
Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Richard Lostritto at 301-796-1667.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**August 2015
Biopharmaceutics**

Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**August 2015
Biopharmaceutics**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	ELIGIBLE PRODUCTS.....	3
A.	Dosage Form.....	3
B.	Solubility	3
C.	Therapeutic Class	3
D.	Time to Maximum Plasma Concentration.....	3
E.	Manufacturing and Testing History.....	4
F.	Excipients	4
IV.	STANDARD DISSOLUTION TEST CONDITIONS	4
A.	Basket Method (USP apparatus 1)	4
B.	Paddle Method (USP apparatus 2)	4
V.	SPECIFICATION.....	5
VI.	REPLACING DISSOLUTION WITH DISINTEGRATION.....	5
VII.	REFERENCES.....	5

Contains Nonbinding Recommendations

Draft — Not for Implementation

1 **Dissolution Testing and Specification Criteria for Immediate-**
2 **Release Solid Oral Dosage Forms Containing Biopharmaceutics**
3 **Classification System Class 1 and 3 Drugs**
4 **Guidance for Industry¹**
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

13
14 **I. INTRODUCTION**
15

16 This guidance is developed to provide manufacturers with recommendations for submission of
17 new drug applications (NDAs), investigational new drug applications (INDs), and/or
18 abbreviated new drug applications (ANDAs), as appropriate, for immediate-release (IR) tablets
19 and capsules that contain highly soluble drug substances. The guidance is intended to describe
20 when a standard release test and criteria may be used in lieu of extensive method development
21 and specification-setting exercises. When final, this guidance will supersede the guidance for
22 industry on [Dissolution Testing of Immediate Release Solid Oral Dosage Forms](#) (August 1997)
23 for biopharmaceutics classification system (BCS) class 1 and 3 drug substances in immediate-
24 release drug products that meet the criteria in this guidance.² For class 2 and 4 drug substances,
25 applicants should still refer to the August 1997 guidance mentioned above.
26

27 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
28 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
29 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
30 the word *should* in Agency guidances means that something is suggested or recommended, but
31 not required.
32
33

¹ This guidance has been prepared by the Dissolution Technical Advisory Group (TAG) team in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

34 **II. BACKGROUND**

35
36 Drug absorption from a solid dosage form after oral administration depends on the release of the
37 drug substance from the drug product, the dissolution or solubilization of the drug under
38 physiological conditions, and the permeation across the gastrointestinal membrane.³ NDAs and
39 ANDAs submitted to FDA contain bioavailability (BA) or bioequivalence (BE) data and in vitro
40 dissolution data that, together with chemistry, manufacturing, and controls (CMC) data,
41 characterize the quality and performance of the drug product. In vitro dissolution data are
42 generally obtained from batches that have been used in pivotal clinical and/or
43 bioavailability/bioequivalence studies, and from other human studies conducted during product
44 development. Knowledge about the solubility, permeability, dissolution, and pharmacokinetics of
45 a drug product is considered when defining dissolution test specifications for the drug approval
46 process.

47
48 The BCS is a scientific framework for classifying drug substances based on their aqueous
49 solubility and intestinal permeability. The definitions of high and low solubility and high and
50 low permeability are used as described in the Biopharmaceutics Classification System (BCS)
51 Guidance.⁴ The different classifications are:

- 52
53 Class 1: High Solubility - High Permeability Drugs
54 Class 2: Low Solubility - High Permeability Drugs
55 Class 3: High Solubility - Low Permeability Drugs
56 Class 4: Low Solubility - Low Permeability Drugs

57
58 This classification can be used as a basis for determining when in vivo BA and BE studies are
59 needed and can be used to determine when a successful in vitro-in vivo correlation (IVIVC) is
60 likely. The BCS suggests that, for certain high solubility drugs, dissolution testing can be
61 standardized. Owing to their high solubility, BCS class 1 and 3 drugs are considered to be
62 relatively low risk regarding the impact of dissolution on performance, provided the in vitro
63 performance meets or exceeds the recommendations discussed herein.

64
65 This guidance establishes standard dissolution methodology and specifications that are
66 appropriate for BCS class 1 and class 3 drugs in IR dosage form. The availability of these
67 standards will facilitate the rapid development of dissolution methodology and related
68 specifications for these classes during drug development and application review.

69
70

³ Amidon GL, Lennernas H, Shah VP, and Crison JR, 1995, A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharm. Res.,12:413-420.

⁴ See <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128219.htm> and guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (May 2015), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

71 **III. ELIGIBLE PRODUCTS**

72
73 In addition to being an IR dosage form, your drug product should meet all of the following
74 conditions in order for the dissolution standards in this guidance to apply.⁵ You also should follow
75 Agency guidances to establish that your drug product is either a BCS class 1 or 3 product.⁶ To
76 help determine if your product meets any particular condition listed below, contact the review
77 division for your specific drug product.

78 79 **A. Dosage Form**

80
81 This guidance applies to solid orally-administered immediate release dosage forms, such as tablets
82 and capsules that are meant to be swallowed. It does not include chewable tablets, and does not
83 apply to orally disintegrating tablets.

84 85 **B. Solubility**

86
87 To be considered BCS class 1 or 3,⁷ the drug substance should be considered highly soluble with
88 the highest dose strength soluble in 250 mL or less of aqueous media over the pH range of 1 to
89 6.8.⁸ The drug substance should also be chemically stable for 24 hours over this same pH range.

90 91 **C. Therapeutic Class**

92
93 This guidance does not apply to narrow therapeutic index (NTI) drugs because of the critical
94 relationship between the bioavailable dose (and therefore dissolution) on clinical performance.
95 For more information on NTI drugs, the current approach to establish the NTI classification of a
96 drug is described in the draft product-specific guidance on Warfarin Sodium, posted December
97 2012, on the FDA Web site for Individual Product Bioequivalence Recommendations,
98 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf>.

100 101 **D. Time to Maximum Plasma Concentration**

102
103 If the time to maximum plasma concentration is critical to the intended use, this guidance does not
104 apply. For example, labeling claims of early or rapid onset of action (e.g., rapid analgesia, rescue
105 medications, etc.) exclude the product from adoption of the dissolution standards proposed herein.
106

⁵ For these classes of products, these recommendations will supersede those in the Dissolution Methods Database, and upon finalization of this guidance FDA will update the Dissolution Methods Database or remove entries from the Database that are covered by this guidance. For products where the method described in a United States Pharmacopeia (USP) drug product monograph differs from the recommendations of this guidance, ANDA applicants may propose to use the approaches in this guidance as an alternative method and seek revision of the relevant monograph.

⁶ *Supra* note 5.

⁷ *Supra* note 5.

⁸ For ANDAs, the highest dose strength for which approval is sought.

Contains Nonbinding Recommendations

Draft — Not for Implementation

107 **E. Manufacturing and Testing History**

108
109 Manufacturing and testing history, including stability testing, should demonstrate that the product
110 will meet the specifications in this guidance when using the standard dissolution test conditions.

111 112 **F. Excipients**

113
114 Excipients chosen for drug product formulations should be consistent with the design of IR drug
115 products. Excipients should be included in normal quantities that are consistent with the product's
116 labeled function. Large quantities of excipients, such as sweeteners and surfactants, may be
117 problematic. You are encouraged to contact the review division for your specific drug product
118 when this is a factor.

119 120 **IV. STANDARD DISSOLUTION TEST CONDITIONS**

121
122 If a product is deemed to be eligible for a standard dissolution method and specification, you
123 should use one of the following methods.⁹ Information on apparatus and number of units to test
124 can be found in the USP General Chapter <711> Dissolution. You should calibrate apparatus
125 before use.¹⁰

126 127 **A. Basket Method (USP apparatus 1)**

- 128
129
- 130 • Stirring rate = 100 RPM
 - 131 • 500 mL of 0.01M HCl aqueous media
 - 132 • No surfactant in media
 - 133 • 37±0.5°C

134 **B. Paddle Method (USP apparatus 2)**

- 135
136
- 137 • Stirring rate = 75 RPM
 - 138 • 500 mL of 0.01M HCl aqueous media
 - 139 • No surfactant in media
 - 140 • 37±0.5°C

141 Although the hydrodynamics of the gastrointestinal tract are complicated and cannot be
142 reproduced by the USP basket or paddle apparatus, a stirring rate of 100 RPM has been found to
143 be discriminatory for the basket method. For the paddle method, 75 RPM can be discriminatory
144 while minimizing coning effects seen with lower rates. The acid conditions of the media reflect
145 the conditions of the stomach whose volume is estimated at 250 mL when a glass of water is co-

⁹ Shah V, Gurbarg M, Noory A, Dighe S, Skelly J, 1992, Influence of higher rates of agitation on release patterns of IR drug products, J Pharm Sci 81(6) 500-503.

¹⁰ See guidance for industry on *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP)* (January 2010), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198649.pdf>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

146 ingested with the oral dosage form. This volume is too low to use with the current basket and
147 paddle apparatus; however, 500 mL of media is commonly used and should be a sufficient
148 volume of media for a highly soluble, rapidly dissolving drug.

149

V. SPECIFICATION

151

152 The drug product dissolution specification will depend on the BCS class of the drug substance and
153 should follow the recommendations below. Applicants may consider further supporting their
154 proposed dissolution specifications with appropriate simulations in addition to dissolution
155 performance data.

156

157 • For BCS class 1 products, a single point dissolution specification of Q=80% in 30 minutes.

158

159 • For BCS class 3 products, a single point dissolution specification of Q=80% in 15 minutes.

160

161 BCS class 3 products that meet the more stringent specifications will better ensure that the
162 bioavailability of the drug is not limited by dissolution, and the rate-limiting step for drug
163 absorption becomes gastric emptying. For ANDAs, these criteria should apply unless supported
164 by data on the dissolution performance of the reference-listed drug.

165

VI. REPLACING DISSOLUTION WITH DISINTEGRATION

167

168 For drug products in both BCS classes 1 and 3, USP disintegration testing can be used in lieu of the
169 dissolution test if the product is shown to meet a dissolution specification of Q=80% in 15 minutes.

170

171 For drug products that meet this criterion, the USP disintegration test, which requires the product
172 to completely disintegrate within 5 minutes (via USP apparatus in 0.01M HCl), may serve as a
173 surrogate for routine release and stability dissolution testing. However, the approved dissolution
174 method should be retained as the primary method and the approved disintegration method as an
175 alternate method. Note that to support post-approval changes for which dissolution testing would
176 be typically be needed, you should use the approved dissolution method.

177

VII. REFERENCES

179

180 Amidon GL, Lennernas H, Shah VP, and Crison JR, 1995, A Theoretical Basis for a
181 Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and
182 In Vivo Bioavailability, *Pharm Res*,12:413-420.

183

184 Dickinson PA, et al., 2008, Clinical Relevance of Dissolution Testing in Quality by Design,
185 *AAPS Journal*, Vol. 10, No. 2.

186

187 FDA guidance for industry, 1995, Immediate Release Solid Oral Dosage Forms. Scale-up and
188 Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing,
189 and In Vivo Bioequivalence Documentation [SUPAC-IR].

190

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 191 FDA guidance for industry, 1997, Dissolution Testing of Immediate Release Solid Oral Dosage
192 Forms.
193
- 194 FDA guidance for industry, 2010, The Use of Mechanical Calibration of Dissolution Apparatus 1
195 and 2 – Current Good Manufacturing Practice (CGMP).
196
- 197 FDA guidance for industry, 2000, Waiver of In Vivo Bioavailability and Bioequivalence Studies
198 for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification
199 System.
200
- 201 FDA guidance for industry, 2015, Waiver of In Vivo Bioavailability and Bioequivalence Studies
202 for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification
203 System.
204
- 205 FDA draft guidance for industry, 2012, Warfarin Sodium.
206
- 207 Shah V, Gurbarg M, Noory A, Dighe S, Skelly J, 1992, Influence of higher rates of agitation on
208 release patterns of IR drug products, J Pharm Sci 81(6) 500-503.
209
- 210 Strauch S, Jantratid E, and Dressman JB, 2009, Comparison of WHO and US FDA biowaivers
211 dissolution test conditions using bioequivalent doxycycline hyclate drug products, J Pharmacy
212 and Pharmacology, 61:331-337.
213
- 214 United States Pharmacopeia (USP) General Chapters <711> Dissolution (2011), <701>
215 Disintegration (2008).
216
- 217 WHO,, 2006, Proposal to waive in vivo bioequivalence requirements for WHO Model List of
218 Essential Medicines immediate-release, solid oral dosage forms. Annex 8 of WHO Expert
219 Committee on Specifications for Pharmaceutical Preparations. Geneva: WHO.
220
- 221 Yu LX, et al., 2002, BCS: The Scientific Basis of Biowaiver Extensions, Pharm Research, 19(7)
222 921-925.
223
224