World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO guideline on biopharmaceutics Classification System -based Biowaivers

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/23.929:

WHO guideline on Biopharmaceutics Classification System - based Biowaivers

Description of Activity	Date
Preparation of first draft working document.	April 2023
Review and finalization of the first draft working document with an informal drafting group.	April - May 2023
1st informal drafting group meeting	15, 16 and 18 May 2023
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	July 2023
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	September 2023
Discussion of the feedback received on the working document in a virtual meeting with an informal consultation group.	September 2023
Preparation of a working document for discussion and possible adoption by the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	September - October 2023
Presentation to the Fifty-seventh meeting of the ECSPP.	October 2023
Any other follow-up action as required.	

WHO guideline on Biopharmaceutics Classification System -based Biowaivers

Background

A recommendation was made to the WHO Norms and Standards for Pharmaceuticals (NSP) Team by the group of experts participating at the *Joint Meeting on Regulatory Guidance for Multisource Products (1 – 3 November 2022),* as well as other parties, such as the WHO Prequalification Team (PQT), to update the WHO BCS-based biowaiver requirements (associated section within the overarching *WHO guidelines on multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability)(1)* to harmonize with those stated in The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M9 on Biopharmaceutics Classification System (BCS) - Based Biowaivers adopted in November 2019 *(2).*

The *WHO guideline on Biopharmaceutics Classification System - Based Biowaivers* will supersede the BCS-based biowaiver section of the *WHO guidelines on multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (1)*. The purpose of this document is to provide recommendations to support the biopharmaceutics classification of Active Pharmaceutical Ingredients (APIs) and the BCS-based biowaiver of bioequivalence studies for Finished Pharmaceutical Products (FPPs).

WHO guideline on Biopharmaceutics Classification System -based Biowaivers

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This text is based on the International Conference on Harmonisation (ICH) Guideline M9: Biopharmaceutics Classification System-Based Biowaivers. November 2019.

1. Introduction

Two finished pharmaceutical products (FPPs) containing the same active moiety of the pharmaceutical ingredient(s) (API{s}) are considered bioequivalent if their bioavailabilities (rate and extent of API 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 (area under the concentration time curve) and C_{max} (maximum concentration) are generally used to assess the rate and extent of API 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 APIs. The BCS categorizes APIs 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 provides recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs. The BCS-based biowaiver principles may be applied to bioequivalence purposes not explicitly specified in the guideline, provided they can be supported by a thorough scientific rationale.

2. Scope

BCS-based biowaivers may be used to substantiate in vivo bioequivalence. Examples include the comparison between products used during clinical development through commercialization, post-approval changes, and applications for generic 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 API to the systemic circulation. FPPs, 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 APIs contained in the combination product meet the criteria, as defined in sections 4 and 5 of this guidance.

3. Glossary

The definitions given below apply to the terms used in this document. They have been aligned as much as possible with the terminology in related World Health Organization (WHO) guidelines and good practices (GxP) and included in the WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guideline: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_5, but may have different meanings in other contexts.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

bioavailability. The rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action. Reliable measurements of active pharmaceutical ingredient (API) concentrations at the site(s) of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the site(s) of action. Bioavailability can therefore be defined as the rate and extent to which the API or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations, it is generally accepted that, in the same subject, an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the site(s) of action.

bioequivalence. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (C_{max} and t_{max}) and extent of absorption (area under the curve {AUC}), 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 (APIs) based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the BCS takes into account the major factors that govern the rate and extent of API absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

biowaiver. The term "biowaiver" is applied to a regulatory pharmaceutical product approval process when the dossier (application) is approved based on evidence of equivalence rather than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle, as described in guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (WHO Technical Report Series, No. 992, Annex 8 {2015}), should be used to identify a suitable alternative comparator product.

dosage form. The form of the completed pharmaceutical product (e.g. tablet, capsule, elixir or suppository).

equivalence requirements. In vivo and/or in vitro testing requirements for approval of a multisource pharmaceutical product for a marketing authorization.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

fixed-dose combination product. A finished pharmaceutical product (FPP) that contains two or more active pharmaceutical ingredients (APIs).

generic product. *See multisource pharmaceutical products*.

innovator pharmaceutical product. Generally the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of complete documentation of quality, safety and efficacy.

interchangeable pharmaceutical product. An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

multisource pharmaceutical products. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

4. Biopharmaceutics Classification of the API

BCS-based biowaivers are applicable to FPPs where the APIs exhibit high solubility and either high permeability (BCS Class I) or low permeability (BCS Class III).

A biowaiver is applicable when the APIs in test and comparator products are identical. A biowaiver may also be applicable if test and comparator 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 an API from that of the comparator product, since 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.

4.1 Solubility

An API 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.

The applicant is expected to establish experimentally the solubility of the API over the pH range of 1.2–6.8 at 37±1 ºC. 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 API should be evaluated if it is within the specified pH range.

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

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 API and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The experiment should be conducted over a suitable timeframe to reach equilibrium and the pH should be adjusted during this period as necessary.

Alternatively, solubility experiments where the highest therapeutic single dose (or a slightly higher amount to avoid recovery problems in the experiments) 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 API.

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

In addition, adequate stability of the API in the solubility media should be demonstrated. In cases where the API is not stable with >10% degradation over the extent of the solubility

assessment, solubility cannot be adequately determined and thus the API 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.

4.2 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 faeces, 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). An unchanged drug in faeces cannot be counted toward the extent of absorption unless appropriate data supports that the amount of parent drug in faeces 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 API is considered to have low permeability for BCS classification purposes.

Active pharmaceutical ingredient stability in the gastrointestinal tract

Additional data to document the API'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 an 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 pharmacopoeial or simulated gastric and intestinal fluids. Other relevant methods may be used with suitable justification. API solutions should be incubated at 37 ºC for a period that is representative of the in vivo contact of the API with these fluids (i.e. one hour in gastric fluid and three hours in intestinal fluid). API concentrations should then be determined using a suitably validated method. Significant degradation (>10%) of an API precludes BCS high permeability classification.

5. Eligibility of a finished pharmaceutical product for a biopharmaceutics classification system-based biowaiver

A FPP is eligible for a BCS-based biowaiver provided that the APIs satisfy the criteria regarding solubility and permeability (BCS Class I and Class III), the FPP is an immediate-release oral dosage form with systemic action, and the FPP is the same dosage form and strength as the comparator product.

FPPs 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 FPP to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and in vitro dissolution performance of the FPP should be satisfied. The FPP acceptance criteria are described in sections 5.1 and 5.2 below.

5.1 Excipients

Ideally, the composition of the test product should mimic that of the comparator product. However, where excipient differences exist, they should be assessed for their potential to affect in vivo absorption. This should include consideration of the API 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 API 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, such as, mannitol, sorbitol and surfactants (e.g. sodium lauryl sulfate). The risk that a given excipient will affect the absorption of an API should be assessed mechanistically by considering:

- the amount of excipient used;
- the mechanism by which the excipient may affect absorption; and
- absorption properties (rate, extent and mechanism of absorption) of the API.

The amount of excipients that may affect absorption in the test and comparator 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 API, are of less concern.

By definition, BCS Class I APIs 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-containing FPPs should focus on potential changes in the rate or extent of absorption. For example, if it is known that the API has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS Class I APIs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered. These excipients that may affect absorption should be considered as detailed in Figure 1, Annex II.

For BCS Class I APIs, 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 comparator product). Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

BCS Class III APIs are considered to be more susceptible to the effects of excipients. These APIs 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 APIs. For BCS Class III APIs, 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 comparator product), and the cumulative difference for these excipients should be within ± 10%. The acceptable differences in excipients are defined in Table 1 below. Examples of acceptable differences in excipients are shown in Annex II. Differences in colorants and flavouring may be permitted when these constitute very small amounts of the formulation. For the types of excipients not listed in Table 1, the same rule should be applied as for the excipients that may affect absorption.

It is known that in some cases the absolute amount of an excipient present in the GI tract is relevant to whether that excipient will exert an effect on absorption, e.g., an effect on relevant transporters. Since the allowable differences for BCS Class III APIs defined in Table 1 are based on %w/w of core weight, it is possible for absolute amounts of excipients in two formulations to differ significantly while still maintaining proportionality within the limits expressed in Table 1. Control over differences in absolute amount of excipients where it is known that effects on absorption can be observed, e.g., amounts of surfactants, is provided in Table 1, however,

possible effects of other excipients is not controlled. Therefore, to control for possible excipient effects based on absolute amount differences between products, the total core weight of the proposed product should not deviate by more than 20% from the total core weight of the comparator product.

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

Table 1: Criteria expected to demonstrate quantitative similarity for products containing Biopharmaceutics Classification System (BCS) Class III active pharmaceutical ingredients (APIs).

Within the context of quantitative similarity, differences in excipients for FPPs containing BCS Class III APIs should not exceed the following targets:	
Excipient class	**Percent of the amount of excipient in the comparator**
Excipients which may affect absorption **Per excipient:** **Sum of differences:**	 **10%** **10%**
	Percent difference relative to core weight* (w/w)
Major excipients types:	
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 APIs should meet criteria regarding excipients for a BCS Class I API. FDC formulations containing only BCS Class III APIs, or BCS Class I and BCS Class III APIs, should meet criteria regarding excipients for a BCS Class III API.

5.2 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 comparator 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 API content or potency of the comparator product should be close to the label claim, and the difference in API content or potency between the test and comparator products should be not more than 5%. The comparative in vitro dissolution tests should use pharmacopoeial 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 comparator 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.

- The sampling intervals employed in dissolution studies should be short for a scientifically sound comparison of the performance of the test and comparator products (e.g. 5, 10, 15, 20 and 30 minutes).
- Samples should be filtered during collection, unless in-situ detection methods are used. For this purpose, filters should be employed in-line, at the end of the sampling probe, or both during sample collection.
- The pH of each dissolution medium should be maintained throughout the test. The pH of each dissolution medium should be measured at the beginning (prior to introduction of the testing unit) and at the end of each dissolution test.
- For gelatin capsules, or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable, if appropriately justified.

Dissolution profiles for the test and comparator products should be generated in the same laboratory by the same staff at the same time using the same equipment. Compilation of 'historical' data is not acceptable.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both comparator 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 APIs, both the test product and comparator 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 comparator API dissolved at time t after initiation of the study and T_t is the mean percent test API dissolved at time t after initiation of the study.

The evaluation of the f2 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 (%CV) 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 comparator products demonstrate that ≥85% of the labelled amount of the API is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. When the %CV for the mean data is too high based on the requirements listed above, f2 calculation is considered unreliable. In such cases, an alternate method for the assessment of similarity in dissolution profiles, such as the bootstrap 90% confidence interval (CI) of expected f2, should be employed in keeping with regional expectations for dissolution similarity assessment.

To qualify for a BCS-based biowaiver for BCS Class III APIs, both the test product and comparator 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 APIs in the FDC to be considered. FDC formulations containing only BCS Class I APIs should meet dissolution criteria for a BCS Class I API. FDC formulations containing only BCS Class III APIs should meet dissolution criteria for a BCS Class III API. For FDCs containing both BCS Class I and BCS Class III APIs, 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 comparator product dissolution profiles are compared at each strength).

6. Documentation

The applicant should provide complete information on the critical quality attributes of the test APIs and FPP and as much information as possible for the comparator product, including, but not limited to polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the APIs or FPP, including literature surveys and applicant derived studies. All study protocols and reports should be provided. Information on validated test methods should be appropriately detailed according to current regulatory guidance 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 comparator 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 comparator batch information [unit dose (strength and assay), batch number, manufacturing date and batch size where known, expiry 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, 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*).

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 6. Geneva: World Health Organization; 2017 (https://www.who.int/publications/m/item/annex-6-trs-1003 accessed on 4 July 2023).
2. Biopharmaceutics Classification System-Based Biowaivers. ICH harmonised guideline M9, current step 4 version, November 2019. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2019 (https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf accessed on 4 July 2023).

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 as the sole data in support of high permeability for BCS classification is limited to passively transported drugs (*see Assay Considerations below*).

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, 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 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 API.

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, such as, by demonstrating independence of measured in vitro permeability on initial drug concentration, for example, 0.01, 0.1 and 1 times the highest strength dissolved in 250 mL, or on transport direction (efflux ratio, such as, 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 (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 ≥85%)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability (f_a = 50-84%)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide

Group	Drug
	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

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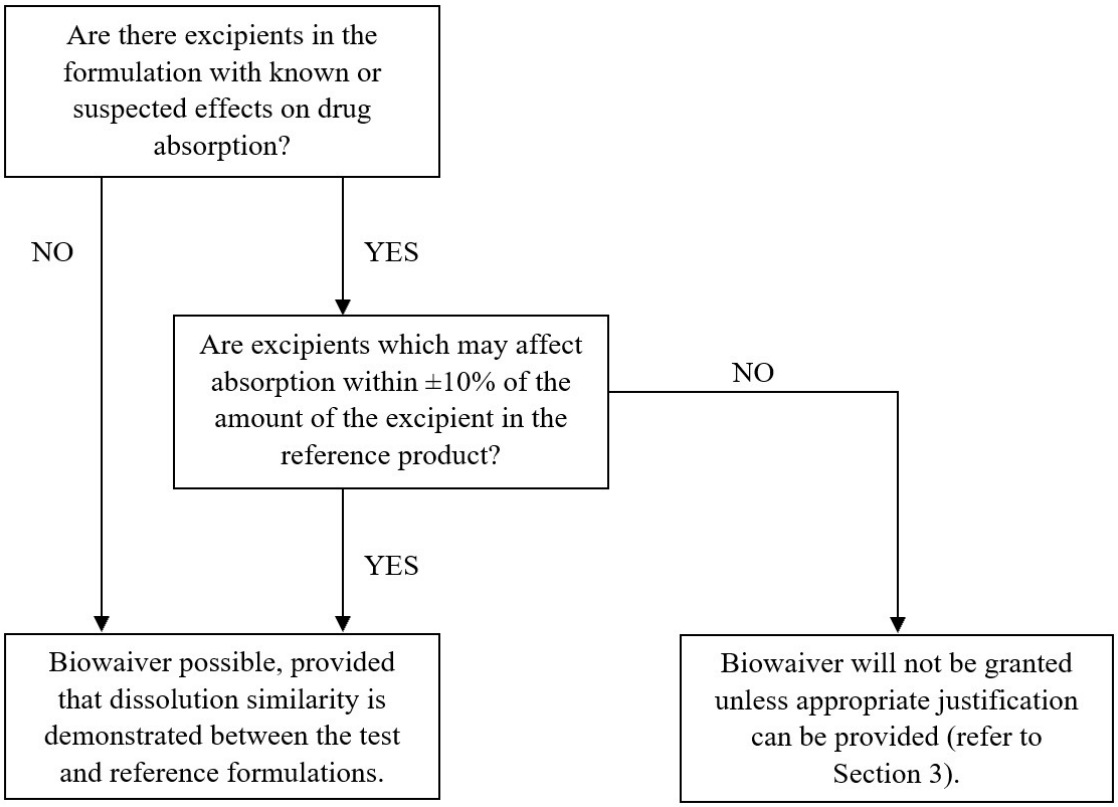
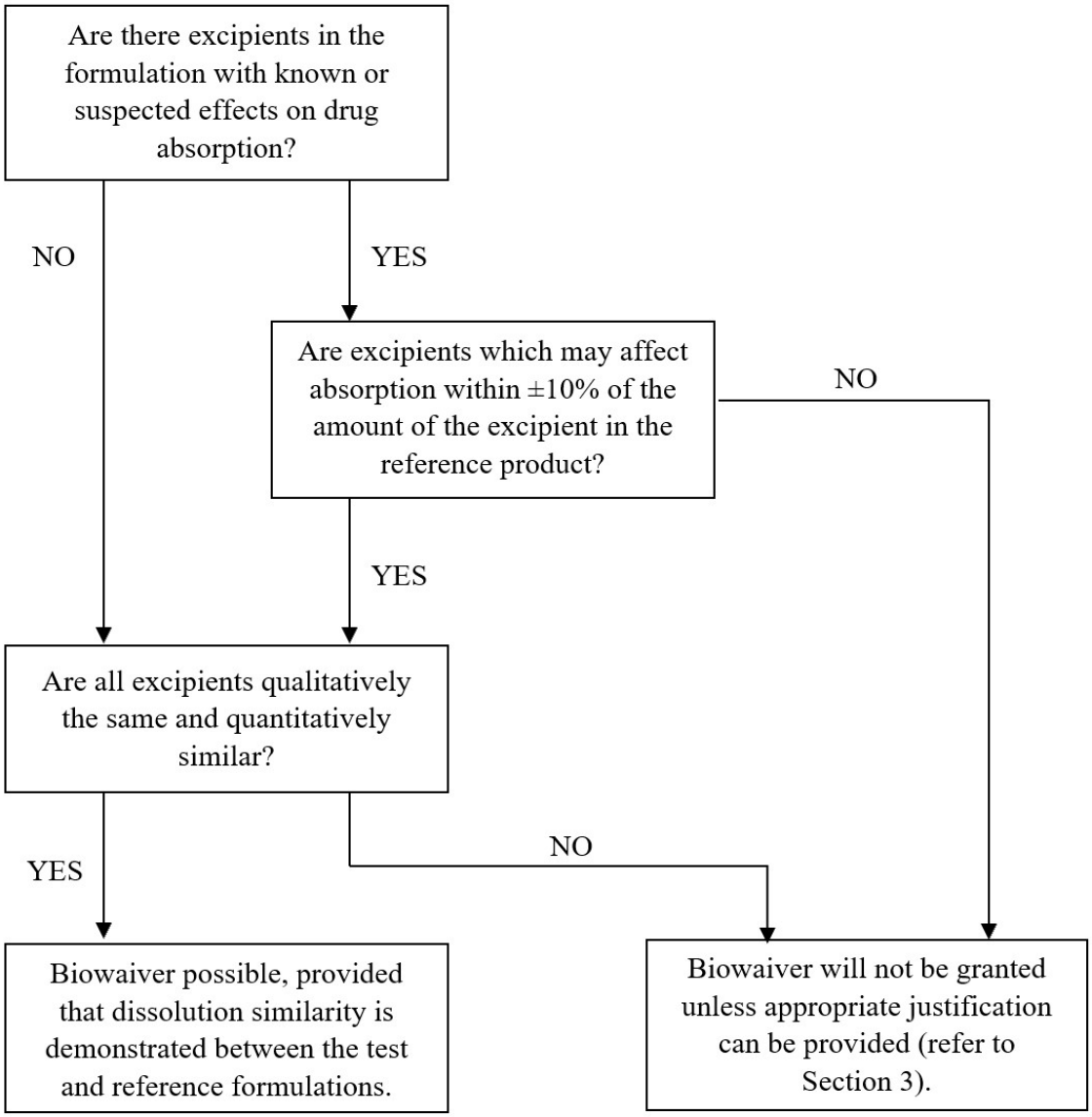
Annex II

Further information on the assessment of excipient differences

Figure 1. Biopharmaceutics Classification System (BCS) Class I active pharmaceutical ingredients (APIs)



628 **Figure 2. Biopharmaceuticals Classification System (BCS) Class III active pharmaceutical ingredients**
629 **(APIs)**
630



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633 **EXAMPLES OF DIFFERENCES IN EXCIPIENTS**

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635 **Example 1: BCS Class I biowaiver**

636

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

641

Component	Amount (mg) comparator	Amount (mg) test
API	100	100
Microcrystalline cellulose (filler)	100	95
Sorbitol (filler)	50	55
HPMC (binder)	10	10
Talc (glidant)	5	5
Total	265	265

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645 **Example 2: BCS Class III biowaiver**

646

647 The test formulation is qualitatively the same as the comparator formulation. Additionally, it contains
648 sorbitol, an excipient with known or suspected effects on API absorption. The amount of sorbitol in
649 the test formulation is within the permitted range of 9 mg to 11 mg based on the amount of sorbitol
650 in the comparator formulation (i.e. 10 mg ± 10%). Any differences in the amount of other excipients
651 are within the criteria outlined in Table 1, Section 5.1.

652

Component	Comparator 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)	
API	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%**

653

654

Example 3: Ineligible BCS Class III biowaiver

The formulation of the test product is qualitatively the same as that of the comparator product. Further, the quantitative differences in excipient content between the products, based on percentage of core weight, satisfy the limits expressed in Table 1, section 5.1. However, the total core weight of the proposed product deviates by more than 20% from the total core weight of the comparator product making the product ineligible for a biowaiver.

Component	Comparator 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)	
API	8	8.0%	8	0.8%	--
Lactose monohydrate (filler)	75	75.0%	802	80.2%	5.2%
Silicon dioxide (glidant)	2	2.0%	20	2.0%	0.0%
Croscarmellose sodium (disintegrant)	13	13.0%	150	15.0%	2.0%
Magnesium stearate (lubricant)	2	2.0%	20	2.0%	0.0%
Total	100	100%	1000	100%	
				Total change:	**7.2%**

Annex III

Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the biopharmaceutics classification system

Appendix 2 (*Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the biopharmaceutics classification system)* from Annex 6, TRS 1003, 2017 (*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability)* to be included as Annex III