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

Guidance for Industry

DRAFT GUIDANCE

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

May 2015
Biopharmaceutics

Revision 1

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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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), and applicants that 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 in vivo bioavailability (BA) and/or bioequivalence (BE) studies. These waivers are intended to apply to: (1) subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period, and (2) in vivo BE studies of IR dosage forms in ANDAs.

Regulations at 21 CFR part 320 address the requirements for BA and BE data for approval of drug applications 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 updates 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 August 2000, and explains when biowaivers can be requested for IR solid oral dosage forms based on an approach termed the Biopharmaceutics Classification System (BCS). This

[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."

[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.

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.[4] 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[5] 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.[6] 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.

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.

[4] 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.

[5] 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.

[6] See footnote 4.

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 over the pH range of 1-6.8. 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 a glass (about 8 ounces) 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 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

An IR drug product is considered *rapidly dissolving* when 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes, using *United States Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm or at 75 rpm when appropriately justified (see section III.C.)) in a volume of 500 mL or less 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 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes using the above mentioned conditions.

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 minimum of three replicate determinations of solubility in each pH condition is

recommended. Depending on study variability, additional replication 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. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. 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.[7] 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 maximum dose divided by 250 should be greater than or equal to the lowest solubility observed over the entire pH range of 1-6.8.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined in human subjects using mass balance, or absolute BA, which are the preferred methods, or intestinal perfusion approaches. Recommended methods not involving human subjects include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), or in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells. In many cases, 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.

[7] Refer to the FDA guidance for industry on *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987), posted at http://www.fda.gov/downloads/Drugs/Guidances/UCM070632.pdf.

- 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). 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) 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)[8,9], using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., digoxin, vinblastine, rhodamine 123). We recommend limiting the use of animal or in vitro permeability test methods 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 linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans.

[8] 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.

[9] See the FDA draft guidance for industry on *Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations,* (Feb 2012).

- 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 on transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

METHOD SUITABILITY: One of the critical steps in using 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 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 cell culture 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. This relationship should allow precise 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.

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 evaluation of the test drug substance. The permeability values of the two internal standards should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. 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 situ or in vitro test, the amount of drug in the membrane should be determined to assist in calculation of mass balance.

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.

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. Therefore, use of simulated fluids such as Gastric and Intestinal Fluids USP may be reasonable.

Drug solutions in these fluids should be incubated at 37^{o}C for a period that is representative of in vivo drug contact with these fluids; for example, 1 hour in gastric fluid and 3 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[10]

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm (or at 75 rpm when appropriately justified) using 500 mL 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 capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

[10] See the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

The dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution). Selection of the dissolution testing apparatus (USP Apparatus I or II) 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 I (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus II (*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 I may be preferred over Apparatus II. 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 a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the 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, Rt is the dissolution value of the reference batch at time t, and Tt 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., 10 minutes), and should not be more than 10 percent at other time points. Note that 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 immediate-release 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, e.g., falls within scale-up and post-approval changes (SUPAC) IR level 1 and 2 changes, in composition to the reference (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. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic, and sponsors are encouraged to contact the review division 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 and should be quantitatively very similar to the reference product.

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 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 before applying the BCS approach to IR products containing prodrugs.

C. Fixed Dose Combinations

a. 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 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.

b. 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.

D. Exceptions

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

1. Narrow Therapeutic Range Drugs[11]

This guidance defines narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic (PD) monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or PD monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

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 for an orally disintegrating tablet can be considered, based on BCS, only if the absorption from the oral cavity is ruled out.

[11] This guidance uses the *term narrow therapeutic range* instead of *narrow therapeutic index*, although the latter is more commonly used.

VI. REGULATORY APPLICATIONS OF THE BCS

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. The sponsors 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 major changes in components, composition, and/or method of manufacture (e.g., similar to SUPAC-IR Level 3 changes[12]) may be possible using the BCS. 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 have rapid, very rapid and similar in vitro dissolution profiles (see sections II and III). 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 BE studies. They do not apply to food effect BA studies or other PK studies. BCS-based biowaivers may be applicable for pharmaceutical alternatives, if appropriately justified. The sponsor should contact the appropriate review division in such situations.

B. ANDAs

BCS-based biowaivers are appropriate for IR test products that meet the criteria for BCS class 1 or 3 as discussed above, provided that the reference listed drug product also meets those criteria and the test product exhibits similar dissolution profiles to the reference listed drug product (see sections II and III). This approach is useful when the test and reference dosage forms are pharmaceutical equivalents. The choice of dissolution apparatus (USP Apparatus I or II) 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 significant postapproval changes (e.g., Level 3 changes in components and composition) to an IR test 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.

[12] See the FDA guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes* (November 1995).

VII. DATA TO SUPPORT A BIOWAIVER REQUEST

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 (see section III.B). 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.

- 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. 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 IIIC).

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, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms. In addition, it is important to provide 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 Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine