|  |  |
| --- | --- |
| Date of submission |  |
| Application number | Master:Duplicate: |
| Product (proprietary) name | Master:Duplicate: |
| Active Pharmaceutical Ingredient API(s) |  |
| Applicant (name and address) |  |
| Manufacturer (name and address) |  |
| FPP Manufacturer(s) used for biowaiver batch(es) (name and address)FPP Manufacturer(s) applied for (name and address) |  |
| API Manufacturer (name and address) |  |
| API manufacturer(s) used in biowaiver test product(s) (name and address)API manufacturer(s) applied for (name and address) |  |
| Dosage form and strength(s) |  |
| Batch number and size (test product) |  |
| Date of manufacture (test product) |  |
| Study Protocol/SOP Number |  |
| Study Report / Reference number |  |
| Study date/s |  |
| Dissolution (and solubility if applicable) testing laboratory name and address |  |
| Foreign Reference product (if applicable)Batch Number & Expiry dateCountry of Procurement |  |
| South African Innovator/ Reference Product:Batch Number & Expiry dateApproved dose range |  |
| **For SAHPRA use only**Biowaiver assessment outcome  |  |

**Disclaimer** This document is adopted from the IPRP Bioequivalence Working Group for Generics (BEWGG) and reflects the views of SAHPRA. It should not be construed to represent the official views of any other given regulatory authority as well as those participating in the IPRP.

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**1** **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 / / labelling |

1. **SUMMARY: REQUIREMENTS AND OUTCOMES (FOR SAHPRA USE ONLY)**

|  |  |
| --- | --- |
| **Requirements**  | **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 |
|  |  |

**3 INTRODUCTION**

Include *inter alia* the following as relevant:

* 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).*

* 1. **Status of the reference/ innovator product in other recognised[[1]](#footnote-1) 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

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*.*

* 1. **Basic pharmacokinetic information**

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

* 1. **Therapeutic indications and dose**

Confirm that the API is not NTI (Narrow Therapeutic Index). *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.

|  |
| --- |
| Comments from review of *Section 3* – *For SAHPRA use only* |
| *Reviewer’s comments:**Discuss information on section 3* – includingrelevant background, appropriateness of choice of reference as appropriate, etc. |

1. **BCS BIOWAIVER ASSESSMENT**
	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**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **TheoreticalpH** | **Repeat** | **Observed pH** | **Adjusted pH** | **Individual Cs values** | **Cs (mean)** | **Quantity dissolved in 250 ml** |
| pH 1,2 | 123 |  |  |  |  |  |
| Intermediate pHs | 123 |  |  |  |  |  |
| pH 4,5 | 123 |  |  |  |  |  |
| Intermediate pHs | 123 |  |  |  |  |  |
| pH 6,8 | 123 |  |  |  |  |  |
| Other intermediate pH values **\*\*** | 123 |  |  |  |  |  |

**\*\*** 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 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, acetylsalicylic 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.

|  |
| --- |
| Comments from review of *Section 4.1* – *For SAHPRA use only* |
| *Reviewer’s comments:* |

* 1. **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.

|  |
| --- |
| Comments from review of *Section 4.2* – *For SAHPRA use only* |
| *Reviewer’s comments:* |

* 1. **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.

|  |
| --- |
| Comments from review of *Section 4.3* – *For SAHPRA use only* |
| *Reviewer’s comments:* |

* 1. ***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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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** | **% Label Claim Released** |
| pH of medium | **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:

f2:

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

Points considered for f2 calculation:

f2:

Very rapidly dissolving: more than 85 % at 15 minutes

Rapid dissolving: more than 85 % at 30 minutes - calculation of similarity ƒ2 factor

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

|  |
| --- |
| Comments from review of *Section 4.4* – *For SAHPRA use only* |
| *Reviewer’s comments:**Discuss information on section 4.4:* Sufficient/adequate number of batches (NOTE: It is required to have more than two batches per product.), 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 |

* 1. **Dissolution testing laboratory**
		1. **Audit(s)**

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

* + 1. **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.

|  |
| --- |
| Comments from review of *Section 4.5* – *For SAHPRA use only* |
| *Reviewer’s comments:* |

1. **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.

|  |
| --- |
| Comments from review of *Section5* – *For SAHPRA use only* |
| *Reviewer’s comments:* |

1. **LIST OF OUTSTANDING ISSUES / DEFICIENCIES / PROPOSED QUESTIONS *(FOR SAHPRA USE ONLY)***
2. **CONCLUSIONS AND RECOMMENDATIONS *(FOR SAHPRA USE ONLY)***
3. **REFERENCES**

## Relevant regulatory guidelines and scientific papers.

**UPDATE HISTORY**

|  |  |  |
| --- | --- | --- |
| **Date** | **Reason for update** | **Version and publication** |
| July 2019 | First publication: IPRP BCS Biowaiver Application Form released for implementation and comment | Version 1, July 2019 |
| December 2019 | Deadline for comment | December 2019 |
| April 2020 | Second publication: Streamlined and aligned to SAHPRA requirements and letterhead. Released for comment | Version 2, April 2020 |
| June 2020 | Comments from ITG working group  | Version 2, April 2020 |
| July 2020 | Amendments of administrative table, abbreviations, wording in sections 3.2 and punctuation in section 4 to comply with SAHPRA’s requirements. Addition of form number. Released for comment | Version 2, April 2020 |
| October 2020 | Comments from industry | Version 2, April 2020 |
| November 2020 | Third publication:Amendment of whole document: reformatting of margins to remove unused space at the start of each page; Change page numbering to page x of y; move update history table to the last page of the document.Amendment of administrative information of the product table, Clarification of some of the information required in sections 3.2 & 3.4;Removal of statement unintentionally included in form in section 5; Correction of section number in section 5;Released for implementation | Version 3, November 2020 |

1. Recognised regulatory authorities (RRAs) include EMA (Centralised Procedures), EU (Decentralised Procedures and MRPs), US FDA, Japan MHLW, Swissmedic, Health Canada, Australia’s TGA, UK MHRA, Zazibona, and WHO Prequalification (PQ) [↑](#footnote-ref-1)