

**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.

**Biowaiver Assessment Report**

**for Additional Strength(s) of Systemically Active Immediate Release Oral Dosage Forms[[1]](#footnote-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 |  |

Table of Contents

1 ADMINISTRATIVE INFORMATION 4

2 GLOSSARY / ABBREVIATIONS 4

3 SUMMARY: REQUIREMENTS and OUTCOMES 5

4 ADDITIONAL STRENGTH BIOWAIVER 6

4.1 Application objective 6

4.2 Nature of the dosage form 6

4.3 Solubility of the drug 6

4.4 Pharmacokinetic characteristics of the drug(s) 6

4.5 Test product formulation(s) 7

4.6 *In vitro* dissolution comparison between the different strengths of the test product 8

5 LIST OF OUTSTANDING ISSUES / DEFICIENCIES / PROPOSED QUESTIONS 12

6 CONCLUSIONS AND RECOMMENDATIONS 12

# 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** |  |

# 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

# 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 |

# ADDITIONAL STRENGTH BIOWAIVER

## 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>* |

## 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>* |

## 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.* |

## 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.* |

## 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>* |

## *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>

f2: <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>

f2: <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.*

# LIST OF OUTSTANDING ISSUES / DEFICIENCIES / PROPOSED QUESTIONS

|  |
| --- |
| ***Assessor’s comments:*** |

# CONCLUSIONS AND RECOMMENDATIONS

|  |
| --- |
|  |

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. [↑](#footnote-ref-1)