A close-up of a logo

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Biopharmaceutics Classification System (BCS)

**Biowaiver Assessment Report**

**Bioequivalence Working Group for Generics**

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Description of Change | Author | Effective Date |
| v 1 | Original publication | BEWGG | 10 Feb 2017 |
| v 2 | Updated version according to ICH M9 guideline recommendations | BEWGG | 7 Nov 2024 |
|  |  |  |  |

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**BCS Biowaiver Assessment Report**

**<Proposed proprietary name>**

**<API> <Product strength(s)> <Product dosage form>**

**<Application/Dossier reference number>**

**Applicant: <Name of the Applicant>**

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# ADMINISTRATIVE INFORMATION

|  |  |
| --- | --- |
| Proposed name / name of the medicine |  |
| Active Pharmaceutical Ingredient - INN or common name of the API(s) |  |
| Dosage form and strength(s) |  |
| Type of application (generic / formulation or other variation(s)) |  |
| Applicant/Sponsor name and address, contact information |  |
| Final (test) product manufacturer Name and address |  |
| API manufacturer(s) Name(s) and address(es) |  |
| Solubility, testing laboratory, name and address |  |
| Caco-2 cell permeability assay testing laboratory, name and address |  |
| Dissolution testing laboratory name and address |  |
| Reference product details: name, HCR/MAH, country of procurement |  |
| Reviewer(s)/Assessor(s) |  |

# GLOSSARY / ABBREVIATIONS

API Active pharmaceutical ingredient / Drug Substance

BA Bioavailability

BCS Biopharmaceutics Classification System

CoA Certificate of Analysis

Drug Active pharmaceutical ingredient (API)

Drug product Pharmaceutical product / medicine / final product

FC / FDC Fixed combination / fixed dose combination

FPP Finished pharmaceutical product

HCR Holder of certificate of registration

MAH Marketing authorisation holder

NTI Narrow therapeutic index

PK Pharmacokinetics

SPC Summary of Product Characteristics / Product monograph / Product information / Labelling

# SUMMARY: REQUIREMENTS and OUTCOMES

|  |  |
| --- | --- |
|  | **Outcome** |
| **Therapeutic index** | Narrow / Non-narrow |
| **Solubility** | High / Low |
| Highest single therapeutic dose |  |
| Lowest measured solubility |  |
| Stable | Yes / No |
| **Human absorption / Permeability** | ≥85 % / <85 % : High / Low |
| Stable | Yes / No |
| **BCS class** | I / III/ not determined |
| **Dosage form** | Oral, systemic, IR,  Same dosage form, same strength as reference product |
| **Test product** | Batch number:  Manufacturing date or expiry date:  Batch size/commercial batch size:  Test product is representative of the product to be marketed: Yes / No |
| **Reference product** | Batch number:  Manufacturing date or expiry date: |
| **CoAs of the test and reference products** | Assays differ within 5 % : Yes/ No |
| **BCS Class I** |  |
| Test and reference products display either very rapid dissolution or rapid dissolution and similar *in vitro* dissolution characteristics | Yes / No |
| Excipients that may affect BA are qualitatively the same and quantitatively similar | Yes /No |
| **BCS Class III** |  |
| Test and reference products display very rapid dissolution | Yes/No |
| Excipients that may affect bioavailability are qualitatively the same and quantitatively similar | Yes/No |
| All other excipients are qualitatively the same and quantitatively similar | Yes/No |
| **Benefit-risk summary** | Acceptable/ Not acceptable |
| **Conclusion** | Approvable / Non-approvable |

# INTRODUCTION

Include *inter alia* the following as relevant:

## Application objective

Reason or justification for application of BCS-based Biowaiver.

Address if manufacturer and the applied API and FPP are the same as those employed in the solubility and dissolution studies.  *(If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, clear identification and justifications should be given by applicant).*

## Status of the reference product

Indicate which is the acceptable reference product.

Justify that the product applied for has the same dosage form and same strength.

Address identicality / differences in API: same or different salts (both BCS class I),same ester, ether, isomer, mixture of isomers, complex or derivative as reference product/originator.

Confirm that it is not sublingual, buccal or modified release. 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.

Note: In case of different salts, the applicant should provide data to justify that both salts have the same toxicological profile, e.g. literature data.

## Basic pharmacokinetic information

Linear PK is necessary to accept mass balance / absolute BA studies with doses different to the highest. References attached.

## Therapeutic indications and dose

Confirm that the API is not NTI. Different countries may have different criteria to define NTI API.

Evidence to support that the API does not have an NTI, e.g., therapeutic index or difference between minimum effective dose and minimum toxic dose is required.

|  |
| --- |
| *Reviewer’s comments:*  *Discuss information on section 4* – includingrelevant background, appropriateness of choice of reference as appropriate, etc. |

# BCS BIOWAIVER ASSESSMENT

## Drug Substance Solubility

Bibliographical and/or experimental (include source of information)

Note whether the following have been submitted:

* A complete report
* A protocol
* Dates of study
* Description of solubility method and conditions.
* Description and validation of the stability-indicating analytical method or cross-reference to the Q section of the dossier

State if solubility has been investigated at saturation or if only the highest single therapeutic dose or strength was investigated.

**Solubility method**

|  |  |
| --- | --- |
| Apparatus |  |
| Volume |  |
| Time |  |
| Dose /amount |  |
| Temperature |  |
| pH values |  |
| Buffer composition |  |

**Solubility at different pH values and replicates**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Theoretical pH | Repeat | Observed pH | Adjusted pH | Individual and mean Cs values | Individual and mean quantity dissolved in 250 mL |
| pH 1.2 | 1 2 3 |  |  |  |  |
| Intermediate pHs | 1 2 3 |  |  |  |  |
| pH 4.5 | 1 2 3 |  |  |  |  |
| Intermediate pHs | 1 2 3 |  |  |  |  |
| pH 6.8 | 1 2 3 |  |  |  |  |
| Other intermediate pH values **\*** | 1 2 3 |  |  |  |  |

**\*** Other intermediate pH values, e.g., pKa

Plot of Solubility (Concentration at saturation, Cs) vs. pH to identify the pH of minimum solubility if the saturation solubility has been investigated.

Add plot

*Summary of the requirements in ICH M9:*

Is the highest single therapeutic dose that can be taken in a single administration according to the SPC, completely soluble in 250 mL or less of aqueous medium over the range of pH 1.2 to 6.8 buffers; at 37 °C ± 1 °C? In cases where the highest single therapeutic dose does not meet this criterion, but the highest strength of the reference product is completely soluble in 250 mL under the aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach.

The equilibrium saturated solubility of the drug substance should be conducted over the pH range of 1.2 to 6.8 at 37±1 ºC, and at least three buffers within this range, including buffers at pH 1.2, 4.5 and 6.8. In addition, solubility at the pH of lowest solubility of the drug substance should be evaluated if it is within the specified pH range. The lowest measured solubility will be used for classification.

A minimum of three replicate determinations at each solubility condition are required to achieve unequivocal solubility classification (shake flask method or other justified method). Solution pH should be verified prior to and after addition of API to buffer. The pH should be adjusted if necessary.

Note whether the drug is stable in the buffers and whether the analytical method is stability-indicating. 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.

Experimental solubility data should be provided to establish the solubility of the drug substance. Literature data may be submitted to further support the solubility data.

*Reviewer’s comments:*

*Discuss information on section 5.1*

## Drug Substance 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. Literature data (such as Product Labelling, SmPC or peer-reviewed papers) can also be used to support high permeability.

Include source of absorption data, literature data or experimental data

|  |  |
| --- | --- |
| **Human** | |
| Complete absorption according to the reference product SPC | Yes / No |
| **Absolute BA** reference (give literature citation) | |
| Dose | Oral |
| Intravenous |
| Number of subjects |  |
| Result |  |
| **Mass balance** reference (give literature citation) | |
| Dose |  |
| Number of subjects |  |
| Result |  |
| ***In vitro Caco-2 permeability assays*** | |
| Test system |  |
| Concentrations |  |
| Result |  |
| ***Other information*** | |
| Drug substance stability in the GI tract |  |
| Influence of the transporters to absorption |  |

*Summary of the requirements in ICH M9:*

Complete absorption – measured extent of absorption is ≥ 85 % generally related to high permeability, based on reliable investigations in human. 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.

For passive transport drugs, permeability can be also assessed by validated and standardized *in vitro* methods using Caco-2 cells. The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. Drug substance stability in the gastrointestinal tract should be demonstrated (degradation≦10%) if Caco-2 studies or mass balance studies were used to investigate permeability (1 h at pH 1.2 and 3 h at pH 6.8).

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

*Notes for consideration*

Dose linearity of pharmacokinetics. In instances of non-linear PK, it should be assessed whether complete absorption has been demonstrated at the highest dose. For example, gabapentin exhibits non-linear PK, showing complete absorption at low doses but incomplete absorption when the transporter is saturated.

*Reviewer’s comments:*

*Discuss information on section 5.2*

## Comparison of Test and Reference Formulations / Excipients

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Component | Function | Test Product | | Reference 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) |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Total: | |  |  |  |  |  |
| Total change (%): | | | | | |  |

*Summary of the requirements in ICH M9:*

BCS I: 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 III: All of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Please refer to ICH M9 guideline for criteria expected to demonstrate quantitative similarity for products containing BCS III.

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.

Fixed dose combinations (FDCs): All APIs/drug substances should be either BCS I or III and fulfil all the requirements of the corresponding BCS class.

*Reviewer’s comments:*

*Discuss information on section 5.3*

## Drug Product *In Vitro* Dissolution Comparison

Complete documentation submitted – study report, study protocol, batch information on test and reference batches including CoAs, administrative details of the dissolution studies: person responsible, centre, dates, etc., detailed experimental conditions, validation of experimental analytical methods, individual and mean results and respective summary statistics.

**Summary of dissolution test method parameters**

|  |  |
| --- | --- |
| Apparatus |  |
| Agitation Speed |  |
| Dissolution Media |  |
| Volume |  |
| Temperature |  |
| Sampling times |  |
| Number of Dosage Units |  |
| Sampling |  |
| Filtration methods | *(in-line filtration)* |
| De-aeration method |  |

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

* Apparatus: paddle or basket
* Number of dosage units: at least 12 units
* 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

* Sampling schedule: e.g., 10, 15, 20, 30 and 45 min
* 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)
* Other conditions: no surfactant; in case of gelatine capsules or tablets with gelatine coatings the use of enzymes may be acceptable.

*Notes for consideration*

Buffer pH should be ensured throughout the experiment.

The difference between test and reference product in the assay of the CoA must be less than 5 %. The objective is to use products with comparable quantities so that a potency correction is not necessary.

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.

*Repeat tables for each strength*

**Test Batch**

**Dissolution Profiles for Lot #:**  n = no. of units/ pH medium

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **n** | **% Label Claim Released** | | | | |
| pH of medium | **x Min** | **x Min** | **x Min** | **x Min** | **x Min** |
| **pH 1.2 (0.1 N HCl)** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| **pH 4.5 (Acetate)** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| **pH 6.8 (Phosphate)** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| **pH of minimum solubility** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |

**Reference Batch**

**Dissolution Profiles for Lot #:**  n = no. of units/ pH medium

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **n** | **% Label Claim Released** | | | | |
| pH of medium | **x Min** | **x Min** | **x Min** | **x Min** | **x Min** |
| **pH 1.2 (0.1 N HCl)** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| **pH 4.5 (Acetate)** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| **pH 6.8 (Phosphate)** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| **pH of minimum solubility** | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |

**Dissolution profile comparison**

*[Repeat per strength]*

Test product (batch number) *vs.* reference product (batch number)

Points considered for f2 calculation:

f2:

*Summary of the requirements in ICH M9:*

For BCS Class I biowaiver, 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.

For BCS Class III biowaiver, 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 the comparison of dissolution profiles, where applicable, the similarity factor *f*2 should be estimated by using the following formula:

*f*2 = 50 • log {[1 + (1/n)Σt=1n (Rt - Tt)2]-0.5 • 100}

In this equation *f*2 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.

*Notes for consideration*

Discussion of dissolution profile differences in terms of clinical/ therapeutical relevance considered inappropriate (no *in vitro in vivo* correlation).

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.

*Reviewer’s comments:*

*Discuss information on section 5.4:* Low enough variability, adequate number of points to calculate f2, correct selection of points to calculate f2, similar, rapid enough, not more than 5 % difference in CoA assay values, etc.

## Dissolution testing laboratory

### Audit(s)

Describe if the QA unit of the centre has audited the study conduct and the data.

### GMP compliance/certification

Describe if GMP inspections have been performed in the facilities where these studies have been conducted, indicate the level of the findings and the regulatory authorities that conducted the studies.

*Reviewer’s comments:*

*Discuss information on section 5.5*

# LIST OF OUTSTANDING ISSUES / DEFICIENCIES / PROPOSED QUESTIONS

# CONCLUSIONS AND RECOMMENDATIONS

# REFERENCES

Relevant regulatory guidelines and scientific papers.