Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System

Draft Guidance

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U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This draft document provides guidance to sponsors and applicants of new drug applications (NDAs) and abbreviated new drug applications (ANDAs), and supplements to these applications, who wish to request a waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies (biowaivers) for certain immediate release solid oral dosage forms. Currently, regulations at 21 CFR 320 ("Bioavailability and Bioequivalence Requirements") address the requirements for BA/BE data for the approval of drug applications and supplemental applications submitted to the Center for Drug Evaluation and Research (CDER). Section 320.22 provides for waivers of in vivo BA/BE studies under some conditions. This guidance for industry clarifies the BA/BE regulations and explains when waivers for in vivo BA/BE studies (biowaivers) can be requested for certain immediate release solid oral dosage forms based on a Biopharmaceutics Classification System.

II. BACKGROUND

In 1974, the Office of Technology Assessment's Drug Bioequivalence Study Panel made eleven recommendations, one of which stated:

> *It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes of drugs should be based on clinical importance, ratios of therapeutic to toxic concentrations in blood, and certain pharmaceutical characteristics.*

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[1] This guidance has been prepared by the Biopharmaceutic Classification System Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Based on this and other recommendations of the panel, FDA proposed and finalized regulations in 1977 entitled *Bioequivalence Requirements and In Vivo Bioavailability Procedures* (42 FR 1624; January 7, 1977). These regulations, which evolved over time and are now codified at 21 CFR Part 320.33, provide criteria for assessing actual or potential bioequivalence problems. For drug products that were considered to pose bioequivalence problems, the regulations required that BA/BE be demonstrated through in vivo studies. For drug products that were not considered to pose bioequivalence problems, BA/BE could be demonstrated through in vitro studies. At the time of the passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman -Hatch), FDA's policy was to require in vivo demonstration of bioequivalence for all post-1962 (post-DESI[2]) non-solution drug products. With occasional exceptions, this approach has continued to the present.

The purpose of this guidance is to describe alternative ways, not based on in vivo methods, acceptable to FDA for demonstrating bioequivalence for certain post-1962 immediate release solid oral drug products based on a classification system that distinguishes rapidly dissolving drug products containing active moieties/active ingredients that are highly soluble and highly permeable from other drug products. For such products, in vivo demonstration of bioequivalence may not be necessary because the BA/BE of a drug product so characterized approaches that of a solution and is thus self-evident (21 CFR 320.22(b) (3)). Furthermore, a suitable in vitro/in vivo correlation can be assumed for a rapidly dissolving drug product of a highly soluble and highly permeable drug substance, as long as its inactive ingredients do not significantly affect absorption of the active ingredients. Conversely, drugs that are poorly permeable, poorly soluble, and/or formulated in slowly dissolving dosage forms may be considered to be drugs with actual or potential BE problems.

III. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The Biopharmaceutics Classification System (BCS) is a general approach that can be used by sponsors and applicants to justify a biowaiver for immediate release (IR) solid oral dosage forms. The approach is based on the fact that in vivo dissolution differences in the gastrointestinal tract are a primary reason for observed differences in bioavailabilities of two IR products containing the same drug substance.[3] In the BCS, a drug is classified as belonging to 1) *high* or *low solubility*

[2] DESI drugs were identified as part of the Drug Efficacy Study Implementation Program, which was a retrospective evaluation of the effectiveness of drugs cleared through the new drug procedures only on the basis of safety between 1938 and 1962. The DESI program was undertaken to implement the requirement set forth in the 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act that drug products be approved for marketing based on a demonstration of effectiveness as well as safety.

[3] Amidon, G. L., H. Lennernas, V. P. Shah, and J. R. Crison, "A Theoretical Basis For a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability," *Pharmaceutical Research*, 12: 413-420 (1995).

class, 2) *a high or low permeability* class, and 3) a IR dosage form is categorized as belonging to a *rapid* or *slow dissolving* class. These classes and methods for classifying a drug are discussed in the following sections. The term *class boundary* is used to indicate how the class should defined.

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of water over the pH range of 1-8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water — the minimum volume anticipated in the stomach at the time of drug administration during the study protocols.

B. Permeability

The permeability class boundary is based on the extent of absorption of a drug substance in humans, or other appropriate measurements of the rate of mass transfer across intestinal membranes, or well-characterized models of human intestinal membranes. A drug substance is considered *highly permeable* when the extent of absorption in humans is determined to be > 90% of an administered dose based on a mass balance determination, or in comparison to an intravenous reference dose in the absence of evidence suggesting instability in the gastrointestinal tract. Other methods to assess permeability are discussed in Section IV.

C. Dissolution

The dissolution class boundary is based on the in vitro dissolution rate of an IR dosage form under specified test conditions and is intended to indicate rapid in vivo dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An IR drug product is considered *rapidly dissolving* when not less than 85% of the label amount of the drug substance dissolves within 30 minutes using the USP apparatus I at 100 rpm (or apparatus II at 50 rpm) in a volume of 900 ml, or less, in each of the following media: (1) acidic media, such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.[4]

[4] The *United States Pharmacopeia*, 23, January 1995. United States Pharmacopeial Convention, Inc. Rockville, Maryland.

IV. METHODOLOGY FOR CLASSIFYING A DRUG

The following experimental approaches are recommended for classifying a drug according to the BCS.

A. Determining Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug under approximate physiological conditions. For this purpose, determination of pH-solubility profiles over a pH range of 1-8 is suggested. Preferably eight or more pH conditions should be evaluated. Buffers that react with the drug should not be used. An acid or base titration method can also be used for determining drug solubility. The solubility class is determined by calculating what volume of an aqueous media is sufficient to dissolve the highest anticipated dose strength. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-8.

Solution stability of a test drug in selected buffers (or pH conditions) should be documented using a validated stability-indicating assay. Data collected on both pH-solubility and pH-stability should be submitted in the biowaiver application along with information on the ionization characteristics, such as pKa(s), of a drug.

B. Determining Permeability Class

Studies of the extent of absorption in humans, or intestinal permeability methods, can be used to determine the permeability class membership of a drug. To be classified as highly permeable, a test drug should have an extent of absorption >90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physical-chemical properties (e.g., octanol:water partition coefficient).

1. Studies of the Extent of Absorption in Humans

Pharmacokinetic mass-balance and absolute bioavailability studies using unlabeled, stable isotopes, or a radiolabeled drug substance can be used to document the extent of absorption of a drug. Sufficient numbers of subjects (e.g., six or more) should be enrolled in a study to provide a reliable estimate of the extent of absorption. For mass-balance studies using a radiolabeled drug, serial blood, urine, and fecal samples should be collected for about 10 elimination half lives. Serial samples of exhaled air should be monitored to determine if significant loss of radioactivity occurs via this route. The dose-normalized ratios of cumulative urinary recovery of radioactivity after oral and intravenous drug administration can be used

to estimate the extent of absorption when the excretion pattern (for example: ratios of radioactivity found in urine and feces) does not vary with the dose and the route of administration. In situations when intravenous administration is infeasible, the cumulative urinary recovery of the oral dose can be considered the minimum amount of dose absorbed.

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug from the gastro-intestinal tract: (1) in vivo intestinal perfusion studies in humans; (2) in vivo or in situ intestinal perfusion studies in animals; (3) in vitro permeation experiments using excised human or animal intestinal tissues; and (4) in vitro permeation experiments across a monolayer of cultured human intestinal cells.

When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans. A correlation can be established using 20 or more selected model drugs for which reliable estimates of extent-of-drug absorption and information on absorption mechanisms (including potential for intestinal efflux via p-glycoprotein or other efflux systems) are available. When a method enables the selected model drugs to be categorized into the correct permeability class, that method can be considered useful for the BCS and can be used to determine the permeability class membership of test drugs.

Once a suitable method has been chosen and assuming experimental conditions are held constant, it is not necessary to reestablish the suitability of the method using 20 or more model drugs. For subsequent experiments, one or two well-characterized model drugs can be used as internal standards and tested simultaneously along with the test drug being classified. Judicious selection of a high permeability internal standard may simplify classification of a test drug (e.g., when the ratio of the permeability of the test drug to that of a highly permeable internal standard is $\geq$ one, the test drug may also be considered highly permeable). A low permeability internal standard is suggested to ensure intestinal membrane integrity. The permeability values of the two internal standards can be used to verify reproducibility of the experimental method. The internal standards should be compatible with the drug being evaluated (i.e., they should exhibit no physical or chemical interactions). A list of potential model drugs and chemicals along with their permeability class membership is provided in Attachment A.

In vitro methods, such as those using a cultured monolayer of human intestinal cells, should be further examined to identify any expressions of specialized transport/efflux systems for the selected experimental conditions (e.g., bidirectional transport studies using model compounds, such as verapamil, of the p-glycoprotein efflux system). Permeability class membership determined using such in vitro methods can be considered reliable when (1) drug absorption is shown to be via a passive transport mechanism, or (2) a linear relationship between doses (including the highest dose strength) of a drug and its rate and extent of absorption can be documented. Passive transport mechanisms can be supported by documenting a lack of dependence of measured permeability value on (1) initial drug concentrations (e.g., 0.1, 1, and 10 times the highest dose strength dissolved in 250 ml), in the donor chamber or perfusion fluid, and (2) transport direction (e.g., a similar rate of transport between apical-to-basolateral and basolateral-to-apical directions for the selected drug concentrations).

V. REQUESTING A WAIVER OF IN VIVO BA/BE STUDIES

Submissions requesting biowaivers based on the BCS should contain documentation on the following:

1. The drug substance for which a waiver is being requested should be highly soluble and highly permeable, as defined above.

2. An IR drug product should be rapidly dissolving, as defined above.

3. For waiver of an in vivo BA study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media. For waiver of bioequivalence, test and reference products should exhibit *similar* dissolution profiles under the dissolution test conditions defined for rapidly dissolving products.

   Two dissolution profiles may be considered *similar* when compared using the f2 metric ($f2 \geq 50$) as described in the guidance for industry on dissolution testing.[5] When both the test and the reference products dissolve 85% or more of the label amount in $\leq$ 15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary.

[5] Guidance for Industry, *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, FDA, CDER, August 1997.

4. The drug should not be a narrow therapeutic index drug.[6] This limitation is expected to be applied primarily to NDA and ANDA bioequivalence studies after approval, as well as bioequivalence studies submitted in an ANDA, recognizing that during the IND period an investigational drug may not be clearly identified as an narrow therapeutic index drug.

5. Excipients used in the dosage form should have been used previously in FDA approved IR solid dosage forms. The quantity of excipients in the IR product should be consistent with their intended function. Large quantities of certain excipients, such as surfactants like sodium lauryl sulfate, may be problematic.

6. All other application commitments should be met.

VI. ADDITIONAL CONSIDERATIONS WHEN PLANNING A REQUEST FOR A WAIVER

When requesting a waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants also should consider the following issues, which could affect their request or the documentation of their request.

A. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance using total radioactivity in urine does not consider the extent of degradation of a drug in the gastrointestinal fluids prior to intestinal membrane permeation. Also, some methods for determining permeability could be based on loss, or clearance, of a drug from fluids perfused into the human and/or animal gastrointestinal tract either in vivo or ex vivo. Documenting that drug loss from the gastrointestinal tract arose from intestinal membrane permeation, rather than a degradation process, will help establish permeability class membership. Stability in gastrointestinal fluids can be documented by (1) pH-stability profiles in the pH range of 1-8 and (2) stability in gastric and intestinal fluids obtained from human subjects or animals. Drug solutions in these fluids can be incubated at 37ºC for about three hours and analyzed using a validated stability indicating assay. Significant degradation or loss (>5%) of a drug in about three hours could suggest potential instability.

B. Evaluation of Excipients

Excipients can sometimes affect the rate and extent of drug absorption. Using excipients

[6] Criteria for identifying a narrow therapeutic index drug are currently being developed by FDA.

that are currently in FDA-approved IR solid oral dosage forms should generally not affect the rate or the extent of absorption of a highly permeable drug that is formulated in a rapidly dissolving IR product. When new excipients, or atypically large amounts of commonly used excipients, are used in an IR dosage form, additional information documenting the absence of an impact on bioavailability could be requested by the Agency. Such information can be supplied via a relative bioavailability study using a simple aqueous solution as the reference product. A request for biowaiver based on the BCS should include a list of all excipients used in the products, the amount used in the test product, intended functions, a brief summary describing the manufacturing process, and a list of equipment used.

C. Exceptions

A request for a waiver of in vivo BA/BE studies based on the BCS, as described in this guidance, would not be considered appropriate for dosage forms intended for retention in the oral cavity (e.g., sublingual or buccal tablets), or for those intended for dissolution in the oral cavity and/or designed for administration without the aid of water.

Permeability class membership of prodrugs may depend on whether conversion to the active moiety occurs in the gastrointestinal tract or following intestinal membrane permeation. The sponsor should consult with the appropriate review division before applying the BCS for requesting biowaivers to IR products containing prodrugs.

VII. REGULATORY APPLICATION OF THE BCS

A. INDs/NDAs — Documenting Bioavailability and Bioequivalence

In establishing a drug's BA in accordance with 21 CFR 320.20, a regulatory objective is to fix the performance of the formulation used in pivotal clinical studies for demonstrating substantial evidence of safety and effectiveness (320.38(b)(1)). The BA of a solid dosage form intended for oral administration can be established relative to a solution or suspension of the drug substance given by the same route of administration (21 CFR 320.25 (d)(2) and (3)) or, if problems with absorption exist, to an intravenously administered drug formulation (320.25(d)(3)). A formulation should be optimized for performance (BA) during the clinical investigational period. If a highly soluble, highly permeable drug substance is formulated so that it is also rapidly dissolving, as defined in Section III, this information can be used to support the waiver of subsequent in vivo BA/BE studies during the IND period, including an in vivo BA study on the pivotal clinical trial material.

The in vivo BA/BE studies considered for waiver in this guidance are designed to

demonstrate release of the drug substance from the drug product, as measured by rate and extent of absorption, and do not include food-effect or clinical pharmacology studies. Two specific examples of BA/BE studies that could be waived are discussed in the following paragraphs.

1. Initial Clinical Trial Formulation for a Phase 1 Study

For a highly soluble, highly permeable drug substance manufactured in a rapidly dissolving IR solid dosage form, as defined in Section III, with in vivo BA documented, additional in vivo BA/BE studies could be waived for subsequent clinical trial formulations, up to and including the *to-be-marketed* formulation, providing dissolution remains rapid and the products exhibit similar dissolution profiles, as defined in Section V.

The choice of dissolution test apparatus (USP I or II) should be based on a comparison of in vitro dissolution and available in vivo pharmacokinetic data on the product. For certain products in vitro (but not in vivo) dissolution may be slow due to the manner in which a disintegrated IR product settles at the bottom of a dissolution vessel. Comparison of in vitro dissolution and in vivo pharmacokinetic data (e.g., BA study using a simple solution dosage form as the reference product) may be useful to justify deviations from dissolution test conditions outlined in Section V.

2. Pivotal Clinical Trial Formulation

Irrespective of whether early clinical trial formulations of a highly soluble, highly permeable drug substance meet the specifications for rapid dissolution as defined in Section III, optimization of the performance of the clinical trial formulation could be achieved so that its dissolution becomes rapid. In this circumstance, an in vivo BA study is recommended, but redocumentation of in vivo BA/BE of subsequent clinical trial formulations, up to, and including, the to-be-marketed formulation, could be waived, provided dissolution remains rapid, as defined, and the products exhibit similar dissolution profiles based on the f2 metric criteria defined in Section V.

B. ANDAs

For a highly soluble, highly permeable drug substance formulated so that its dissolution is rapid as defined in Section III, an in vivo BE study can be waived, provided the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product, as defined in Section V. Where feasible, the choice of dissolution apparatus (USP I

or II) should be limited to that established for the innovator product.

C. Postapproval Changes

For significant postapproval changes to a rapidly dissolving IR product containing a highly soluble, highly permeable drug substance, such as Level 3 changes in components and composition,[7] the need for in vivo bioequivalence redocumentation for postapproval changes may be waived provided dissolution remains rapid, as defined, and the products exhibit similar dissolution profiles, as defined in Section V. For a pioneer product, dissolution profiles of the postchange product should be compared with that of the prechange product and found similar, as defined. For a generic drug product, dissolution profiles of the postchange product should be compared with the reference listed drug products and found similar, as defined.

Many complex situations may arise in the regulatory application of the BCS. When questions arise, FDA encourages sponsors and applicants to contact the appropriate review staff in CDER's Office of Clinical Pharmacology and Biopharmaceutics and Office of Generic Drugs.

[7] Guidance for industry, *Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes*, November 1995.

ATTACHMENT A: SUGGESTED MODEL DRUGS

Suggested model drugs for use in establishing method suitability as described in section IV. The permeability class memberships of these compounds were determined based on data available to the FDA. Potential *Internal Standards* (IS) are also identified.

Drug	Permeability Class
Ketoprofen	High
Naproxen	High
Verapamil	High (Potential candidate for characterization of P-glyco protein efflux in in vitro systems)
Carbamazepine	High
Propranolol	High
Metoprolol	High (Potential IS Candidate)
Theophylline	High
Caffeine	High
Antipyrine	High (Potential IS Candidate)
Furosemide	Low
Hydrochlorthiazide	Low
alpha-Methyldopa	Low
Atenolol	Low
Ranitidine	Low
Polyethylene glycol (400-4000)	Low (Potential IS Candidate)
Mannitol	Low (Potential IS Candidate)