Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Guidance for Industry

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

December 2017
Biopharmaceutics

1005598 FNL

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System
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)

December 2017
Biopharmaceutics

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), and applicants who submit new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications for immediate-release (IR) solid oral dosage forms, and who wish to request a waiver of an in vivo bioavailability (BA) and/or bioequivalence (BE) study requirement. These recommendations are intended to apply to waivers requested during the IND period and the NDA stage or for ANDAs, i.e., (1) subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR solid oral dosage forms during the IND period, and (2) in vivo BE studies of IR solid oral dosage forms in NDAs, ANDAs, and supplements to these applications.

Regulations at 21 CFR 320 address the requirements for BA and BE data for approval of NDAs, ANDAs, and supplemental applications. Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22.[2] This guidance finalizes the 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*,[3] published in May 2015, and explains when biowaivers can be requested for IR solid

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

[2] In addition to waiver of an in vivo BE requirement under 21 CFR 320.22, there are certain circumstances in which BE can be evaluated using in vitro approaches under 21 CFR 320.24(b)(6). The scientific principles described in this guidance regarding waiver of an in vivo requirement also apply to consideration of in vitro data under that regulation. In such circumstances, an in vivo data requirement is not waived, but rather, FDA has determined that in vitro data is the most accurate, sensitive, and reproducible for a product, as required under 21 CFR 320.24(a). Nonetheless, for ease of the reader, in this guidance we will refer to either the decision to waive an in vivo BE requirement under 21 CFR 320.22 or the decision to accept in vitro BE data in accordance with 21 CFR 320.24(a) as a "biowaiver."

oral dosage forms based on an approach termed the Biopharmaceutics Classification System (BCS).[4] This guidance includes biowaiver extension to BCS class 3 drug products, and additional modifications, such as criteria for high permeability and high solubility.

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. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: (1) dissolution, (2) solubility, and (3) intestinal permeability.[5] According to the BCS, drug substances are classified as follows:

Class 1: High Solubility – High Permeability
Class 2: Low Solubility – High Permeability
Class 3: High Solubility – Low Permeability
Class 4: Low Solubility – Low Permeability

In addition, some IR solid oral dosage forms are categorized as having rapid or very rapid[6] dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors/applicants justify requests for biowaivers.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo.[4] However, when the in vivo dissolution of an IR solid oral dosage form is rapid or very rapid in relation to gastric emptying and the drug has high solubility, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal (GI) transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing class 1 and class 3 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients.

---

[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] See *The Biopharmaceutics Classification System (BCS) Guidance* at: http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128219.htm.

[5] Amidon GL, Lennernäs H, Shah VP, and Crison JR, 1995, A Theoretical Basis For a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharm Res, 12: 413-420.

[6] Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, et al, 2002, Biopharmaceutics classification system: The scientific basis for biowaiver extensions, Pharm Res, 19(7):921-5.

The BCS approach outlined in this guidance can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., class 1) as well as highly soluble and low permeable drug substances (i.e., class 3) in IR solid oral dosage forms that exhibit rapid or very rapid in vitro dissolution using the recommended test methods. The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

A. Solubility

The solubility class boundary is based on the highest strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with an 8 fluid ounce glass of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans, and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capable of predicting the extent of drug absorption in humans can be used (e.g., in situ animal, in vitro epithelial cell culture methods). A drug substance is considered to be *highly permeable* when the systemic BA or the extent of absorption in humans is determined to be 85 percent or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose.

C. Dissolution[7]

An IR drug product is considered *rapidly dissolving* when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes, using *United States Pharmacopeia* (USP) Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (or at 75 rpm when appropriately justified (see section III.C.) in a volume of 500 mL or less (or 900 mL when appropriately justified) in each of the following media: (1) 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.

An IR product is considered *very rapidly dissolving* when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes, using the above mentioned conditions.

[7] See also the draft guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms.* When final, this guidance will represent the FDA's current thinking on this topic.

III. RECOMMENDED METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS.

A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37 ± 1°C in aqueous media with a pH in the range of 1 - 6.8. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile within the pH range of 1 - 6.8. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance to include pH = pKa, pH = pKa + 1, pH = pKa - 1, and at pH = 1 and 6.8. A sufficient number of pH conditions should be determined for both ionizable and non-ionizable compounds. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replicates may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used with justification. Solution pH should be verified (measured and adjusted to the target pH if required) after addition of the drug substance to a buffer. Solution pH should also be measured at the end of the equilibrium solubility study.

Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification supporting the ability of such methods to predict equilibrium solubility of the test drug substance. The concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.[8] If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported. The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest strength in the pH range of 1 - 6.8. A drug substance should be classified as highly soluble when the highest strength is soluble in ≤ 250 mL of aqueous media over the pH range of 1 - 6.8. 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. If the solubility classification is likely to change with the highest single dose as criterion, additional PK dose proportionality information in a wide dose range covering the therapeutic dose range will be necessary.

[8] Refer to the guidance for industry *Submitting Documentation for the Stability of Human Drugs and Biologics*.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined via human pharmacokinetic studies (mass balance, or absolute BA) which are preferred methods, or through in vivo intestinal perfusion in human subjects. Alternatively, methods not involving human subjects, which include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), and in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells, may also be used.

A single method may be sufficient: (i) when the absolute BA is 85 percent or more, or (ii) when 85 percent or more of the administered drug is excreted unchanged in urine, or (iii) when 85 percent or more of the administered drug is recovered in urine as parent and metabolites with evidence indicating stability in the GI tract. When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. In case of conflicting information from different types of studies, it is important to note that human data supersede in vitro or animal data.

1. Pharmacokinetic Studies in Humans

- Mass Balance Studies

Pharmacokinetic (PK) mass balance studies using unlabeled, stable isotopes or a radiolabeled drug substance can be used to document the extent of absorption of a drug. A sufficient number of subjects should be enrolled to provide a reliable estimate of extent of absorption.

When mass balance studies are used to demonstrate high permeability, additional data to document the drug's stability in the GI tract is required, unless 85 percent or more of the drug is excreted unchanged in urine. Please see method details in section III.B.3.

- Absolute Bioavailability Studies

Oral BA determination using intravenous administration as a reference can be used. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption. When the absolute BA of a drug is shown to be 85 percent or more, additional data to document drug stability in the GI fluid is not necessary.

2. Intestinal Permeability Methods

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

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane efflux transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and/or multidrug resistance associated protein 2 (MRP2). When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp, BCRP, MRP2) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction (efflux ratio >2),[9,10] using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., digoxin, vinblastine, rhodamine 123, methotrexate). The use of animal or in vitro permeability test methods is recommended only for drug substances that are transported by passive mechanisms (efflux ratio of the test drug should be < 2). PK studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear PK in humans.

For BCS-based permeability determination, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A proportional relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) or linear PK of a drug is demonstrated in humans.

- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 mL) in the perfusion fluid.

- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 mL) is demonstrated, or lack of dependence on transport direction (i.e., efflux ratio 0.5 to 2) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp, BCRP, MRP2).

METHOD SUITABILITY: One of the critical steps in using in vivo or in situ perfusion, or in vitro permeability methods for permeability classification is to demonstrate the suitability of the method. To demonstrate suitability of a permeability method intended for BCS-based

[9] KM Giacomini, SM Huang, DJ Tweedie, LZ Benet, KLR Brouwer, X Chu, A Dahlin, R Evers, V Fischer, et al. March 2010, The International Transporter Consortium, Membrane transporters in drug development, *Nature Reviews Drug Discovery*, 9:215-236.

[10] See the guidance for industry *Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*. When final, this guidance will represent the FDA's current thinking on this topic.

permeability determination, a rank-order relationship between experimental permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals, and for in vitro tissue or cell monolayer methods, twenty model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability (e.g., a minimum of three per group). This relationship should allow accurate differentiation between drug substances of low and high intestinal permeability attributes.

To demonstrate the suitability of a method, model drugs should represent a range of zero, low (e.g., < 50 percent), moderate (e.g., 50 – 84 percent), and high (≥ 85 percent) absorption. Sponsors/applicants may select compounds from the list of drugs and/or chemicals provided in Attachment A, or they may select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

For a given test method with set conditions, selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may be used to facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low and a high permeability model drug should be used as internal standards (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two internal standards are in addition to the fluid volume marker (or a zero permeability compound such as PEG 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of internal standards should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). When it is not feasible to follow this protocol, the permeability of internal standards should be determined in the same subjects, animals, tissues, or monolayers, following (or, if appropriate, in parallel to) evaluation of the test drug substance. The permeability values of the two internal standards should not differ substantially between experiments conducted to demonstrate the assay's method suitability and those for the test drug. For example, the laboratory may set acceptance criteria for the permeability values of its high, low, and zero permeability standard compounds.

At the end of an in vitro test, the amount of drug in the tissue or cell monolayer, apical and basolateral chambers should be determined to assist in calculation of mass balance. If recovery from the apical and basolateral chambers is > 80 percent, there is no need to measure drug in the tissue or cell monolayers.

When intestinal permeability methods are used to demonstrate high permeability, additional data to document the drug's stability in the GI tract is required. Please see method details in section III.B.3.

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the GI fluid prior to intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human and/or animal GI tract either in vivo or in situ. Documenting the fact that drug loss from the GI tract arises from intestinal membrane permeation, rather than a degradation process, will help establish permeability. Stability in the GI tract may be documented using simulated gastric and intestinal fluids. Obtaining GI fluids from human subjects requires intubation and may be difficult. Stability in the GI tract may therefore be documented using simulated gastric and intestinal fluids such as Gastric and Intestinal Fluids USP or, with suitable justification, other biorelevant media.

Drug solutions in these fluids should be incubated at 37ºC for a period that is representative of in vivo drug contact with these fluids, for example, one hour in gastric fluid and three hours in intestinal fluid. Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (> 5 percent) of a drug in this study could suggest potential instability.

C. Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity[7]

Dissolution testing should be carried out in USP Apparatus 1 (typically at at 100 rpm) or USP Apparatus 2 (typically at 50 rpm, or at 75 rpm when appropriately justified) using 500 mL (or 900 mL with appropriate justification) of the following dissolution media: (1) 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. For gelatin capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

The dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution) and FDA's guidance on Mechanical Calibration of Dissolution Apparatus 1 and 2.[11] Selection of the dissolution testing apparatus (USP Apparatus 1 or 2) during drug development should be based on a comparison of in vitro dissolution and in vivo PK data available for the product. The USP Apparatus 1 (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus 2 (*paddle method*) is generally preferred for tablets. For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus 1 may be preferred over Apparatus 2, or alternatively

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

rotation speed for Apparatus 2 may be modified with justification. If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).

A minimum of 12 dosage units of the test and reference drug product for each strength should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the entire dissolution profile of the drug product (e.g., 5, 10, 15, 20, and 30 minutes).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2).

$$f_2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent of dissolution between the two curves; where n is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t.

Two dissolution profiles are considered similar when the f_2 value is ≥ 50. To allow the use of mean data, the coefficient of variation should not be more than 20 percent at the earlier time points (e.g., 15 minutes), and should not be more than 10 percent at other time points. Only one measurement should be considered after 85 percent dissolution of both products. In addition, when both test and reference products dissolve 85 percent or more of the label amount of the drug in 15 minutes using all three dissolution media recommended above, the profile comparison with an f_2 test is unnecessary.

IV. BIOWAIVERS BASED ON BCS

This guidance is applicable for BA/BE waivers (biowaivers) based on BCS, for BCS class 1 and class 3 IR solid oral dosage forms.

For BCS class 1 drug products, the following should be demonstrated:

- the drug substance is highly soluble
- the drug substance is highly permeable
- the drug product (test and reference) is rapidly dissolving, and
- the product does not contain any excipients that will affect the rate or extent of absorption of the drug (see section V.A.)

For BCS class 3 drug products, the following should be demonstrated:

- the drug substance is highly soluble
- the drug product (test and reference) is very rapidly dissolving (see section II.C.), and

- the test product formulation is qualitatively the same and quantitatively very similar (see section V.A.)

V. ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

When requesting a BCS-based biowaiver for in vivo BA/BE studies for IR solid oral dosage forms, sponsors/applicants should note that the following factors can affect their request or the documentation of their request.

A. Excipients

(i) BCS class 1 drug products: Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the Agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Excessive quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic, and sponsors/applicants are encouraged to contact the review division[12] when this is a factor.

(ii) BCS class 3 drug products: Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs. The composition of the test product must be qualitatively the same (except for a different color, flavor, or preservative that could not affect the BA) and should be quantitatively very similar to the reference product. Quantitatively very similar includes the following allowable differences:

- Changes in the technical grade of an excipient
- Changes in excipients, expressed as percent (w/w) of the total formulation less than or equal to the following percent ranges:

[12] 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.

- Filler (± 10%)
- Disintegrant, Starch (± 6%)
- Disintegrant, Other (± 2%)
- Binder (± 1%)
- Lubricant, Calcium or Magnesium Stearate (± 0.5%)
- Lubricant, Other (± 2%)
- Glidant, Talc (± 2%)
- Glidant, Other (± 0.2%)
- Film Coat (± 2%)

The total additive effect of all excipient changes should not be more than 10 percent.

B. Prodrugs

Permeability of prodrugs will generally depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug (i.e., active moiety) conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant. Sponsors may wish to consult with appropriate review staff[12] before applying the BCS approach to IR products containing prodrugs.

C. Fixed Dose Combinations Containing BCS Class 1, or Class 3, or a Combination of Class 1 and 3 Drugs

(i) If all active components belong to BCS class 1: BCS-based biowaivers are applicable for IR fixed dose combination products if all the drugs in the combination belong to BCS class 1, provided there is no PK interaction[13] between the components, and the excipients fulfill the considerations outlined in section V.A.(i). If there is a PK interaction, the excipients should fulfill the considerations outlined in section V.A.(ii). Otherwise, in vivo bioequivalence testing is required.

(ii) If all components of the combination belong to BCS class 3 or a combination of class 1 and 3: BCS-based biowaivers are applicable for IR fixed dose combination products in this situation provided the excipients fulfill the considerations outlined in section V.A.(ii). Otherwise, in vivo bioequivalence testing is required.

For fixed drug combination products where BCS classes 1 or 3 are combined with any other BCS class drugs, this biowaiver approach is not applicable.

[13] See the guidance for industry *Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*. When final, this guidance will represent the FDA's current thinking on this topic.

D. Exceptions

BCS-based biowaivers are **not** applicable for the following:

1. Narrow Therapeutic Index Drugs[14]

This guidance does not apply to narrow therapeutic index (NTI) drug products because of the critical relationship between the bioavailable dose and clinical performance. Sponsors should contact the appropriate review division[15] to determine whether a drug should be considered to have a narrow therapeutic index.

2. Products Designed to be Absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets). Similarly, a biowaiver based on BCS for an orally disintegrating tablet can be considered only if the absorption from the oral cavity can be ruled out. The sponsor/applicant can discuss the information required to rule out absorption from oral cavity with the Agency.[16]

VI. REGULATORY APPLICATIONS OF THE BCS–BASED BIOWAIVERS

A. INDs/NDAs

Evidence demonstrating in vivo BA or information to permit FDA to waive this evidence must be included in NDAs (21 CFR 320.21(a)). A specific objective of such BA information is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. Sponsors/applicants may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension, or intravenous injection (21 CFR 320.25(d)(2) and 320.25(d)(3)). The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following changes in components, composition, and/or method of manufacture may be possible using the BCS-based waiver approach. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms exhibit either rapid or very rapid dissolution (as appropriate), have similar in vitro dissolution profiles (see sections II and III), and for a BCS class 3 IR drug product, it meets the criteria for allowable

[14] This guidance uses the term *narrow therapeutic range* instead of *narrow therapeutic index*, although the latter is more commonly used.
[15] See footnote 12.
[16] Ibid.

differences in composition described previously (see section V). This approach is useful only when the drug substance belongs to BCS class 1 or 3, and the formulations pre- and post-change are pharmaceutical equivalents (under the definition at 21 CFR 320.1(c)). BCS-based biowaivers are intended only for subsequent in vivo BA or BE studies. They do not apply to food effect BA studies or other PK studies. BCS-based biowaivers may be applicable for pharmaceutical alternatives including other oral dosage forms (e.g., powders), if appropriately justified. The sponsor should contact the appropriate review division in such situations.

B. ANDAs

BCS-based biowaivers are appropriate for IR generic drug products that meet the criteria for BCS class 1 or 3 as discussed in section II and III. The proposed drug product (i.e., test product) should exhibit similar dissolution profiles to the reference listed drug product (see sections II and III). The choice of dissolution apparatus (USP Apparatus 1 or 2) should be the same as that established for the reference listed drug product.

C. Supplemental NDAs/ANDAs (Postapproval Changes)

BCS-based biowaivers are appropriate for postapproval changes in components, composition and manufacturing process for an IR solid oral drug product that meets the criteria for BCS class 1 or 3 as discussed above, and both pre- and post-change products exhibit similar dissolution profiles (see sections II and III). This approach is useful only when the drug products pre- and post-change are pharmaceutical equivalents.

VII. DATA TO SUPPORT A BIOWAIVER REQUEST

As described above, the drug product for which a biowaiver is being requested should include a drug substance that is highly soluble (BCS class 1 and BCS class 3) and highly permeable (BCS class 1), and the drug product should be rapidly dissolving (BCS class 1) or very rapidly dissolving (BCS class 3). Sponsors/applicants requesting biowaivers based on the BCS should submit the following information to the Agency for review.

A. Data Supporting High Solubility

Data supporting high solubility of the test drug substance should be developed (see section III.A). The following information should be included in the application:

- A description of test methods, including information on analytical method(s) and composition of the buffer solutions.

- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants (pKa(s)).

- Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/mL), and volume of media required to dissolve the highest strength.

- A graphic representation of mean pH-solubility profile.

B. Data Supporting High Permeability

Data supporting high permeability of the test drug substance should be developed (Refer to section III.B. of this guidance: Determining Drug Substance Permeability Class). The following information and data should be included in the application:

- A description of test methods, including information on analytical method(s) and composition of the buffer solutions.

- A rationale for the dose or drug concentrations used in studies.

- For human PK studies, information on study design and methods used along with the PK data.

- For direct permeability methods, information supporting the suitability of a selected method that encompasses a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations in the donor fluid, description of the analytical method, method used to calculate extent of absorption or permeability, and where appropriate, information on efflux potential (e.g., bidirectional transport data).

- A list of selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of a method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95 percent confidence interval) with identification of the low/high permeability class boundary and selected internal standard. Information to support high permeability of a test drug substance (mean, standard deviation, coefficient of variation) should include permeability data on the test drug substance, the internal standards, GI stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

C. Data Supporting Rapid, Very Rapid, and Similar Dissolution

For submission of a biowaiver request, an IR product should be rapidly dissolving (BCS class 1) or very rapidly dissolving (BCS class 3). Data supporting rapid dissolution attributes of the test and reference products should be developed (see section III.C). The following information should be included in the application:

- A description of test methods, including information on analytical method(s) and composition of the buffer solutions.

- A brief description of the IR products used for dissolution testing, including information on batch or lot number, expiry date, dimensions, strength, and weight.

- Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods in section III.C for each of the proposed strengths. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation), should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.

- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media (see section III.C.).

- Dissolution data supporting rapid or very rapid dissolution should be demonstrated for each strength to be marketed.

D. Additional Information

The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation versus direct compression).

A list of excipients used, and their intended functions should be provided for both the test and reference products. Ideally, excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms. Please refer to section V.A. of this guidance for additional considerations pertaining to new excipients. In addition, it is important to provide a quantitative comparison of excipients between the test and reference product for BCS class 3 drug products.

ATTACHMENT A

This attachment includes model drugs suggested for use in establishing suitability of a permeability method as described in section III. Zero permeability markers and efflux substrates are also identified.

Group	Drug
High Permeability ($f_a \geq 85$ percent)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability (f_a = 50-84 percent)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability ($f_a < 50$ percent)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide Polyethylene glycol 400 Enalaprilat
Zero Permeability	FITC-Dextran (MW $\geq$ 3000) Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine