|  |  |  |  |
| --- | --- | --- | --- |
| Therapeutic Goods Administration |  | | |
|  | TGA use only |  |
|  |  |  |

This form, when completed, will be classified as '**For official use only**'.  
For guidance on how your information will be treated by the TGA see: Treatment of information provided to the TGA at <<https://www.tga.gov.au/treatment-information-provided-tga>>.

# Biopharmaceutics Classification System (BCS)-based biowaiver template

* Refer to guidance document ‘[Completing the biowaiver templates](https://www.tga.gov.au/publication/guidance-15-biopharmaceutic-studies)’ when completing this template.
* **Do not** include any text in fields or text boxes indicated for “**TGA use only”**.

For more information, refer to [TGA website regarding bioequivalence data summary templates](https://www.tga.gov.au/form/summary-bioavailability-or-bioequivalence-study)

## Administrative information

|  |  |
| --- | --- |
| Active Pharmaceutical Ingredient (API) in Australian Approved Name format |  |
| Dosage form and strength(s) |  |
| Daily dose |  |
| Final (test) product manufacturer name and address |  |
| Dissolution testing laboratory name and address |  |
| Test product details: batch size and batch number |  |
| Reference product name, sponsor, and country of procurement |  |

## Summary of requirements and outcomes

Select the finding in the outcome column that applies to your proposed products (test products)

|  |  |
| --- | --- |
| **Requirements** | **Outcome** |
| Therapeutic range (and dose) | Narrow  Non-narrow |
| Solubility | High  Low |
| Stable drug substance throughout *in vitro* testing | Yes  No |
| Human absorption | >85%  <85% |
| Permeability | High  Low |
| BCS class | I  II  III  IV |
| Dosage form characteristics | Oral  Systemically acting  Immediate release  (Note, all three must apply) |
| Comparison of excipients in the formulations between test and reference products | Quantitatively - and qualitatively identical  Qualitatively identical but not quantitatively identical  Neither quantitatively nor qualitatively identical (only applicable for BCS class I) |
| Dissolution profiles | Similar and very rapidly dissolving  Similar and rapidly dissolving  Non-similar  Non-very rapidly dissolving  Non-rapidly dissolving |
| Certificates of Analysis (CoAs) | Difference between test and reference product assays within 5%  Yes  No |

|  |  |
| --- | --- |
| TGA use only - Comments for Section 2 | |
| Benefit risk summary | Acceptable  Not acceptable |
| Conclusion | Acceptable  Not acceptable |

## Introduction

Provide brief introduction of the drug substance and the proposed finished drug products (test products)

|  |
| --- |
|  |

Is the Active Pharmaceutical Ingredient (API) a narrow therapeutic index (NTI) drug substance?

|  |  |
| --- | --- |
| Yes | **Stop** The drug substance should not belong to the group of narrow therapeutic index drugs. Please discuss suitability of a BCS-based biowaiver with TGA if you wish to proceed further. To contact TGA, see [TGA contact details for enquiries about prescription medicines](https://www.tga.gov.au/prescription-medicines#contacts).  Provide location in the dossier of TGA correspondence regarding the suitability of a BCS-based biowaiver (if any): |
| No | Provide evidence to support the API is not a NTI below. |
|  | |

### 3.1 Application objective

Reason for application of biowaiver and BCS Classification

|  |
| --- |
|  |

Were the drug substance and test product used in the studies for the BCS-based biowaiver justification:

* manufactured by the same proposed drug substance and drug product manufacturers listed in Module 3, and
* manufactured in the same manner as proposed for marketing purposes?

|  |  |
| --- | --- |
| Yes | Go to section 3.2 |
| No | State the difference in the formulation proposed for marketing and those used for comparative dissolution studies and justify below why a BCS-based biowaiver can be applied: |
|  |

### 3.2 Comparison between the test and reference products

What were the similarities and differences between the test and reference products?

|  |
| --- |
|  |

### 3.3 Basic pharmacokinetic information

Was the mass balance and absolute BA studies conducted on the highest strength dose?

|  |  |
| --- | --- |
| Yes | Go to section 4 |
| No | Go to next question in this section |

Were linear pharmacokinetics observed over the dose range?

|  |  |
| --- | --- |
| Yes | Provide source of the evidence: |
| No | Please discuss suitability of a BCS-based biowaiver with TGA if you wish to proceed further. To contact TGA, see [TGA contact details for enquiries about prescription medicines](https://www.tga.gov.au/prescription-medicines#contacts).  Provide location in the dossier of TGA correspondence regarding the suitability of a BCS-based biowaiver (if any): |

|  |
| --- |
| TGA use only - Comments from review of Section 3 |
|  |

## BCS biowaiver assessment

### 4.1 Solubility

Location of the information

|  |  |
| --- | --- |
| Study report |  |
| Study protocol |  |
| Description of solubility method and conditions |  |
| Description and validation of the stability-indicating analytical method |  |

Dates of the study

|  |
| --- |
|  |

Name and address of the study site

|  |
| --- |
|  |

#### 4.1.1 Solubility method

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

### 4.1.2 Solubility at different pH values and replicates

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Theoretical pH | Repeat | Observed pH | Adjusted pH | Individual concentration at saturation (Cs) values | Cs (mean) | Quantity dissolved in 250 ml |
| pH 1.2 | 1 |  |  |  |  |  |
| 2 |  |  |  |
| 3 |  |  |  |
| Intermediate pH: | 1 |  |  |  |  |  |
| 2 |  |  |  |
| 3 |  |  |  |
| pH 4.5 | 1 |  |  |  |  |  |
| 2 |  |  |  |
| 3 |  |  |  |
| Intermediate pH: | 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

Insert the solubility (concentration at saturation) vs. pH plots based on the data provided in the table above to identify the pH of minimum solubility below.

|  |
| --- |
|  |

|  |
| --- |
| TGA use only - Comments from review of Section 4.1 |
|  |

### 4.2 Human absorption (methods and results)

#### 4.2.1 Absolute bioavailability (BA) (in human)

|  |  |
| --- | --- |
| Reference citation of the absolute BA data source |  |
| Oral dose |  |
| Intravenous dose |  |
| Number of subjects |  |
| Absolute BA result |  |

#### 4.2.2 Mass balance (in human)

|  |  |
| --- | --- |
| Reference citation of the mass balance data source |  |
| Dose |  |
| Number of subjects |  |
| Mass balance result |  |

#### 4.2.3 *In vivo* or *in vitro* permeability

|  |  |
| --- | --- |
| Test system |  |
| Concentration |  |
| Result |  |

#### 4.2.4 Other information

|  |  |
| --- | --- |
| Influence of the transporters to absorption |  |

|  |
| --- |
| TGA use only - Comments from review of Section 4.2 |
|  |

### 4.3 Comparison of test and reference formulations / excipients

|  |  |  |  |
| --- | --- | --- | --- |
| Ingredient | Function | Test product quantity | Reference product quantity (if known) |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

|  |
| --- |
| TGA use only - Comments from review of Section 4.3 |
|  |

### 4.4 *In vitro* dissolution comparison

Location of the information

|  |  |
| --- | --- |
| Study report |  |
| Study protocol |  |
| Batch information on test and reference batches including certificates of analysis (CoAs) |  |
| Validation of experimental analytical methods |  |
| Individual and mean results and respective summary statistics |  |

Dates of the study

|  |
| --- |
|  |

Name and address of the study site

|  |
| --- |
|  |

#### 4.4.1 Summary of dissolution test method parameters

|  |  |
| --- | --- |
| Apparatus | Are sinkers used?  Yes  No |
| Rate of operation | 50 rpm for paddle  100 rpm for basket  other system:  If other system was selected, provide explanation: |
| Dissolution media |  |
| Volume |  |
| Temperature |  |
| Sampling times |  |
| Number of Dosage Units |  |
| Sample handling and storage |  |
| Filtration methods (e.g. in-line filtration or immediately after sampling) |  |
| De-aeration method |  |

##### 4.4.1.1 Test batch dissolution results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Batch number: | | | | n =       dosage units/ pH medium | | |
| n  pH of medium | % Label Claim Released | | | | | |
| (Mins) | (Mins) | (Mins) | | (Mins) | (Mins) |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH of minimum solubility: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Batch number: | | | | n =       dosage units/ pH medium | | |
| n  pH of medium | % Label Claim Released | | | | | |
| (Mins) | (Mins) | (Mins) | | (Mins) | (Mins) |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH of minimum solubility: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |

Provide the mean dissolution results of the above test batches below:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Mean of the dissolution results | | | | | |
| n  pH of medium | % Label Claim Released | | | | |
| (Mins) | (Mins) | (Mins) | (Mins) | (Mins) |
| pH: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| pH: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| pH: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| pH of minimum solubility: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |

##### 4.4.1.2 Reference batch dissolution results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Batch number: | | | | n =       dosage units/ pH medium | | |
| n  pH of medium | % Label Claim Released | | | | | |
| (Mins) | (Mins) | (Mins) | | (Mins) | (Mins) |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH of minimum solubility: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Batch number: | | | | n =       dosage units/ pH medium | | |
| n  pH of medium | % Label Claim Released | | | | | |
| (Mins) | (Mins) | (Mins) | | (Mins) | (Mins) |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |
| pH of minimum solubility: | | | | | | |
| Mean |  |  |  | |  |  |
| %RSD |  |  |  | |  |  |

Provide the mean dissolution results of the above reference batches below:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Mean of the dissolution results | | | | | |
| n  pH of medium | % Label Claim Released | | | | |
| (Mins) | (Mins) | (Mins) | (Mins) | (Mins) |
| pH: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| pH: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| pH: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |
| pH of minimum solubility: | | | | | |
| Mean |  |  |  |  |  |
| %RSD |  |  |  |  |  |

#### 4.4.2 Dissolution profile comparison

|  |  |
| --- | --- |
| Strength: | Test product batch number:  Reference product batch number: |

|  |  |  |  |
| --- | --- | --- | --- |
| pH | Similarity factor (f2) | Time points used for f2 calculation | Discussion of dissolution profile similarity\* |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

\* Discussion provided **must not** be in terms of clinical/therapeutical relevance (i.e. *in vitro* *in vivo* correlation).

|  |
| --- |
| TGA use only - Comments from review of Section 4.4 |
|  |

### 4.5 Testing laboratory

#### 4.5.1 Audit(s)

|  |  |
| --- | --- |
| Name of testing facility | Location of internal quality assurance methods and results |
|  |  |
|  |  |

#### 4.5.2 GLP compliance/certification

|  |  |  |
| --- | --- | --- |
| Name of the testing facility | Location of the monitoring, auditing or inspection reports | Location of the compliance certifications/accreditations |
|  |  |  |
|  |  |  |

|  |
| --- |
| TGA use only - Comments from review of Section 4.5 |
|  |

## Essential similarity/appropriateness of drug product specification (if applicable)

|  |  |
| --- | --- |
| What are your proposed drug product dissolution specifications? |  |

Do the proposed drug product dissolution specifications reflect the dissolution profile characteristics in this BCS-based biowaiver?

|  |  |
| --- | --- |
| Yes ► | Go to section 6 |
| No ► | Justify why wider dissolution specifications are proposed: |

|  |
| --- |
| TGA use only - Comments from review of Section 5 |
|  |

## References of relevant regulatory guidelines and scientific papers

|  |
| --- |
|  |

## List of questions to the applicant

|  |
| --- |
| TGA use only – List of questions |
|  |

## Applicant’s response to the list of questions

|  |
| --- |
|  |

## TGA’s assessment and conclusion

TGA’s assessment of applicant’s responses

|  |
| --- |
| TGA use only – Assessment of applicant’s answers to the list of questions |
|  |

TGA’s overall conclusion and recommendations

|  |
| --- |
| TGA use only – Conclusion and recommendations |
|  |