M9 Biopharmaceutics Classification System-Based Biowaivers

Guidance for Industry

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

May 2021
ICH

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FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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Contains Nonbinding Recommendations

M9 Biopharmaceutics Classification System-Based Biowaivers 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 (1)[2]

A. Background and Objective (1.1)

Two drug products containing the same drug substance or substances are considered bioequivalent if their bioavailabilities (rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e., similarity in terms of safety and efficacy. In in vivo bioequivalence studies, the pivotal pharmacokinetic parameters area under the concentration time curve (**AUC**)[3] and maximum concentration ($\mathbf{C_{max}}$), are generally used to assess the rate and extent of drug absorption.

The biopharmaceutics classification system (**BCS**)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies, i.e., it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance or substances. The BCS categorizes drug substances into one of four BCS classes as follows:

- Class I: high solubility, high permeability
- Class II: low solubility, high permeability
- Class III: high solubility, low permeability
- Class IV: low solubility, low permeability

[1] This guidance was developed within the Expert Working Group (Multidisciplinary) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Assembly at *Step 4* of the ICH process, November 2019. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory members of the ICH regions.

[2] Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2019.

[3] Words found in the GLOSSARY (p. 9) are bolded at first use in this guidance.

This guidance provides recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products. The BCS-based biowaiver principles may be applied to bioequivalence purposes not explicitly noted in the guidance, provided they can be supported by a thorough scientific rationale.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

B. Scope (1.2)

BCS-based biowaivers may be used to substantiate in vivo bioequivalence. Examples include comparison between products used during clinical development through commercialization, post-approval changes, and applications for generic drug products in accordance with regional regulations.

The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation. Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination (**FDC**) products are eligible for a BCS-based biowaiver when all drug substances contained in the combination drug product meet the criteria as defined in sections II. (2) and III. (3) of this guidance.

II. BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCE (2)

BCS-based biowaivers are applicable to drug products where the drug substance or substances exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III).

A biowaiver is applicable when the drug substance(s) in test and reference products are identical. A biowaiver may also be applicable if test and reference products contain different salts provided that both belong to BCS Class I (high solubility and high permeability). A biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, because these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept. Pro-drugs may be considered for a BCS-based biowaiver when absorbed as the pro-drug.

A. Solubility (2.1)

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 milliliter (mL) or less of aqueous media over the pH range of 1.2–6.8 at 37±1°C. In cases where the highest single therapeutic dose does not meet this criterion, but the highest strength of the reference product is soluble under the

aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach.

The sponsor is expected to establish experimentally the solubility of the drug substance over the pH range of 1.2–6.8 at 37±1°C. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the drug substance should be evaluated if it is within the specified pH range. These experiments should demonstrate that solubility is maintained over relevant timeframes to accommodate the expected duration of absorption.

Solubility should be evaluated by a method appropriate to the properties of the drug substance.

Equilibrium solubility experiments may be performed, using a shake-flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental apparatus will permit it. The pH for each test solution should be measured after the addition of the drug substance and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The pH should be adjusted if necessary. The experiment should be conducted over a suitable timeframe to reach equilibrium.

Alternatively, solubility experiments where the highest therapeutic single dose is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered.

The lowest measured solubility over the pH range of 1.2–6.8 will be used to classify the drug substance.

A minimum of three replicate determinations at each solubility condition/pH using appropriate compendial media is necessary to demonstrate solubility using a suitably validated method.

In addition, adequate stability of the drug substance in the solubility media should be demonstrated. In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined and thus the drug substance cannot be classified. In addition to experimental data, literature data may be provided to substantiate and support solubility determinations, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.

B. Permeability (2.2)

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance. High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced before

absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged drug in feces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.

Human in vivo data derived from published literature (e.g., product knowledge and bioavailability studies) may be acceptable, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.

Permeability can be also assessed by validated and standardized in vitro methods using Caco-2 cells (see Annex I). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. If high permeability is inferred by means of an in vitro cell system, permeability independent of active transport should be proven as outlined in Annex I, "Caco-2 cell permeability assay method considerations."

If high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes.

Drug Substance Stability in the Gastrointestinal Tract

Additional data to document the drug's stability in the gastrointestinal tract should be provided if mass balance studies are used to demonstrate high permeability, unless ≥85% of the dose is recovered as unchanged drug in urine. Demonstration of stability in the gastrointestinal tract is required if in vitro Caco-2 studies are used to support high permeability. Stability in the gastrointestinal tract may be documented using compendial or simulated gastric and intestinal fluids. Other relevant methods may be used with suitable justification. Drug solutions should be incubated at 37ºC for a period that is representative of the in vivo contact of the drug substance with these fluids, i.e., one hour in gastric fluid and three hours in intestinal fluid. Drug concentrations should then be determined using a suitably validated method. Significant degradation (>10%) of a drug precludes BCS high permeability classification.

III. ELIGIBILITY OF A DRUG PRODUCT FOR A BCS-BASED BIOWAIVER (3)

A drug product is eligible for a BCS-based biowaiver provided that the drug substance or substances satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release oral dosage form with systemic action, and the drug product is the same dosage form and strength as the reference product. In cases where the highest single therapeutic dose does not meet the high solubility criterion, but the highest strength of the reference product is soluble under the required conditions, BCS-based biowaivers can be supported based on demonstration of dose proportional pharmacokinetics (i.e., AUC and C_{max}) over a dose range that includes the highest single therapeutic dose.

Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. Furthermore, the BCS-based biowaiver approach is applicable only when the mode of administration includes water. If administration without water is also

intended (e.g., orodispersible products), a bioequivalence study in which the product is dosed without water should be conducted.

In order for a drug product to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and in vitro dissolution performance of the drug product should be satisfied. The drug product acceptance criteria are described in sections III.A. (3.1) and III.B. (3.2) below.

A. Excipients (3.1)

Ideally, the composition of the test product should mimic that of the reference product. However, where excipient differences exist, they should be assessed for their potential to affect in vivo absorption. This should include consideration of the drug substance properties as well as excipient effects. To be eligible for a BCS-based biowaiver, the sponsor should justify why the proposed excipient differences will not affect the absorption profile of the drug substance under consideration, i.e., rate and extent of absorption, using a mechanistic and risk-based approach. The decision tree for performing such an assessment is outlined in Figures 1 and 2 in Annex II.

The possible effects of excipients on aspects of in vivo absorption such as solubility, gastrointestinal motility, transit time, and intestinal permeability, including transporter mechanisms, should be considered. Excipients that may affect absorption include sugar-alcohols, e.g., mannitol, sorbitol, and surfactants, e.g., sodium lauryl sulfate. The risk that a given excipient will affect the absorption of a drug substance should be assessed mechanistically by considering:

- The amount of excipient used
- The mechanism by which the excipient may affect absorption
- Absorption properties (rate, extent, and mechanism of absorption) of the drug substance

The amount of excipients that may affect absorption in the test and reference formulations should be addressed during product development, such that excipient changes are kept to a minimum. Small amounts included in the tablet coating, or levels below documented thresholds of effect for the specific drug substance, are of less concern.

By definition, BCS Class I drugs are highly absorbed, and have neither solubility nor permeability limited absorption. Therefore, they generally represent a low risk group of compounds in terms of the potential for excipients to affect absorption, compared to other BCS classes. Consideration of excipient effects for BCS Class I drug products should focus on potential changes in the rate or extent of absorption. For example, if it is known that the drug has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS Class I drugs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered.

For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product.

Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

BCS Class III drug substances are considered to be more susceptible to the effects of excipients. These drugs are not considered highly permeable and may have site-specific absorption, so there are a greater number of mechanisms through which excipients can affect their absorption than for BCS Class I drugs. For BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product, and the cumulative difference for these excipients should be within ± 10%. This is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II. Differences in colorants and flavoring may be permitted when these constitute very small amounts of the formulation.

It is recognized that there are limitations to the application of Table 1, e.g., difficulty in determining the film coat weight for the reference product. Table 1 is provided as a target to give clarity to sponsors. Deviations from this will require appropriate justification, based on the principles described above.

Table 1: Criteria Expected to Demonstrate Quantitative Similarity for Products Containing BCS Class III Drugs.

Within the context of quantitative similarity, differences in excipients for drug products containing BCS Class III drugs should not exceed the following targets:	
Excipient Class	**Percent of the Amount of Excipient in the Reference**
Excipients which may affect absorption	
Per excipient:	10%
Sum of differences:	10%
	Percent Difference Relative to Core Weight* (w/w)
All excipients:	
Filler	10%
Disintegrant	
Starch	6%
Other	2%
Binder	1%
Lubricant	
Stearates	0.5%
Other	2%
Glidant	
Talc	2%
Other	0.2%

Total % change permitted for all excipients (including excipients which may affect absorption):	10%

*Note: Core does not include tablet film coat or capsule shell.

BCS-based biowaivers are applicable to FDCs which are the same dosage form and strength. FDC formulations containing only BCS Class I drugs should meet criteria regarding excipients for a BCS Class I drug. FDC formulations containing only BCS Class III drugs, or BCS Class I and BCS Class III drugs, should meet criteria regarding excipients for a BCS Class III drug.

B. In Vitro Dissolution (3.2)

When applying the BCS based biowaiver approach, comparative in vitro dissolution tests should be conducted using one batch representative of the proposed commercial manufacturing process for the test product relative to the reference product. The test product should originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. During a (clinical) development phase, smaller batch sizes may be acceptable, if justified. The comparative in vitro dissolution experiments should use compendial apparatus and suitably validated analytical method or methods.

The following conditions should be employed in the comparative dissolution studies to characterize the dissolution profile of the product:

- Apparatus: paddle or basket.
- Volume of dissolution medium: 900 mL or less (it is recommended to use the volume selected for the quality control (**QC**) test).
- Temperature of the dissolution medium: 37±1°C.
- Agitation: paddle apparatus - 50 revolutions per minute (**rpm**).

  basket apparatus - 100 rpm.
- At least 12 units of reference and test product should be used for each dissolution profile determination.
- Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be employed. Additional investigation may be required at the pH of minimum solubility (if different from the buffers above).
- Organic solvents are not acceptable, and no surfactants should be added.
- Samples should be filtered during collection, unless in situ detection methods are used.
- For gelatin capsules or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable, if appropriately justified.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both reference and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods (e.g., the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically substantiated. All experimental results should be provided.

To qualify for a BCS-based biowaiver for BCS Class I drug substances, both the test product and reference product should display either very rapid (≥85% for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution characteristics, or rapid (≥85% for the mean percent dissolved in ≤ 30 minutes) and similar in vitro dissolution characteristics (i.e., based on f2 comparison), under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, similarity of the profiles should be demonstrated as below.

For the comparison of dissolution profiles, where applicable, the similarity factor f2 should be estimated by using the following formula:

$$f2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

In this equation, *f2* is the similarity factor, *n* is the number of time points, *R(t)* is the mean percent reference drug dissolved at time t after initiation of the study, and *T(t)* is the mean percent test drug dissolved at time t after initiation of the study.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded).
- The time points should be the same for the two products.
- Mean of the individual values for every time point for each product.
- Not more than one mean value of ≥85% dissolved for either of the products.
- To allow the use of mean data, the coefficient of variation should not be more than 20% at early time-points (up to 10 minutes) and should not be more than 10% at other time points.

Two dissolution profiles are considered similar when the f2 value is ≥50. When both test and reference products demonstrate that ≥85% of the labeled amount of the drug is dissolved in 15 minutes, comparison with an f2 test is unnecessary, and the dissolution profiles are considered similar. When the coefficient of variation is too high, f2 calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be made.

To qualify for a BCS-based biowaiver for BCS Class III drug substances, both the test product and reference product should display very rapid (≥85 % for the mean percent dissolved in ≤15 minutes) in vitro dissolution characteristics under the defined conditions.

For FDC formulations, dissolution profiles should meet the criteria for all drug substances in the FDC to be considered. FDC formulations containing only BCS Class I drugs should meet dissolution criteria for a BCS Class I drug. FDC formulations containing only BCS Class III drugs should meet dissolution criteria for a BCS Class III drug. For FDCs containing both BCS Class I and BCS Class III drugs, the dissolution criteria for the applicable BCS class for each component should be applied.

For products with more than one strength, the BCS approach should be applied for each strength, i.e., it is expected that test and reference product dissolution profiles are compared at each strength.

IV. DOCUMENTATION (4)

The sponsor should provide complete information on the critical quality attributes of the test drug substance(s) and drug product, and as much information as possible for the reference product, including, but not limited to: polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the drug substance(s) or drug product, including literature surveys and sponsor-derived studies. All study protocols and reports should be provided. Information on validated test methods should be appropriately detailed according to current regulatory guidances and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics.

The report should include all excipients, their qualitative, and, where appropriate, quantitative differences between the test and reference products.

A full description of the analytical methods employed, including validation and qualification of the analytical parameters, should be provided. A detailed description of all test methods and media, including test and reference batch information [unit dose (strength and assay), batch number, manufacturing date and batch size where known, expiration date] should also be provided. The dissolution report should include a thorough description of experimental settings and analytical methods, including information on the dissolution conditions, such as apparatus, deaeration, filtration during sampling, volume, etc.

In addition, complete information with full description of the methods applied should be provided for the Caco-2 cell permeability assay method, if applicable (see Annex I).

V. GLOSSARY (5)

AUC: Area under the concentration versus time curve

BCS: Biopharmaceutics Classification System

C_{max}: Maximum concentration

FDC: Fixed-dose combination

QC: Quality control

rpm: Revolutions per minute

ANNEX I: CACO-2 CELL PERMEABILITY ASSAY METHOD CONSIDERATIONS

Permeability assays employing cultured Caco-2 epithelial cell monolayers derived from a human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation, express cell polarity with an apical brush border, tight intercellular junctions, and several active transporters as in the small intestine. Due to a potential for low or absent expression of efflux (e.g., P-gp, BCRP, MRP2) and uptake (e.g., PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays as the sole data in support of high permeability for BCS classification is limited to passively transported drugs (see Assay Considerations).

Method Validation

The suitability of the Caco-2 cell assays for biopharmaceutics classification system (BCS) permeability determination should be demonstrated by establishing a rank-order relationship between experimental permeability values and the extent of drug absorption in human subjects using zero, low (<50%), moderate (50–84%), and high (≥85%) permeability model drugs. A sufficient number of model drugs are recommended for the validation to characterize high, moderate, and low permeability (a minimum 5 for each), plus a zero-permeability marker; examples are provided in Table 2. Further, a sufficient number (minimum of 3) of cell assay replicates should be employed to provide a reliable estimate of drug permeability. The established relationship should permit differentiation between low, moderate, and high permeability drugs.

Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance (TEER) measures and/or other suitable indicators, before and after an experiment. In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (see Table 2).

Reporting of the method validation should include a list of the selected model drugs, along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of the 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% confidence interval) with identification of the high permeability class boundary and selected high permeability model drug used to classify the test drug substance.

In addition, a description of the study method, drug concentrations in the donor fluid, description of the analytical method, and equation used to calculate permeability, should be provided. Additionally, information on efflux potential, e.g., bidirectional transport data, should be provided for a known substrate.

Assay Considerations

Passive transport of the test compound should be demonstrated. This may be verified using a suitable assay system that expresses known efflux transporters, e.g., by demonstrating independence of measured in vitro permeability on initial drug concentration, e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 milliliter (mL), or on transport direction (efflux ratio, i.e., ratio of apparent permeability (P_{app}) between the basolateral-to-apical and apical-to-basolateral directions <2 for the selected drug concentrations).

Efflux ratio = $P_{appBL \rightarrow AP}/P_{appAP \rightarrow BL}$.

Functional expression of efflux transporters should be verified by using bidirectional transport studies demonstrating asymmetric permeability of selected efflux transporter substrates, e.g., digoxin, vinblastine, rhodamine 123, at non-saturating concentrations.

The test drug substance concentrations used in the permeability studies should be justified. A validated Caco-2 method used for drug permeability determinations should employ conditions established during the validation and include a moderate and a high permeability model drug in the donor fluid along with the test drug as internal standards to demonstrate consistency of the method. The choice of internal standards should be based on compatibility with the test drug, i.e., they should not exhibit any significant physical, chemical, or permeation interactions. The permeability of the internal standards may be determined following evaluation of the test drug in the same monolayers or monolayers in the same plate, when it is not feasible to include internal standards in the same cell culture well as the test drug permeability evaluation. The permeability values of the internal standards should be consistent between different tests, including those conducted during method validation. Acceptance criteria should be set for the internal standards and model efflux drug. Mean drug and internal standards recovery at the end of the test should be assessed. For recoveries <80%, a mass balance evaluation should be conducted, including measurement of the residual amount of drug in the cell monolayer and testing apparatus.

Evaluation of the test drug permeability for BCS classification may be facilitated by selection of a high permeability internal standard with permeability in close proximity to the moderate/high permeability class boundary. The test drug is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

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, in vitro gastrointestinal stability information, and data supporting passive transport mechanism.

Table 2. Examples of Model Drugs for Permeability Assay Method Validation

Group	Drug
High Permeability ($f_a \geq 85\%$)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability (f_a = 50-84%)	Chlorpheniramine Creatinine

Group	**Drug**
	Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability (f_a < 50%)	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

ANNEX II: FURTHER INFORMATION ON THE ASSESSMENT OF EXCIPIENT DIFFERENCES

Figure 1. BCS Class I Drug Substances

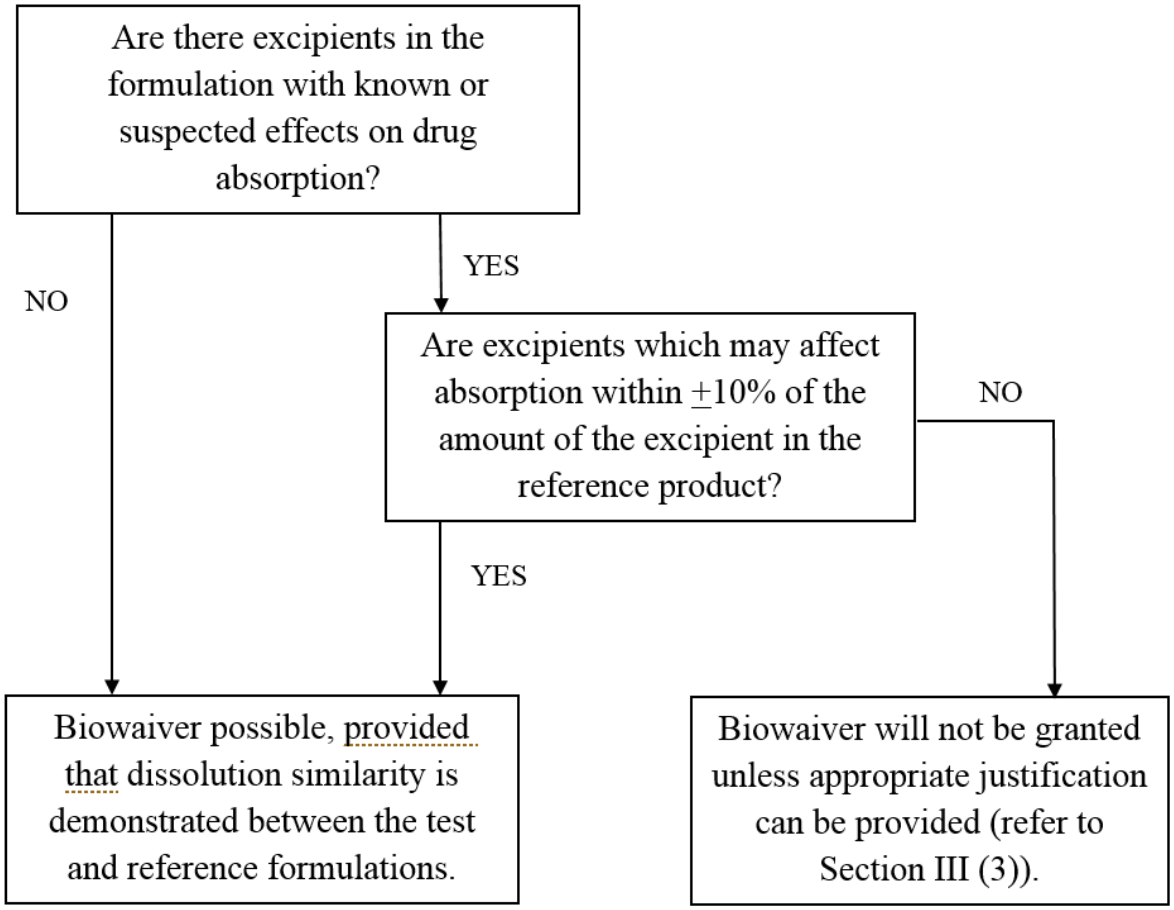
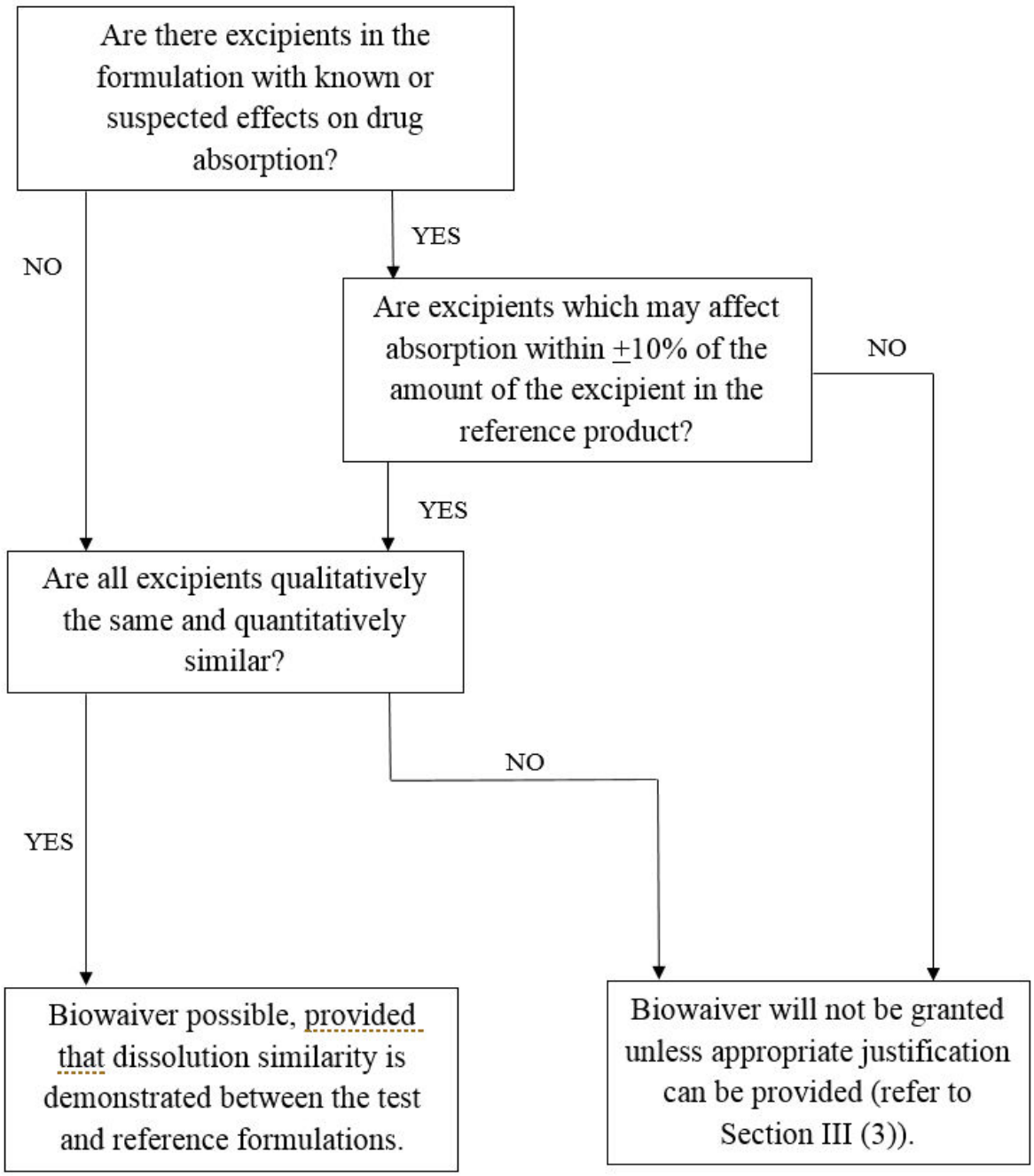


Figure 2. BCS Class III Drug Substances



EXAMPLES OF ACCEPTABLE DIFFERENCES IN EXCIPIENTS

Example 1: BCS Class I Biowaiver

The formulation of the test product is qualitatively the same as that of the reference product. Additionally, it contains sorbitol, an excipient with known or suspected effects on drug absorption. The amount of sorbitol in the test formulation is within the permitted range of 45 milligrams (mg) to 55 mg based on the amount of sorbitol in the reference formulation (i.e., 50 mg ± 10%).

Component	Amount (mg) Reference	Amount (mg) Test
Drug substance	100	100
Microcrystalline cellulose (filler)	100	95
Sorbitol (filler)	50	55
HPMC (binder)	10	10
Talc (glidant)	5	5
Total	265	265

Example 2: BCS Class III Biowaiver

The test formulation is qualitatively the same as the reference formulation. Additionally, it contains sorbitol, an excipient with known or suspected effects on drug absorption. The amount of sorbitol in the test formulation is within the permitted range of 9 mg to 11 mg based on the amount of sorbitol in the reference formulation (i.e., 10 mg ± 10%). Differences in the amount of other excipients are within the criteria outlined in Table 1, Section III.A. (3.1).

Component	Reference Product		Test Product		Absolute % difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
Drug substance	100	49.3%	100	46.5%	--
Lactose monohydrate (filler)	85	41.9%	97	45.1%	3.2%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate (lubricant)	2	1.0%	2	0.9%	0.1%
Total	203	100%	215	100%	
				Total change:	4.3%