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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

TABLE OF CONTENTS

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

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

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

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

[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.

II. BACKGROUND

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

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

Class 1: High Solubility - High Permeability Drugs
Class 2: Low Solubility - High Permeability Drugs
Class 3: High Solubility - Low Permeability Drugs
Class 4: Low Solubility - Low Permeability Drugs

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

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

[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.

III. ELIGIBLE PRODUCTS

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

A. Dosage Form

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

B. Solubility

To be considered BCS class 1 or 3,[7] the drug substance should be considered highly soluble with the highest dose strength soluble in 250 mL or less of aqueous media over the pH range of 1 to 6.8.[8] The drug substance should also be chemically stable for 24 hours over this same pH range.

C. Therapeutic Class

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

D. Time to Maximum Plasma Concentration

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

---

[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.

E. Manufacturing and Testing History

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

F. Excipients

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

IV. STANDARD DISSOLUTION TEST CONDITIONS

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

A. Basket Method (USP apparatus 1)

- Stirring rate = 100 RPM
- 500 mL of 0.01M HCl aqueous media
- No surfactant in media
- 37±0.5°C

B. Paddle Method (USP apparatus 2)

- Stirring rate = 75 RPM
- 500 mL of 0.01M HCl aqueous media
- No surfactant in media
- 37±0.5°C

Although the hydrodynamics of the gastrointestinal tract are complicated and cannot be reproduced by the USP basket or paddle apparatus, a stirring rate of 100 RPM has been found to be discriminatory for the basket method. For the paddle method, 75 RPM can be discriminatory while minimizing coning effects seen with lower rates. The acid conditions of the media reflect 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.

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

V. SPECIFICATION

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

- For BCS class 1 products, a single point dissolution specification of Q=80% in 30 minutes.
- For BCS class 3 products, a single point dissolution specification of Q=80% in 15 minutes.

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

VI. REPLACING DISSOLUTION WITH DISINTEGRATION

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

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

VII. REFERENCES

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.

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

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

FDA guidance for industry, 1997, Dissolution Testing of Immediate Release Solid Oral Dosage Forms.

FDA guidance for industry, 2010, The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP).

FDA guidance for industry, 2000, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.

FDA guidance for industry, 2015, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.

FDA draft guidance for industry, 2012, Warfarin Sodium.

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.

Strauch S, Jantratid E, and Dressman JB, 2009, Comparison of WHO and US FDA biowaivers dissolution test conditions using bioequivalent doxycycline hyclate drug products, J Pharmacy and Pharmacology, 61:331-337.

United States Pharmacopeia (USP) General Chapters <711> Dissolution (2011), <701> Disintegration (2008).

WHO,, 2006, Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Annex 8 of WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva: WHO.

Yu LX, et al., 2002, BCS: The Scientific Basis of Biowaiver Extensions, Pharm Research, 19(7) 921-925.