|  |  |
| --- | --- |
| 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  |
| npH 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  |
| npH 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  |
| npH 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  |
| npH 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 |
|       |