M9 BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

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INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

M9

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ICH HARMONISED GUIDELINE

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M9

ICH Consensus Guideline

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INTRODUCTION

1.1. Background and Objective

Two drug products containing the same active substance 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 AUC (the area under the concentration time curve), and C_{max} (the maximum concentration), are generally used to assess the rate and extent of drug absorption.

The BCS (Biopharmaceutics Classification System)-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. 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

This guidance will provide recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products.

1.2 Scope

BCS-based biowaivers may be used to demonstrate bioequivalence for example between products used in early clinical development through commercialization, for line extensions of the same pharmaceutical form of innovator products, in applications for generic drug products, and post-approval changes that would otherwise require *in vivo* bioequivalence evaluation, 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 2 and 3 of this guidance.

2. BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCE

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

A biowaiver is only applicable when the drug substance(s) in test and reference products are identical. For example, a biowaiver is not applicable when the drug substance in the test product is a different salt, ester, isomer, or mixture of isomers from that in the reference product. Pro-drugs may be considered for a BCS-based biowaiver when absorbed as the pro-drug.

2.1. Solubility

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 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 applicant is expected to establish experimentally the equilibrium saturated solubility of the drug substance over the pH range of 1.2 – 6.8 at 37 ± 1ºC using a shake-flask technique or an alternative method, if justified. At least three buffers within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pKa of the drug substance should be evaluated if it is within the specified pH range. 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 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 is necessary to demonstrate solubility using a validated stability-indicating method, with appropriate compendial references for the media employed.

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 this case a BCS-based biowaiver cannot be applied. 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.

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 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 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 (for example, product knowledge and previously published 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. *In vitro* cell permeability assays (Caco-2) used in support of high permeability should be appropriately validated and standardized as outlined in Annex 1. 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, “Assay Considerations”.

If high permeability is not demonstrated, the drug substance is considered to have low permeability (e.g. BCS class III).

<u>Instability in the Gastrointestinal Tract</u>

If mass balance studies or *in vitro* Caco-2 studies are used to demonstrate high permeability, additional data to document the drug’s stability in the gastrointestinal tract should be provided,

unless ≥ 85% of the dose is recovered as unchanged drug in urine. Stability in the gastrointestinal tract may be documented using compendial and simulated gastric and intestinal fluids or, with suitable justification, other relevant methods. 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 validated stability indicating assay method. Significant degradation (>10 percent) of a drug in this study could suggest potential instability.

3. SUPPORT OF THE ELIGIBILITY OF A DRUG PRODUCT FOR A BCS-BASED BIOWAIVER

A drug product is eligible for a BCS-based biowaiver provided that the drug substance(s) 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 a dosage form that is pharmaceutically equivalent to 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 additional data. An example of such additional data is demonstration of dose proportional pharmacokinetics (i.e. AUC and C_{max}) over a dose range that includes the highest therapeutic dose.

Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. As such, an orodispersible product is eligible for a biowaiver application only if there is no buccal or sublingual absorption and the product is labelled to be taken with water only.

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 3.1 and 3.2 below.

3.1. Excipients

Excipient differences between the proposed test and the reference products 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 applicant 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 fora 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 ± 10.0% of the amount of excipient in the reference product.

BCS Class III drug substances are considered to be more susceptible to the effects of excipients. These drugs are poorly 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). This is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II.

Table 1: Allowable differences in excipients for drug products containing BCS Class III drugs.

Excipient class	Percent of the amount of excipient in the reference	Percent difference relative to core weight (w/w)
Excipients which may affect absorption:	**± 10.0%**	
All excipients:		
Filler		± 10.0%
Disintegrant		
Starch		± 6.0%
Other		± 2.0%
Binder		± 1.0%
Lubricant		
Ca or Mg stearate		± 0.5%
Other		± 2.0%
Glidant		
Talc		± 2.0%
Other		± 0.2%
	Total % change permitted:	**10.0%**

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

For FDC formulations containing only BCS Class I drugs, criteria regarding excipients should follow that for a BCS Class I drug. For FDC formulations containing only BCS Class III drugs, or BCS Class I and BCS Class III drugs, criteria regarding excipients should follow that for a BCS Class III drug. This is applicable to FDCs which are pharmaceutically equivalent.

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 one batch of 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 apparatuses and validated analytical 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 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. Pharmacopoeial buffers should be employed. Additional investigation may be required at the pH of minimum solubility (if different from the buffers above). Purified water may be used as an additional dissolution medium in some regions.
- Organic solvents are not acceptable and no surfactants should be added.
- Samples should be filtered during collection
- 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, the use of the basket apparatus at 100 rpm is recommended. Additionally, use of sinkers in the paddle apparatus to overcome issues such as coning may be considered with justification.

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) or rapid (≥85 for the mean percent dissolved in ≤30 minutes) and similar *in vitro* dissolution characteristics under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, statistical 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; 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 twelve individual values for every time point for each product.
- Not more than one mean value of ≥85% dissolved for any 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 label amount of the drug is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. In case the coefficient of variation is too high, f2 calculation is considered not accurate and reliable 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. For FDC formulations containing only BCS I drugs, criteria regarding dissolution should follow that for a BCS Class I drug. For FDC formulations containing only BCS Class III drugs, criteria regarding dissolution should follow that 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.

4. DOCUMENTATION

The applicant should provide complete information on the critical quality attributes of the test drug substance 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 or drug product, including literature surveys and applicant derived studies. All study protocols including standards, quality assurance and testing methods should be appropriately detailed and validated according to current regulatory guidance's and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics. The tabular presentation should include standard deviation and coefficient of variation.

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

A full description of the analytical methods employed, including validation, e.g. method linearity, accuracy and precision, should be provided. A detailed description of all test methods and media, including test and reference batch information [unit dose (milligram and %), batch number, manufacturing date and batch size where known, expiry date, and any comments] 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, 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 Annex I).

5. GLOSSARY

AUC: Area under the concentration versus time curve

BCS: Biopharmaceutics Classification System

C_{max}: Maximum concentration

FDC: Fixed-dose combination

Pharmaceutically equivalent: Medicinal products containing the same amount of the same active substance(s) in the same dosage forms.

pKa: Acid dissociation constant at logarithmic scale

rpm: rotation 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, 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 (e.g., P-gp, BCRP, MRP2) and uptake (e.g., PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays in support of high permeability for BCS classification is limited to passively transported drugs (for definition see Assay Considerations).

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 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 the full permeability range (a minimum 5 for each permeability category, high, moderate and low is recommended; examples are provided in Table 1). 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, prior to and after an experiment. In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability.

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 percent confidence interval) with identification of the high permeability class boundary and selected high permeability internal standard 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, equation used to calculate permeability, and where

appropriate, information on efflux potential, e.g., bidirectional transport data should be provided for a known substrate.

Assay considerations

As noted above, the use of Caco-2 cell assays in support of BCS permeability determination is limited to passively transported drugs. A passive transport mechanism can be inferred when the pharmacokinetics of the drug (assessed as AUC and C_{max} parameters) are dose proportional over the relevant clinical dose range. Alternatively, the absence of an active transport mechanism 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 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).

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

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 as internal standards to demonstrate consistency of the method, i.e., included in the donor fluid along with the test drug. 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 membrane.

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 ($f_a \geq 85$ 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

Group	Drug
	Chlorothiazide
	Polyethylene glycol 400
	Enalaprilat
Zero Permeability	FITC-Dextran
	Polyethylene glycol 4000
	Lucifer yellow
	Inulin
	Lactulose
Efflux Substrates	Digoxin
	Paclitaxel
	Quinidine
	Vinblastine

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ANNEX II: FURTHER INFORMATION ON THE ASSESSMENT OF EXCIPIENT DIFFERENCES

Figure 1. BCS Class I Drug Substances

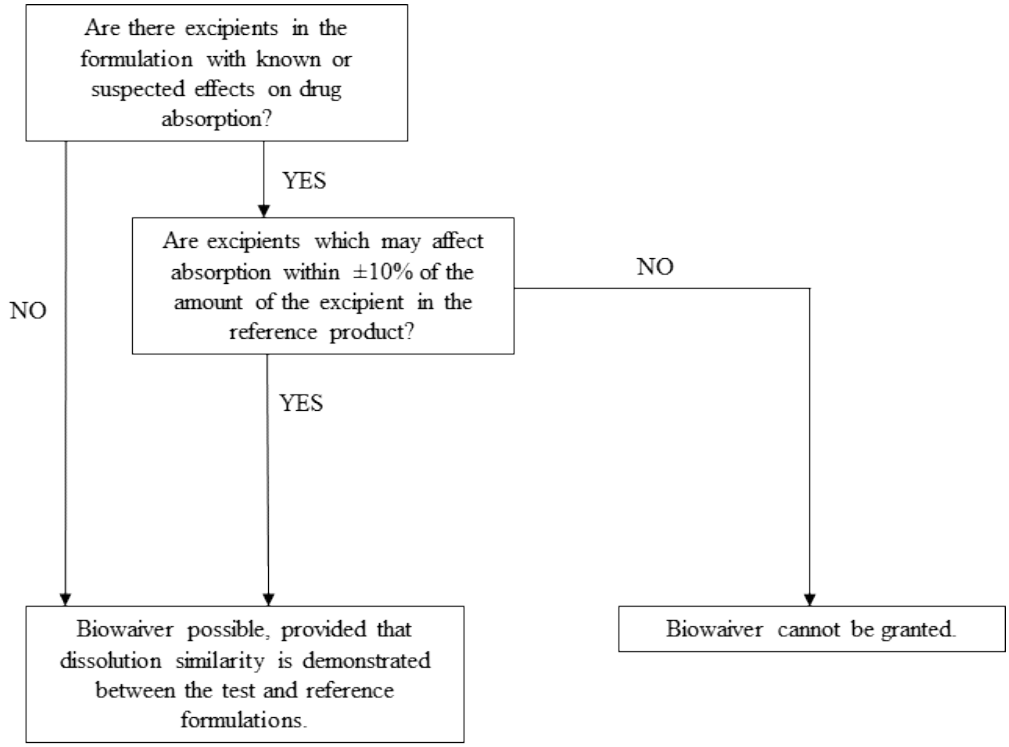
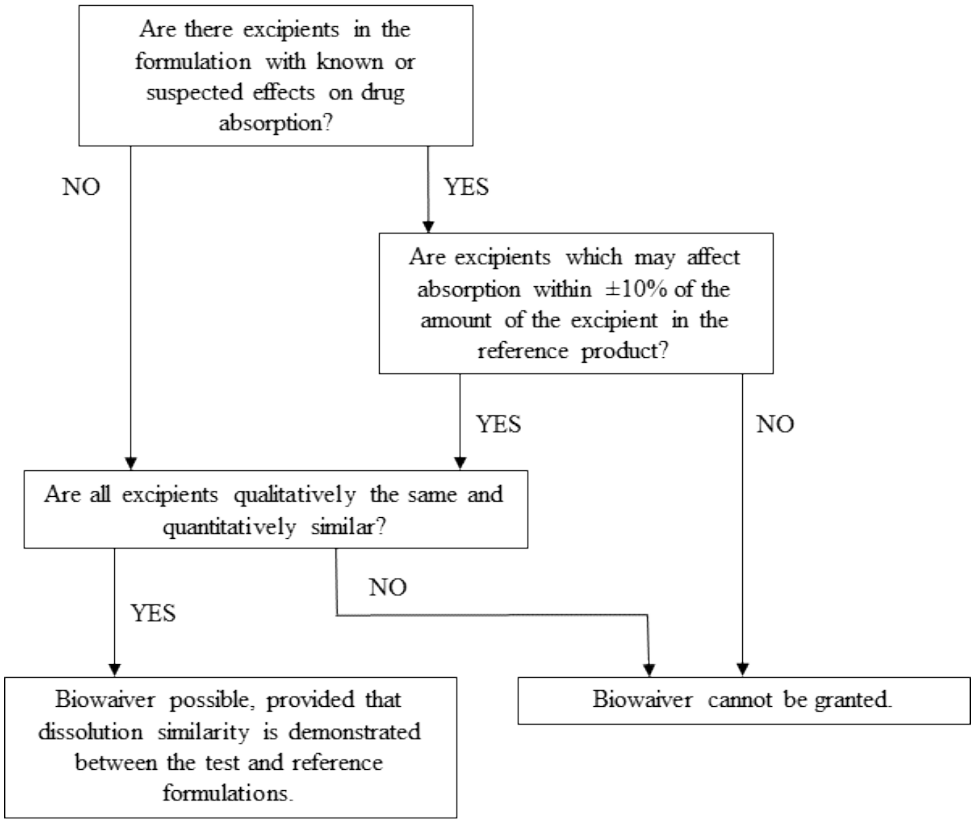


Figure 2. BCS Class III Drug Substances



EXAMPLES OF ACCEPTABLE DIFFERENCES IN EXCIPIENTS

Example 1: BCS Class I Biowaiver

The amount of sorbitol (an excipient that affects absorption) in the test formulation is different from the reference formulation. The permitted range is 45 mg to 55 mg of sorbitol based on the amount in the reference formulation (50 mg ± 10.0%).

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

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413 **Example 2: BCS Class III Biowaiver**

414 The test formulation is qualitatively the same as the reference formulation. The amount of
415 sorbitol (an excipient that affects absorption) in the test formulation is different from the
416 reference formulation. The permitted range is 9 mg to 11 mg of sorbitol based on the amount
417 in the reference formulation (10 mg ± 10.0%). For the other excipients the differences were
418 within the criteria provided in Table 1.

Component	Reference Product		Test Product		Absolute percent 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%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate	2	1.0%	2	0.9%	0.1%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Total	203	100%	215	100%	
				Total change:	**4.3%**

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