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Biowaiver Assessment Report for Additional Strength(s) of Systemically Active Immediate Release Oral Dosage Forms

Bioequivalence Working Group for Generics

Version 1 - 4 February 2019

Version	Description of Change	Author	Effective Date
v 1	Original publication	BEWGG	4 February 2019

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 view 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 for Generics has developed a series of reference documents covering a number of technical and procedural aspects of biowaiver assessments.

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.

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Biowaiver Assessment Report

for Additional Strength(s) of Systemically Active Immediate Release Oral Dosage Forms[1]

<Proposed proprietary name>

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

<Application/Dossier reference number>

Applicant: <Name of the Applicant>

IPRP Country	
Date of assessment report	
Deadline for comment *(if applicable)*	
IPRP countries concerned	

[1] Some of the IPRP Agencies only accept additional strength biowaivers for immediate release oral dosage forms and those Agencies that accept for other dosage forms, under those circumstances, have different or further requirements to those included in this document. Contact the Agency in question for more details.

Table of Contents

1 ADMINISTRATIVE INFORMATION

Proposed name /Trade name of the medicine	
Active Pharmaceutical Ingredient - INN or common name of the API(s)	
Dosage form	
Strength(s)	
Name and Address of Applicant/Sponsor	

2 GLOSSARY / ABBREVIATIONS

API	Active pharmaceutical ingredient / Drug substance
Drug	Active pharmaceutical ingredient (API)
Drug product	Pharmaceutical product / Medicinal product / Medicine/ Final product
FC / FDC	Fixed combination /Fixed dose combination
SPC	Summary of Product Characteristics / Product Monograph / Package Insert / Labelling
NTI	Narrow therapeutic index

3 SUMMARY: REQUIREMENTS and OUTCOMES

Requirements	Outcome
Therapeutic Index	Narrow / Non-narrow
Solubility	High / Low
Dosage form	e.g., Tablet, Capsule
Pharmacokinetic Characteristics	Linear / Non-linear (less than proportional) / Non-linear (greater than proportional)
Qualitative composition of the excipients of the different strengths	Sufficiently similar / Unacceptable differences
Quantitative composition of the excipients of the different strengths	Proportional / Identical amount of excipients / Identical amount of excipients except filler (diluent) / Others (to be described)
Dissolution profiles	e.g., Similar and rapidly dissolving / Similar and very rapidly dissolving / Similar and non-rapidly dissolving / Non-similar
Certificates of Analysis	Assays within 5% Yes / No
Conclusion	Approvable / Non-approvable

4 ADDITIONAL STRENGTH BIOWAIVER

4.1 Application objective

Clearly state the reason for the application of a biowaiver for not providing bioequivalence study data for all proposed dose strengths.

Assessor's comments: *<Please comment here>*

4.2 Nature of the dosage form

Clearly state the nature of the proposed dosage form. Please state if all the strengths have the same dosage form and mechanism of release. If not, please justify.

Assessor's comments: *<Please comment here>*

4.3 Solubility of the drug

Bibliographical and/or experimental data may be submitted. If providing data generated by or on behalf of, the API or Drug Product manufacturer, please provide the date(s) and site of solubility study, a description of the solubility method and conditions used for the analysis of the API, and the corresponding solubility data.

Provide any cited references.

Assessor's comments: *<Please comment here>*

This information is not as essential as in the case of a BCS biowaiver, but it is always useful e.g. to understand and/or interpret the dissolution results.

Some jurisdictions might only require the QC method, but others may require dissolution data in several pH buffers. In some cases sink conditions may not be achieved; therefore, incomplete dissolution may be explained based on solubility limitations.

4.4 Pharmacokinetic characteristics of the drug(s)

State whether the drug displays linear or non-linear pharmacokinetics. State concentrations at which non-linearity occurs and provide any known explanations. Provide copies of any cited literature.

Assessor's comments: *<Please comment here>*

The linearity/non-linearity information is essential to waive bioequivalence studies for the additional strengths. The bioequivalence study must have been conducted with the most sensitive strength, except if there are safety/tolerability concerns.

4.5 Test product formulation(s)

Please provide details regarding the bioequivalence study Test product (biobatch) and the additional strengths for the Drug Product for which this biowaiver application is submitted. The tables below should be completed to describe all drug product ingredients and quantities including film-coating and capsule components.

Biowaiver batches should be at least of pilot scale (10% of production scale, or 100,000 units, whichever is greater).

	Test product (Biobatch)	**Additional strength 1**	**Additional strength 2**	**Additional strength 3**
Drug Product Batch number				
Batch size (number of dose units)				
Date of manufacture				
Expiry date				
Assay/Potency				
API lot number				

Ingredients (Quality Standard)	**Quantity in formulation (mg and %)**			
	Test product (Biobatch)	**Additional strength 1**	**Additional strength 2**	**Additional strength 3**

Note that the biobatch Test product is used as the Reference batch for comparison.

Amend the current tables or add additional tables if there is more than one biobatch or more than three additional strengths.

Assurances

☐ Yes ☐ No The different strengths are manufactured by the same manufacturing process.

Assessor's comment: *<If No, please describe and justify any differences>*

☐ Yes ☐ No The qualitative composition of the different strengths is the same.

Assessor's comment: *<If No, please describe and justify any differences>*

☐ Yes ☐ No The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of drug substances(s) is the same for all strengths *(for immediate release products, the coating components, capsule shell, colour agents, and flavours are not required to follow this rule).*

☐ Yes ☐ No The composition of the strengths are quantitatively identical in excipients, i.e. the quantity of all excipients are identical and only the quantity of drug is changed because it represents less than 5% or 10% of the weight, or less than 10 mg (where applicable). Alternatively, the difference in the quantity of drug between strengths is compensated with the filler to maintain the same core weight for all strengths.

Assessor's comments: *<If No, please describe and justify any differences>*

Level change according to Japan and South Korea

If you have the change level (such as Level A, B, C, D, I, and II as required in Japan or South Korea), please describe.

Assessor's comments: *<Please describe and justify any differences>*

4.6 *In vitro* dissolution comparison between the different strengths of the test product

Complete the dissolution summary table and applicable dissolution data tables as required.

Comparative dissolution profiles should be provided in at least three (3) media within the physiological range (pH 1 - 7.5) (e.g., water, 0.1N HCl, and pharmacopoeial buffer media at pH 4.5, 6.8 or 7.5) using a validated or proposed QC method. The following is an example of the experimental conditions:

- 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 rpm *as applicable*; Basket apparatus - usually 100 rpm
  State if a sinker was used
- 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 are recommended)
- Other conditions: No surfactant, except in case of the QC medium.
  (In case of gelatine capsules or tablets with gelatine coatings, the use of enzymes may be acceptable)

Summary of dissolution test method parameters

Apparatus	
Rate of Operation	
Dissolution Media (buffer composition)	
Volume	
Temperature	
Sampling times	
Sampling handling and storage	
Number of Dosage Units	
Sampling time (release)	
Filtration methods	*(in-line filtration or immediately after sampling)*
De-aeration method	
Reference pharmacopoeia	e.g., JP, USP, BP, Int. Ph

Dissolution Results for the Reference and Test Batches

Reference = Bioequivalence 'Test' batch (Biobatch)

Dissolution Profiles for Reference Batch number: XXXXX **Strength: XXX**

n = X units	% Label Claim Released				
	x Minutes	x Minutes	x Minutes	x Minutes	x Minutes
pH 1 (0.1 N HCl)					
Mean					
(Range)					
%RSD					
pH 4.5 (Acetate)					
Mean					
(Range)					
%RSD					
pH 6.8 (Phosphate)					
Mean					
(Range)					
%RSD					
Release medium (if different to above)					
Mean					
(Range)					
%RSD					

(Add as many strengths as necessary)

Dissolution Profiles for Test Batch number: XXXXX **Strength: XXX**

n = X units	% Label Claim Released				
	x Minutes	x Minutes	x Minutes	x Minutes	x Minutes
pH 1 (0.1 N HCl)					
Mean					
(Range)					
%RSD					
pH 4.5 (Acetate)					
Mean					
(Range)					
%RSD					
pH 6.8 (Phosphate)					
Mean					
(Range)					
%RSD					
Release medium (if different to above)					
Mean					
(Range)					
%RSD					

(Add as many strengths as necessary)

Dissolution profile comparison

Additional strength 1 of the Test product (batch number) *vs.* Bio-batch strength (Test batch of the strength employed in the bioequivalence study) (batch number):

Time points used for f2 calculation: <Insert here>

f_2: <Insert here>, if necessary

Additional strength 2 of the Test product (batch number) *vs.* Bio-batch strength (Test batch of the strength employed in the bioequivalence study) (batch number):

Time points used for f2 calculation: <Insert here>

f_2: <Insert here>, if necessary

Assessor's comments:

Discuss information on section 4.9:

i.e.; Low enough variability, adequate number of points to calculate f2, correct selection of points to calculate f2 (which varies between countries), similar, not more than 5 % difference in CoA assay values, etc.

In Japan and South Korea, you may use an alternative criteria based on average dissolution rate and the individual dissolution variability. If appropriate please complete the tables below.

Media	Agitation speed (rpm)	Comparison time (min)	Average dissolution rates			Equivalence criterion	Equivalence result
			Test	Reference	Differences		
pH1	50	15	98.8	90.0	+8.8	≥ 85% or ± 10%	Equivalence

Note: An example has been included to clarify what is required. The example should be deleted.

Media	Agitation speed (rpm)	Last comparison time (min)	Result		Equivalence result
pH6.8	50	60	The number of test product is out of range ± 15%	0/12	Equivalence
			The number of test product is out of range ± 25%	0/12	

Note: An example has been included to clarify what is required. The example should be deleted.

5 LIST OF OUTSTANDING ISSUES / DEFICIENCIES / PROPOSED QUESTIONS

Assessor's comments:

6 CONCLUSIONS AND RECOMMENDATIONS
