Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Guidance for Industry

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

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Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances Guidance for Industry[1]

I. INTRODUCTION

This guidance is developed to provide manufacturers with recommendations for submission of new drug applications (NDAs), investigational new drug applications (INDs), or abbreviated new drug applications (ANDAs), as appropriate, for orally administered immediate-release (IR) drug products that contain highly soluble drug substances.[2] The guidance is intended to describe when a standard release test and criteria may be used in lieu of extensive method development and acceptance criteria-setting exercises. This guidance finalizes the guidance for industry on *Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs* (August 2015).[3] The revised title of this guidance better reflects its focus on the solubility of the drug substance in the drug product. Therefore, a direct reference to biopharmaceutics classification system (BCS) class 1 and class 3 is not necessary because permeability requirements are not within the focus of this guidance. The recommendations in this guidance clarify the recommendations in the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997) for high solubility drug substances in IR drug products[4] that meet the conditions described in section III in this guidance. For drug substances that do not meet the conditions in this guidance, sponsors/applicants should follow the recommendations provided in the August 1997 guidance mentioned above.

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[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] *Drug substance* is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. 21 CFR 314.3(b).

[3] 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.

[4] *Drug product* is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. 21 CFR 314.3(b).

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.

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 substance under physiological conditions, and the permeation across the gastrointestinal membrane.[5,6] 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: *(1)* batches used in pivotal clinical and/or BA/BE studies, *(2)* batches used as stability registration batches, and *(3)* batches used in other human studies conducted during product development. In general, knowledge about the solubility, permeability, dissolution, and pharmacokinetics of a drug substance and drug product are considered when defining dissolution acceptance criteria as part of the drug approval process.

Immediate-release solid oral dosage form drug products containing high solubility drug substances are considered to be relatively low risk regarding the impact of dissolution on in vivo performance, provided the in vitro performance meets or exceeds the recommendations discussed herein.

This guidance establishes standard dissolution methodology and acceptance criteria that are appropriate for highly soluble drug substances that are formulated in IR dosage forms. The availability of these standards will facilitate the rapid development of dissolution methodology and related acceptance criteria with no requirement to show discriminatory ability of the dissolution method for these products during drug product development. In addition, these standards will facilitate FDA's evaluation of the data submitted in the application.

III. ELIGIBLE DRUG PRODUCTS

In addition to being an IR dosage form, the drug product should meet all of the following conditions in order for the dissolution standards in this guidance to apply. The FDA's Biopharmaceutics Classification System (BCS) guidance should be followed to establish that the drug product contains highly soluble drug substance.[7] Sponsors/applicants may contact FDA for

[5] 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(3):413-420.

[6] Amidon GL, Lennernas H, Shah VP, and Crison JR, 2014, 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, 1995-Backstory of BCS, The AAPS Journal, 16(5):894-898.

[7] See guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

assistance in applying the BCS guidance or in determining whether a particular drug product meets any of the particular conditions listed below.[8,9]

A. Dosage Form

This guidance applies to solid orally-administered IR drug products, such as tablets and capsules, that are meant to be swallowed. This guidance does not apply to orally disintegrating tablets (ODT).[10] However, if absorption from the oral cavity can be ruled out for the ODT, then the dissolution of the ODT may fall under this guidance. This guidance also does not apply to sublingual dosage forms which can be ODTs as well, as the scientific principles upon which this guidance is premised do not apply to the sublingual route of delivery, since sublingual dosage forms are intended for absorption in the oral cavity. This guidance may apply to chewable tablets[11] if the dissolution studies are conducted on the intact tablets and the product meets the conditions described in this guidance.

B. Solubility

To be considered a highly soluble drug product, the drug substance should be considered highly soluble with the highest drug product's strength[12] soluble in 250 mL or less of aqueous media over the pH range of 1 to 6.8 at 37°C ± 1°C. In other words, the highest strength divided by 250 should be less than or equal to the lowest solubility observed over the entire pH range of 1 - 6.8. For drug products where the highest single dose administered is higher than the highest strength, additional information may be necessary. The drug substance should be chemically stable at least up to the last dissolution time point in the specified dissolution media for the drug product, plus the interval of the longest analysis time including sample preparation and chromatography run times. Additional details regarding solubility testing methods can be found in the BCS guidance.

C. Therapeutic Index

This guidance does not apply to narrow therapeutic index (NTI) drug products because of the critical relationship between the bioavailable dose and clinical performance. NTI drug products pose higher therapeutic risks owing to their associated smaller differences between

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[8] For drug products to which the criteria in this guidance apply, the current methods listed in the FDA's Dissolution Methods Database will be replaced by the dissolution methods recommended in this guidance, on a case-by-case basis, upon submission of supplements in the corresponding NDA or ANDA submission. For products where the dissolution 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 updated method and seek revision of the relevant monograph.

[9] When the submission is for an NDA, contact the specific drug product's review division with questions. When the submission is for an ANDA, submit a Controlled Correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a *controlled correspondence* as well as the process to submit a *controlled correspondence*, see the guidance for industry *Controlled Correspondence Related to Generic Drug Development*.

[10] See guidance for industry *Orally Disintegrating Tablets.*

[11] See draft guidance for industry *Quality Attribute Considerations for Chewable Tablets.* When final, this guidance will represent the FDA's current thinking on this topic.

[12] For ANDAs, the highest strength for which approval is sought.

effective/ineffective and/or toxic/safe doses. The streamlined approach described in the guidance might not be able to detect the batch-to-batch difference(s) that might impact NTI performance with respect to safety or efficacy.[13]

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) exclude the drug product from adoption of the dissolution standard proposed herein.

E. Manufacturing and Testing History

Manufacturing and testing history, including stability testing throughout its shelf-life, should demonstrate that the drug product will meet the acceptance criteria in this guidance when using the standard dissolution testing conditions described herein.

F. Excipients

Excipients chosen for drug product formulation should be consistent with the design of IR drug products. Excipients should be included in quantities that are consistent with the excipients' labeled function and the target population. Excessive quantities of excipients, such as certain sweeteners and surfactants that can impact the drug absorption, may be problematic. For example, mannitol induces a dose proportional decrease in small intestinal transit time.[14] When this is a factor, we encourage sponsors/applicants to contact FDA[9] for guidance on a specific drug product.

IV. STANDARD DISSOLUTION TESTING CONDITIONS

If a drug product meets the eligibility requirements described in section III for a standard dissolution method and acceptance criterion, one of the following methods may be used.[15] Information on apparatus and number of units to test can be found in the USP General Chapter <711> Dissolution. The apparatus should be calibrated before use.[16]

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[13] The current approach to establish bioequivalence of NTI drugs is described here: Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, Muldowney L, Chen M-L, Davit B, Conner D, Woodcock J, 2015, Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs, Clinical Pharmacology & Therapeutics, 97(3):286-291.

[14] Adkin, D.A., Davis, S.S., Sparrow, R.A., Huckle, P.D., Phillips, A.J., Wilding, I.R., 1995, The effect of different concentrations of mannitol in solution on small intestinal transit—implications for drug absorption, Pharm. Res., 12: 393–396.

[15] Shah V, Gurbarg M, Noory A, Dighe S, Skelly J, 1992, Influence of Higher Rates of Agitation on Release Patterns of Immediate-Release Drug Products, J Pharm Sci, 81(6): 500-503.

[16] See guidance for industry *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP).*

A. Basket Method (USP apparatus 1)

- Stirring rate = 100 RPM
- 500 mL of 0.1N HCl in aqueous medium
- No surfactant in medium
- 37±0.5°C

B. Paddle Method (USP apparatus 2)

- Stirring rate = 50 RPM
- 500 mL of 0.1N HCl in aqueous medium
- No surfactant in medium
- 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 rotation speed of 100 RPM has been found to be discriminatory for the basket method. For the paddle method, 50 RPM (or 75 RPM with appropriate justification) can be discriminating while minimizing coning effects seen with lower stirring rates.[15] For the paddle method (USP apparatus 2), it is acceptable to add a few turns of a wire helix to ensure that capsule dosage forms are fully immersed in the dissolution bath. 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-ingested with the oral dosage form. This volume is too low to use with the current basket and paddle apparatus; however, 500 mL of medium is commonly used and is an appropriate volume of medium for a highly soluble, rapidly dissolving drug substance. The 500 mL dissolution medium should be an appropriate volume to provide sink conditions for dissolution of the high soluble drug. Proper justification should be provided if 900 mL volume of the medium is used. Besides the recommended 0.1N HCl in aqueous medium, other dissolution media within the physiological pH range may be acceptable if appropriate justification is provided.

V. DISSOLUTION ACCEPTANCE CRITERIA

The drug product dissolution acceptance criterion is based on the high solubility of the drug substance. If an alternate acceptance criterion is proposed, the sponsor/applicant should provide additional data to support the proposed acceptance criterion. Additional supportive information could include appropriate in silico modeling in addition to dissolution performance data. For immediate release solid oral drug products containing a high solubility drug substance (as defined herein), the dissolution criterion is Q=80% in 30 minutes.

VI. POSTAPPROVAL CONSIDERATIONS

In regard to post-approval changes, with respect to the dissolution documentation that is needed to support the proposed change(s), the recommendations provided in the SUPAC-IR Guidance[17] should be followed.

[17] See guidance for industry *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.