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Guideline on Biopharmaceutics Classification System-Based Biowaivers

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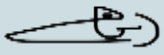
Signature		**Signature**	
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Acronyms:

API	Active Pharmaceutical ingredient.
BCS	Biopharmaceutics Classification System
BE	Bioequivalence.
Cmax	Maximum plasma concentration
f2	Similarity factor.
FDC	Fixed Dose Combination
ODT	Oral dispersible tablets.
QC	Quality control
rpm	Revolutions per minute

Definitions

Bioequivalence	Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailability, in terms of rate (Cmax and tmax) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.
Biopharmaceutics Classification System (BCS)	The BCS is a scientific framework for classifying active pharmaceutical ingredients based upon their aqueous solubility and intestinal permeability.
Biowaiver	The regulatory pharmaceutical product approval process whereby the dossier (application) is approved based on evidence of equivalence rather than through in vivo equivalence testing.
Dosage form	The form of the finished pharmaceutical product (for example, tablet, capsule, suspension or suppository).
Fixed-dose combination product	A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

CHAPTER ONE

Introduction

Two drug products containing the same active ingredient(s) are considered bioequivalent if their bioavailability—meaning the rate and extent of medicine absorption—falls within predefined acceptable limits when administered at the same molar dose. These limits are established to ensure that the products perform similarly in vivo, ensuring safety and efficacy. In bioequivalence studies, key pharmacokinetic parameters such as AUC (area under the concentration-time curve) and C_{max} (maximum concentration) are typically used to evaluate the rate and extent of medicine absorption.

The BCS (Biopharmaceutics Classification System)-based biowaiver approach aims to reduce the need for in vivo bioequivalence studies by offering a potential surrogate. In some cases, in vivo bioequivalence studies may be waived if in vitro data can justify an assumption of equivalence in in vivo performance. The BCS is a scientific framework that classifies drug substances based on their aqueous solubility and intestinal permeability. The BCS categorizes medicines into the following four classes:

Class I: High solubility, high permeability

Class II: Low solubility, high permeability

Class III: High solubility, low permeability

Class IV: Low solubility, low permeability

This guidance provides recommendations to assist in the biopharmaceutics classification of drug substances and the use of the BCS-based biowaiver for bioequivalence studies. The BCS biowaiver principles may also be applied to bioequivalence purposes not explicitly outlined in the guidelines, as long as a thorough scientific rationale is provided to support their use.

Purpose

The BCS-based biowaiver approach allows in vivo bioequivalence studies to be waived if in vitro data show that a test product performs equivalently to a reference product. This is typically suitable for highly soluble medicines with known absorption profiles, excluding those with a narrow therapeutic index. It applies only to immediate-release oral solid forms intended for systemic use and excludes sublingual, buccal, or modified-release formulations; for Oro dispersible forms, oral cavity absorption must not occur. The biowaiver can support bioequivalence determinations for generics, product extensions, required variations, and comparisons of clinical trial and marketed formulations.

Scope

BCS-based biowaivers can be used to demonstrate in vivo bioequivalence. Examples of their application include comparisons between products used from clinical development to commercialization, post-approval changes, and applications for generic drug products, in line with regional regulations.

The BCS-based biowaiver is applicable only to immediate-release, solid oral dosage forms or suspensions intended to deliver the medicine to the systemic circulation. Drug products with a narrow therapeutic index are not eligible for a BCS-based biowaiver under this guidance. Fixed-dose combination (FDC) products may qualify for the biowaiver if all active ingredients in the combination product meet the established criteria.

Structure

This is the first version of this guideline and is organized into four chapters. CHAPTER ONE covers the Introduction, Purpose, Scope, and Structure. CHAPTER TWO outlines the detailed procedures and methods. CHAPTER THREE defines responsibilities in relation to this guideline. CHAPTER FOUR includes the document history and version control and references.

CHAPTER TWO

Procedure

2. Biopharmaceutics Classification of The Drug Substance

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

A biowaiver is granted when the drug substance(s) in both the test and reference products are identical. It may also apply if the test and reference products contain different salts, as long as both are classified as BCS Class I (high solubility and high permeability). However, a biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex, or derivative of the drug substance compared to the reference product, as these differences may result in distinct bio availabilities that cannot be predicted using the BCS-based biowaiver experiments. Pro-drugs may be eligible for a BCS-based biowaiver if they are absorbed as the pro-drug.

2.1. Solubility

A drug substance is classified as highly soluble if its highest single therapeutic dose is completely soluble in 250 mL or less of aqueous media across the pH range of 1.2–6.8 at 37±1°C. If the highest single therapeutic dose does not meet this criterion, but the highest strength of the reference product is soluble under the same conditions, additional data should be submitted to justify the use of the BCS-based biowaiver approach.

The sponsor is required to experimentally determine the solubility of the drug substance across the pH range of 1.2–6.8 at 37±1°C. Solubility should be evaluated at least three pH values within this range, including pH 1.2, 4.5, and 6.8, and at the pH of lowest solubility of the drug substance, if it falls 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 using a method appropriate to the properties of the drug substance. Equilibrium solubility experiments can be performed using the shake-flask technique or an alternative method if justified. Small volumes of solubility media may be used if the experimental equipment allows it. The pH of each test solution should be measured both after the drug substance is added and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. If necessary, the pH should be adjusted. The experiment should run for a suitable duration to reach equilibrium.

Alternatively, solubility experiments where the highest single therapeutic dose is tested in a 250 mL volume (or a proportionally smaller volume for smaller doses) of buffer can also 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.

Additionally, the stability of the drug substance in the solubility media must be adequate. If the drug substance degrades by more than 10% during the solubility assessment, it cannot be properly classified. Literature data can also be used to support solubility determinations, but such data should come from peer-reviewed sources and provide enough detail for a proper evaluation of the quality of the studies.

2.2. Permeability

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 medicine), or as the sum of parent medicine, 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 prior to absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged medicine in feces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent medicine in feces to be

accounted for absorbed medicine 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 medicine'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 medicine 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. Medicine 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. medicine concentrations should then be determined using a suitably validated method. Significant degradation (>10%) of a medicine precludes BCS high permeability classification.

2.3 Eligibility of A Drug Product for A BCS-Based Biowaiver

A drug product is eligible for a BCS-based biowaiver if the drug substance(s) meet the solubility and permeability criteria (BCS Class I and III), the product is an immediate-release oral dosage form with systemic action, and it matches the reference product in terms of dosage form and

strength. If the highest single therapeutic dose does not meet the high solubility criterion, but the highest strength of the reference product is soluble under the specified conditions, the BCS-based biowaiver can be granted if dose-proportional pharmacokinetics (i.e., AUC and Cmax) are demonstrated across a dose range that includes the highest therapeutic dose.

Drug products intended for buccal or sublingual absorption are not eligible for a BCS-based biowaiver. Additionally, the BCS-based biowaiver is only applicable to drug products that are intended to be taken with water. For products designed to be administered without water (e.g., Oro dispersible formulations), a bioequivalence study where the product is dosed without water must be conducted.

To qualify for a BCS-based biowaiver, the drug product must also meet criteria related to its composition (excipients) and in vitro dissolution performance.

2.3.1 Excipients

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 number 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 medicines 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 medicine has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS Class I medicines that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered.

For BCS Class I medicines, 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 medicines 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 medicine. For BCS Class III medicines, 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 medicines.

Within the context of quantitative similarity, differences in excipients for drug products containing BCS Class III medicines should not exceed the following targets:	
Excipient class	**Percent of the amount of excipient in the reference**
Excipients which may affect absorption	
Per excipient: **Sum of differences:**	**10%** **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 medicines should meet criteria regarding excipients for a BCS Class I medicine. FDC formulations containing only BCS Class III medicines, or BCS Class I and BCS Class III medicines, should meet criteria regarding excipients for a BCS Class III medicines.

2.3.2 In vitro Dissolution

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(s).

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 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. Pharmacopeial 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:

$$f2 = 50 \bullet \log \{[1 + (1/n)\Sigma t{=}1n\ (Rt - Tt)2]\text{-}0.5 \bullet 100\}$$

In this equation f2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference medicine dissolved at time t after initiation of the study and T(t) is the mean percent test medicine 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 labelled amount of the medicine 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 medicines should meet dissolution criteria for a BCS Class I medicine. FDC formulations containing only BCS Class III medicines should meet dissolution criteria for a BCS Class III medicine. For FDCs containing both BCS Class I and BCS Class III medicines 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.

2.4 Documentation

The sponsor should provide complete information on the critical quality attributes of the test drug substance(s) and drug product. Information should also be provided for the reference product, to the extent possible, and must include, but is not limited to: polymorphic form, enantiomeric purity, and any data concerning bioavailability or bioequivalence issues related to the drug substance(s) or product. This includes literature reviews and sponsor-conducted studies. All study protocols and reports must be submitted.

The reporting format should include tabular and graphical presentations, showing both individual and mean results along with summary statistics. The report must clearly identify all excipients, noting their qualitative and, where relevant, quantitative differences between the test and reference products.

A complete description of the analytical methods used, including the validation and qualification of the analytical parameters, must be provided. Detailed descriptions of the test methods and media should be included, specifying information such as test and reference batch details (e.g., unit dose,

strength, assay, batch number, manufacturing date, batch size, and expiry date). The dissolution report should include a thorough description of experimental settings and analytical methods, including information on the dissolution conditions such as apparatus, de-aeration, 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 Appendix I).

CHAPTER THREE

Responsibilities:

Applicants for Marketing Authorizations	• Submit complete BE study data. • Select appropriate reference product. • Ensure study design meets guideline requirements. • Address regulatory queries.
Pharmaceutical Companies / Manufacturers	• Develop and manufacture the generic product under GMP • Ensure batch consistency for BE studies • Provide formulation and quality documentation • Oversee outsourced activities (CROs)
Contract Research Organizations (CROs)	• Conduct BE studies under GCP/GLP • Ensure ethical approvals • Use validated analytical methods • Maintain accurate data and complete study reports
Health Care Policy Makers	• Create policies supporting safe, effective, affordable generics • Strengthen regulatory capacity • Promote public trust in generic medicines
DSC BE Assessors	• Scientifically evaluate BE submissions • Review analytical, clinical, and statistical data • Ensure guideline compliance • Prepare assessment reports and recommendations
DSC CROs inspectors	• Verify compliance with guidelines while conducting inspections • Issue approvals or requests for additional information

CHAPTER FOUR

Document History and Version Control

Version	Description	Review Date
1	Initial Release	July 2026
2		
3		

References:

International Council for Harmonization (ICH) (2020), *ICH guideline M9 Guidelines biopharmaceutics Classification system- Based Biowaiver EMA/CHMP/ICH/493213/2018 (10/02/2020)*

World Health Organization (WHO) (2024), *WHO guidelines on BCS- based Biowaiver (Annex 7, 2024)*

Glossary of ICH terms and definitions *Compiled by CIOMS from the International Council for Harmonization (ICH)'s Version 8 5 June 2025.*

Annexes:

Appendix 1: 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 medicine absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation, and 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 and uptake 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 medicines.

Method validation

The suitability of the Caco-2 cell assays for BCS permeability determination should be demonstrated by establishing a rank-order relationship between experimental permeability values and the extent of medicine absorption in human subjects using zero, low (<50%), moderate (50–84%), and high (≥85%) permeability model medicines. A sufficient number of model medicines 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 medicine permeability. The established relationship should permit differentiation between low, moderate and high permeability medicines.

Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance (TEER) measures and/or other suitable indicators, prior to and after an experiment.

In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (refer to Table 2).

Reporting of the method validation should include a list of the selected model medicines 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 medicine (mean, standard deviation, coefficient of variation), permeability class of each model medicine, 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 medicine used to classify the test drug substance.

In addition, a description of the study method, medicine 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 medicine concentration, e.g., 0.01, 0.1, and 1 time the highest strength dissolved in 250 ml, or on transport direction (efflux ratio, i.e., ratio of apparent permeability (Papp) between the basolateral-to-apical and apical-to-basolateral directions <2 for the selected medicine concentrations).

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 medicine permeability determinations should employ conditions established during the validation, and include a moderate and a high permeability model medicine in the donor fluid along with the test medicine as internal standards to demonstrate consistency of the method. The choice of internal standards should be based on compatibility with the test medicine, 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 medicine 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 medicine 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 medicine. Mean medicine 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 medicine in the cell monolayer and testing apparatus.

Evaluation of the test medicine 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 medicine 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.

Appendix 2: Further Information on The Assessment of Excipient Differences

Figure 1. BCS Class I drug substances

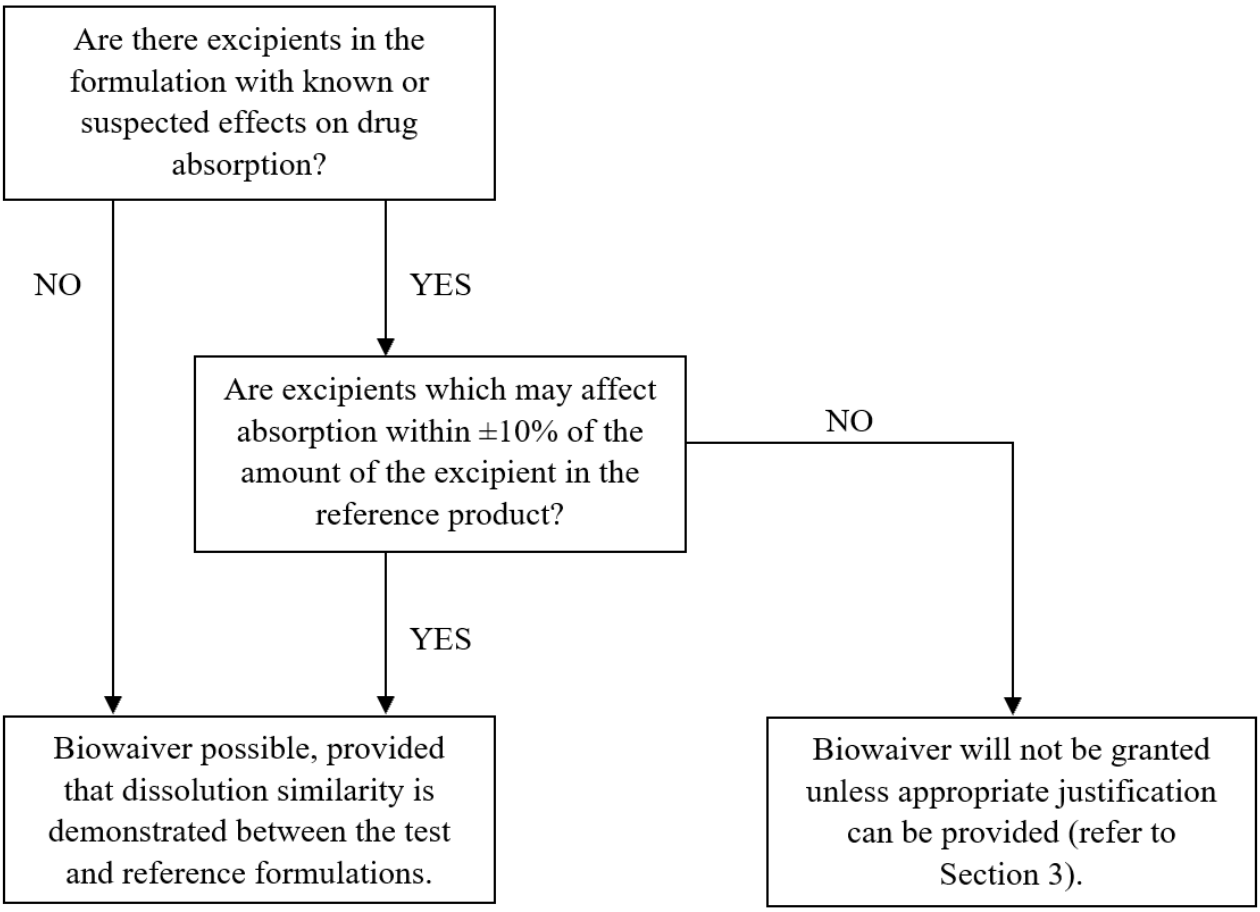

Figure 2. BCS Class III drug substances