implemented (incorporated into the regulatory process at ICH Step 5) in a
149 region, it can be used in that region. Timing might differ for each region.
150

151 **4. CONSIDERATIONS FOR IMPLEMENTATION**
152

153 **4.1 General Consideration**
154

155 When sponsors or manufacturers change their existing methods to the implemented
156 Q4B-evaluated pharmacopoeial texts that are referenced in Section 2.1 of this annex,
157 any change notification, variation, and/or prior approval procedures should be handled
158 in accordance with established regional regulatory mechanisms pertaining to
159 compendial changes.
160

161 **4.2 FDA Consideration**
162

163 Based on the recommendation above, and with reference to the conditions set forth in
164 this annex, the pharmacopoeial texts referenced in Section 2.1 of this annex can be
165 considered interchangeable. However, FDA might request that a company
166 demonstrate that the chosen method is acceptable and suitable for a specific material
167 or product, irrespective of the origin of the method.
168

169 FDA finds unsuitable for regulatory purposes the *not more than (NMT) 2% relative*
170 *standard deviation (RSD)* exception to the 25 mg/25% threshold. Accordingly, for
171 those items below the 25 mg/25% threshold, testing by Content Uniformity should be
172 performed.
173

174 **4.3 EU Consideration**
175

176 For the European Union, the monographs of the Ph. Eur. have mandatory
177 applicability. Regulatory authorities can accept the reference in a marketing
178 authorisation application, renewal or variation application citing the use of the
179 corresponding text from another pharmacopoeia as referenced in Section 2.1, in
180 accordance with the conditions set out in this annex, as fulfilling the requirements for
181 compliance with the Ph. Eur. Chapter 2.9.40. on the basis of the declaration of
182 interchangeability made above.
183

184 **4.4 MHLW Consideration**
185

186 The pharmacopoeial texts referenced in Section 2.1 of this annex can be used as
187 interchangeable in accordance with the conditions set out in this annex. Details of
188 implementation requirements will be provided in the notification by MHLW when this
189 annex is implemented.
190

191
192 **5. REFERENCES USED FOR THE Q4B EVALUATION**
193

194 **5.1** The PDG Stage 5B sign-off document: *Japanese Pharmacopoeial Forum*, Volume
195 13, number 2 (May 2004).
196

197 **5.2** The pharmacopoeial references for Uniformity of Dosage Units for this annex are:
198

199 **5.2.1** *European Pharmacopoeia* (Ph. Eur.):

200
201
202
203
204
205
206
207
208
209
210
211
212
213
214

Uniformity of Dosage Units General Chapter

Supplement 6.1 (official April 2008) Uniformity of Dosage Units (reference
01/2008: 20940)

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).

5.2.3 *United States Pharmacopoeia (USP):*

<905> Uniformity of Dosage Units, *Pharmacopoeial Forum*, Volume 34,
Number 5, to be official December 2009.