IPRP
International Pharmaceutical Regulators Programme

Biopharmaceutics Classification System (BCS) Biowaiver Assessment Report

Former Bioequivalence Working Group

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Version	Description of Change	Author	Effective Date
v 1	Original publication	BE WG	Feb 10, 2017

Disclaimer

This document reflects the views of subject matter experts participating in the IPRP Bioequivalence Working Group for Generics (BEWGG) and should not be construed to represent the official views of any given regulatory authority participating in the IPRP.

In order to achieve the IPRP's objective to promote collaboration and convergence in generic drug regulation, the Bioequivalence Working Group has developed a series of reference documents covering a number of technical and procedural aspects of Biowaiver assessment.

These documents were developed among participating IPRP members as model documents.

The implementation of these documents by a given IPRP member, either as a whole or in part, is not mandatory. Each IPRP member works within their own specific regulatory setting and some or all aspects of a document may, for a variety of reasons, not be applicable. Equally, a given IPRP member may for practical reasons choose to revise the format or written language of a model document.

BCS Biowaiver Assessment Report

<Proposed proprietary name>
<API> <Product strength(s)> <Product dosage form>

<Application/Dossier reference number>

Applicant: <Name of the Applicant>

IGDRP Country	
Date of application / Start of assessment	
Date of assessment report	
Deadline for comment *(if applicable*)	
IGDRP countries concerned	

Table of Contents

1 ADMINISTRATIVE INFORMATION

Proposed name / name of the medicine in the IGDRP country	
Active Pharmaceutical Ingredient - INN or common name of the API(s)	
Pharmaco-therapeutic group (ATC code/classification)	
Dosage form and strength(s)	
Dose	
Applicant/Sponsor name and address, contact information	
Final (test) product manufacturer Name and address	
API manufacturer(s) Name and address	
Dissolution (and solubility if applicable) testing laboratory name and address	
Test product details : batch size and batch number	
Reference product details : name, HCR, country of procurement	
Type of application (generic / formulation or other variation(s))	
Reviewer(s)/Assessor(s)	

2 GLOSSARY / ABBREVIATIONS

API	Active pharmaceutical ingredient / Drug Substance
Drug	Active pharmaceutical ingredient (API)
Drug product	Pharmaceutical product / medicine/ final product
FC / FDC	Fixed combination /FDC fixed dose combination
FPP	Finished pharmaceutical product
HCR	Holder of certificate of registration/marketing authorisation holder
NTI	Narrow therapeutic index
PHCR	Proposed holder of certificate of registration/marketing authorisation
PK	Pharmacokinetics
SPC	Summary of Product Characteristics / Product monograph / Package insert / labelling

3 SUMMARY: REQUIREMENTS and OUTCOMES

		Outcome
	Therapeutic range *(and dose)*	Narrow / Non-narrow
	Solubility	High / Low
	Stable	Yes / No
	Human absorption / Permeability:	>85 % / 90 % / < 85 %/90 % : High Low
	BCS class	I / II / III / IV
	Dosage form	Oral, systemic, IR same dosage form
	Comparison of excipients in the formulations	Sufficiently similar / Unacceptable differences
	Dissolution profiles	Similar and rapidly dissolving / similar and very rapidly dissolving/ Non-similar / Non-very rapidly dissolving / Non-rapidly dissolving
	CoAs	Assays within 5 %
	BCS Class I	
	Test and reference products very rapid or rapid dissolution	Yes / No
	Excipients that may affect BA the same (quantity and quality)	Yes /No
	BCS Class III	
	Test and reference products very rapid dissolution	Yes/No
	Excipients that may affect BA the same	Yes/No
	Other excipients very similar	Yes/No
	Benefit risk summary	Acceptable/ Not acceptable
	Conclusion	Approvable / Non-approvable

4 INTRODUCTION

Include *inter alia* the following as relevant:

4.1 Application objective

Reason or justification for application of Biowaiver, BCS Classification.

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).*

4.2 Status of the reference/originator product in other IGDRP/EU countries

Indicate which is the reference product in each country or jurisdiction.

Justify that the product applied for has the same dosage form *or is a pharmaceutical alternative if acceptable for a particular country.*

Address identicality / differences in API: same or different salts (both BCS class I) *for those countries where a different salt is acceptable*; same ester, ether, isomer, mixture of isomers, complex or derivative as reference product/originator. If different salts were accepted by a group of countries, it is necessary to show that the literature data justifies that both salts have the same toxicological profile. If data is not available in the literature the Applicant has to perform toxicological studies. In both cases this is additional data that needs to be assessed by other assessors.

Confirm that it is not sublingual, buccal or modified release. If the dosage form is an orodispersible tablet it is essential to demonstrate that the labelling of the reference product states that it is taken with water. Some countries / jurisdictions do not allow a BCS Biowaiver if the product is taken without water.

4.3 Basic pharmacokinetic information

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

4.4 Therapeutic indications and dose

Confirm that the API is not NTI. *Some countries do not allow a BCS Biowaiver for NTI APIs, different countries may have different criteria to define NTI API.* Examples from Health Canada guideline include: cyclosporine; digoxin; flecainide; lithium; phenytoin; sirolimus; tacrolimus; theophylline; warfarin. European Union, on a case-by-case basis the CHMP has agreed the NTID status of cyclosporine and tacrolimus. WHO TRS 937 Annex 8 also includes examples.

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

Reviewer's comments: *Discuss information on section 4* – including relevant background, appropriateness of choice of reference as appropriate, etc.

5 BCS BIOWAIVER ASSESSMENT

5.1 Solubility

Bibliographical and/or experimental (include source of information)

Note whether the following have been submitted:

- A complete report
- A protocol
- Dates and site 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

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 Cs values	Cs (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, pKa-1, pKa+1

Plot of Solubility (Concentration at saturation) vs. pH to identify the pH of minimum solubility.
Add plot

Notes for consideration:

Is the maximum/highest dose (or strength in some jurisdictions) that can be taken in a single administration according to the SPC, soluble in 250 ml in at least three buffers (preferably 1.2; 4.5; 6.8/7.5) in range pH 1 to 6.8/7.5 buffers and at the pKa if within specified range; at 37 °C +/- 1 °C?

Replicate determinations are required to achieve unequivocal solubility classification (shake flask method or other justified method). Solution pH should be verified prior and after addition of API to buffer.

Note whether the drug is stable in the buffers and whether the analytical method is stability-indicating. For example acetylsalicilic acid or capecitabine are highly soluble but unstable and the BCS biowaiver is not allowed in the European Union. Capecitabine can however be waived in the USA based on their recommendations for capecitabine.

In some jurisdictions the concentration at saturation is necessary and the demonstration of solubility in 250 ml does not suffice.

Reviewer's comments: *Discuss information on section 5.1*

5.2 Absorption (methods and results)

Include source of absorption data, literature data or experimental data

Human	
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 vivo* or *in vitro* permeability**	
Test system	
Concentrations	
Result	
Other information	
Influence of the transporters to absorption	

Notes for consideration

Complete absorption – measured extent of absorption is ≥ 85 % / 90 % generally related to high permeability, based on reliable investigations in human.

Discussion of the literature: mass balance and absolute BA studies.

Supportive information (e. g. Caco-2 monolayers, animal data)

Has complete absorption been shown for the highest dose in case the PK is non-linear (less than proportional due to saturation of absorption, e.g. gabapentin has complete absorption at low doses, but incomplete when the transporter is saturated)?

Dose linearity of pharmacokinetics. Absorption should be investigated at the highest dose if PK is not linear.

Reviewer's comments:

Discuss information on section 5.2

5.3 Comparison of Test and Reference formulations / Excipients

Component	Function	Test	Reference

Notes for consideration:

BCS I Similar quantities of the same excipients advisable

BCS III Very similar qualitatively and quantitatively to exclude different effects on membrane transporters

Well established excipients in usual/normal quantities. Description of function of each.

The test and reference product quantities of excipients that might affect bioavailability should be qualitatively and quantitatively the same, e.g. sorbitol, mannitol, sodium lauryl sulphate or other surfactants (e.g. PS80, Cremophors, Pluronics), and cyclodextrin.

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

Reviewer's comments:

Discuss information on section 5.3

5.4 *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	
Rate of Operation	
Dissolution Media	
Volume	

Temperature	
Sampling times	
Number of Dosage Units	
Sampling	
Filtration methods	*(in-line filtration)*
De-aeration method	

Usual experimental conditions are e.g.:

- Apparatus: paddle or basket
- Number of Dosage units: 12
- Volume of dissolution medium: 900 ml or less
- Temperature of the dissolution medium: 37±1 °C
- Agitation:
  paddle apparatus - usually 50 or 75 rpm *as applicable*;
  basket apparatus - usually 100 rpm (*specify for country)*
- Sampling schedule: e.g. 10, 15, 20, 30 and 45 min
- Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; USP/Ph.Eur. buffers recommended)
- Other conditions: no surfactant; in case of gelatine capsules or tablets with gelatine coatings the use of enzymes may be acceptable.

Notes on CoA comparison:

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.

Test Batches

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

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (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 Profiles for Lot # n = no. of units/ pH medium

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (0.1 N HCl)					
Mean					
%RSD					
pH 4.5 (Acetate)					
Mean					
%RSD					
pH 6.8 (Phosphate)					
Mean					
%RSD					
pH of minimum solubility					
Mean					
%RSD					

Mean dissolution profiles of 2 batches (24 tablets)

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (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 Batches: Country 1

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

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (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 Profiles for Lot # n = no. of units/ pH medium

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (0.1 N HCl)					
Mean					
%RSD					
pH 4.5 (Acetate)					
Mean					
%RSD					
pH 6.8 (Phosphate)					
Mean					
%RSD					
pH of minimum solubility					
Mean					
%RSD					

Mean dissolution profiles of 2 batches (24 tablets)

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (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 Batches: Country 2 (add as many countries as necessary)

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

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (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 Profiles for Lot # n = no. of units/ pH medium

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (0.1 N HCl)					
Mean					
%RSD					
pH 4.5 (Acetate)					
Mean					
%RSD					
pH 6.8 (Phosphate)					
Mean					
%RSD					
pH of minimum solubility					
Mean					
%RSD					

Mean dissolution profiles of 2 batches (24 tablets)

n pH of medium	% Label Claim Released x Min	x Min	x Min	x Min	x Min
pH 1 (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

Test product (batch number) *vs.* reference product (batch number, country 1):

Points considered for f2 calculation:

f_2:

Test product (batch number) vs. reference product (batch number, country 2):

Points considered for f2 calculation:

f_2:

Very rapidly dissolving: more than 85 % at 15 minutes

Rapid dissolving: more than 85 % at 30 minutes - calculation of similarity *f*2 factor

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

Since most countries do not accept the reference from another jurisdiction, two different tables are required for the reference products. Duplicate tables as necessary – tables for test should be on one page (two tables per page) and the reference tables on one page to facilitate comparison.

The results of the test will be the same for all jurisdictions *(but more than one batch of test and reference may be required in some regions). Then, 24 values will be available for each product. If only one batch is necessary, the additional tables can be deleted.*

Dissolution studies at the pH of minimum solubility may not be necessary in certain countries. In other countries they are necessary if that pH is different to the specified dissolution media.

Reviewer's comments: *Discuss information on section 5.4:* Sufficient/adequate number of batches, 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.

5.5 Dissolution testing laboratory

5.5.1 Audit(s)

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

5.5.2 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*

6 ESSENTIAL SIMILARITY / APPROPRIATENESS OF FINAL PRODUCT SPECIFICATIONS

(if applicable)

Notes for consideration:

If the approval is based on very rapid dissolution or rapid dissolution the specifications should not be at longer times, 15 and 30 min respectively. Include dissolution specification and actual profile characteristics, e.g. very rapid / rapid.

Reviewer's comments:
Discuss information on section.6

7 LIST OF OUTSTANDING ISSUES / DEFICIENCIES / PROPOSED QUESTIONS

8 CONCLUSIONS AND RECOMMENDATIONS

9 REFERENCES

Relevant regulatory guidelines and scientific papers.