Australian Government
Department of Health
Therapeutic Goods Administration

Completing the biowaiver templates

Information for applicants

Version 1.0, December 2019

TGA Health Safety Regulation

Contents

Introduction

This document will assist applicants completing the following biowaiver templates for inclusion in an application for a new prescription generic medicine:

- Biopharmaceutics Classification System (BCS)-based biowaiver template
- Additional strengths biowaiver template

The following sections include information and instructions to clarify what is required in certain sections of the templates.

Information related to biowaivers can be included in different places in a dossier even when following Common Technical Document (CTD) protocol. The biowaiver templates consolidate key information and the locations of critical data in one place.

We will use the completed template to record our evaluation comments. The amended template will then be included as part of the assessment reports.

When to use a biowaiver template

Biopharmaceutics Classification System based biowaiver template

Complete the Biopharmaceutics Classification System (BCS)-based biowaiver template when your submission contains a BCS-based biowaiver.

If you have multiple strengths in your application, complete only one BCS-based biowaiver template for all proposed strengths.

For more information about BCS-based biowaivers, refer to the European Union Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) adopted by TGA.

Additional strengths biowaiver template

Complete the additional strengths biowaiver template when:

- the proposed product is a systemically active immediate release oral dosage form, and
- you have proposed multiple strengths in your submission, and
- you have not included a bioequivalence study for all proposed strengths.

For more information about additional strength biowaivers, refer to European Union Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1/Corr**.

Including biowaiver templates in an application

Inclusion in Module 1 of the CTD

Submit the completed template in your dossier. It must be included in:

- pdf format
- CTD Module 1.9.2

The completed template in Microsoft Word or rich text (RTF) formats should be made available upon request.

For more information about CTD and dossier requirements, refer to the following TGA webpages:

- Common Technical Document (CTD)
- Electronic submissions
- General dossier requirements

If you have trouble accessing documents on the TGA website, refer to TGA webpage on accessing documents.

Replacing existing mandatory requirements

Applications for new generic medicines that include a BCS-based biowaiver usually require CTD Module 2.5 to be completed.

When you submit a completed BCS-based biowaiver template, Module 2.5 is generally not needed.

Exception

If the proposed Product Information (PI) contains clinical information that is different to the reference product's PI, you must provide Module 2.5 in addition to the completed BCS-based biowaiver template.

Related templates

Bioequivalence Study Information Form (BSIF)

There is a TGA template to summarise bioequivalence studies, i.e. Bioequivalence Study Information Form (BSIF). This template can be submitted in conjunction with the additional strengths biowaiver template. For further information, refer to TGA guidance for BSIF.

Equivalent overseas templates

If you have had an application **accepted** for evaluation by a comparable overseas regulator and the dossier included any of the following IPRP templates:

- BCS-based biowaivers

- Additional strength biowaivers (immediate- and modified-release solid oral dosage forms)

Then you can include the completed template in your application to the TGA.

They are considered equivalent to a completed TGA biowaiver template. Include it in your Australian dossier in Module 1.9.2 instead of the TGA templates.

The reduced CTD requirements will also apply when IPRP BCS-based biowaiver template is provided, as detailed in Replacing existing mandatory requirements.

Completing the biowaiver templates

When completing the templates:

- provide **succinct** and **accurate** responses
- check you have included all information
- check you have included correct references.

Do not change the format or content of the template (heading, instructions, requests and tables) unless instructed to do so (see below).

Locating information from the dossier

Many questions in the template request the location of a piece of information within the dossier. The responses to this type of questions must include:

- the module
- the volume
- the tab index
- the page number.

For example:

- 1.9.2, Solubility study report, p 5

The use of hyperlinks to the data within the dossier is preferable as this will greatly assist in the evaluation process.

Sourcing evidence from literature

When your response relies on publically available information, published literature or any other third party source, this information must be easily accessible to the evaluators. You must:

- provide a full copy of the information, and
- in your response, state where the full copy is located (refer to instructions above on Locating information from the dossier).

Attaching information

If your response to a question in the template requires further information, you can add attachments at the end of the document. Include a link in your response to where the attachment is located in the template by creating a hyperlink.

Caution on the size of electronic documents when submitted via email

Ensure the email containing the completed template is in total less than 30MB For more information, see TGA's general dossier requirements submitted via email.

Information needed in responses

Guidance on the type of information you should provide, and how you should present it, for some sections in each of the template is given below, under the corresponding section titles.

- BCS-based biowaiver template
- Additional strength biowaiver template

BCS-based biowaiver template

Section 3 - Introduction

Under 'Provide brief introduction of the drug substance and the proposed finished drug products (test products)' provide the following information, as relevant:

- physiochemical properties of the active pharmaceutical ingredient (API), such as particle size distribution and polymorphic form
- proposed strength of products (test products)
- dosage form (for example, uncoated tablet, gelatin hard capsule, orodispersible tablet) and if all test products have the same dosage form

Under 'Is the Active Pharmaceutical Ingredient (API) a narrow therapeutic index (NTI) drug substance?' if you answer 'No', address the margin between the minimum effective and minimum toxic plasma concentration of the drug, in the space for supporting evidence.

For instance, by considering issues such as dose titration, different dosages used in different therapeutic areas, experience with overdose, animal toxicity studies, etc.

3.1 - Application objective

Under 'Reason for application of biowaiver and BCS Classification' provide the following information:

- address if the test product meets the summary requirements for a BCS-based biowaiver according to Appendix III of CPMP/EWP/QWP/1401/98 Rev 1/Corr**
  - if there are any deviations from the guideline, justify your approach
- state the BCS classification of your proposed products.

3.2 - Comparison between the test and reference product

Under 'What were the similarities and differences between the test and reference products?' address the following (if relevant):

- reference product trade name, dosage form, API and API quantity per single unit
  - if the dosage form is an orodispersible tablet, confirm the reference product must be taken with water and include location of the evidence. This evidence can be, for example, dose and method of administration on the product label or packaging insert.
- confirm if the test and reference product have the same dosage form, API and BCS Classification.
  - if the test and reference products are pharmaceutically alternatives, justify why they are suitable to be used for comparative studies. This includes:

When providing information based on experimental studies, include the location in the dossier of the experimental study reports in the space to include literature citation (for example, free text field to include 'Reference citation of the absolute BA data source').

4.2.3 - In vivo or in vitro permeability

Other supportive information could be provided for permeability, for example, Caco-2 monolayers studies or animal study. Ensure you have included the location in the dossier of the full study report in the space provided for 'test system' (see instructions above on how to locate information from the dossier).

Alternatively, attach this information in the template (refer to instructions above on attaching information).

4.3 - Comparison of test and reference formulations / excipients

Choose one of the following options to provide test and reference formulations / excipients information:

- Complete the table and modify the table as necessary by:
  - adding additional rows
  - deleting unused rows
  - adding extra tables for additional strengths
- You may replace the table with a table that you originally prepared for the submission, **if** the information in your table contains the **same** requested information in the template. The replaced table should **not** be an image or a picture.

If you are not clear with ingredient function for the reference product, leave the function information 'blank' in the table.

4.4.1.1 - Test batch dissolution results

In vitro dissolution should be investigated on more than one single batch. Two tables are prepared for two batches of the same strength product.

Provide mean dissolution results for all the test batches in the 'Mean of the dissolution results' table.

Choose one of the following options to provide dissolution results:

- Complete the tables and modify as necessary by:
  - adding rows for studies conducted using buffer not listed in the table
  - adding columns to add more sampling time points
  - deleting unused rows
  - if there are more than one batch, strength or API,

    adding tables

    indicating the strength or API above the dissolution tables.
- You may replace the table with a table that you originally prepared for the submission, **if** the information in your table contains the **same** requested information in the template. The replaced table should **not** be an image or a picture.

For more information on comparative dissolution profiles refer to CPMP/EWP/QWP/1401/98 Rev 1/Corr** Appendix III IV.1 *In vitro* Dissolution.

4.4.1.2 - Reference batch dissolution results

Follow the instructions given previously for section 4.4.1.1 above to include the reference product dissolution results.

4.4.2 - Dissolution profile comparison

The dissolution profile comparison table for the test and reference products in the template is provided only for one product strength. Add more tables as required for other strengths. Delete unused rows.

4.5.1 – Audit(s)

Choose one of the following options to provide internal quality assurance audit information:

- Complete the table, adding more rows as needed, or
- You may replace existing tables with tables which contains the **same** information **if** these have been included in dossier. The replaced table should **not** be an image or a picture.

4.5.2 - GLP compliance/certification

Follow the instructions given previously for section 4.5.1 above to include GLP compliance/certification information.

Section 5 - Essential similarity/appropriateness of drug product specification (if applicable)

When answering 'what are your proposed drug product dissolution specifications?' consider if the specification limit is based on very rapid dissolution or rapid dissolution.

If so, the proposed specifications should not be at longer times. For example, 15 min for very rapid dissolution and 30 min for rapid dissolution.

Section 8 – Applicant's response to the list of questions

Only complete this section if we have raised questions during the evaluation.

Our questions will be located in section 7 of this template under the space provided for 'TGA use only – List of questions'. You may also find a copy of the questions raised in the consolidated s31 request letter.

If you intend to attach any information as part of your answer to this section, refer to attaching information section above.

Additional strengths biowaiver template

Section 3 – Additional strength biowaiver

3.1 - Application objective

Under 'Reason for the application of a biowaiver for not providing bioequivalence study data for all proposed dose strengths' provide the following information, as relevant:

- Address if the test product meets the biowaiver criteria according to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**.

If there are any deviations from the guideline, justify your approach.

3.3 - Solubility

Solubility of the drug substance can be based on literature or experimental data. If solubility is based on experimental data, when answering 'What is the solubility of the drug substance?' include the following:

- the date(s) and site of solubility study
- a brief description of the solubility method
- conditions used for the analysis of the API
- location in the dossier of the solubility data.

3.4 – Pharmacokinetic characteristics

Under 'provide evidence on whether the API is NTI' provide the following:

- narrow therapeutic range designation on the reference product labelling including Product Information and Consumer Medicine Information, or
- address the margin between the minimum effective and minimum toxic plasma concentration of the drug. For instance, by considering issues such as dose titration, different dosages used in different therapeutic areas, experience with overdose, animal toxicity studies, etc.

3.5.1 - Product details

Complete the product detail table and modify the table as necessary by:

- adding more columns if there are more than three (3) additional strengths
- deleting unused columns

3.5.2 - Product formulation(s)

Provide all drug product ingredients and quantities including film-coating and capsule components in the table provided. Modify the table as necessary by:

- adding additional rows or columns
- deleting unused rows or columns

3.6.2 - Dissolution results of biobatch

Choose one of the following options to provide dissolution results:

- Complete the table and modify as necessary by:
  - adding rows for studies conducted using buffer not listed in the table
  - adding columns to add more sampling time points
  - deleting unused rows
  - if there are more than one batches or API,

    adding tables, and

    For different API, indicate APIs above the dissolution tables.

- You may replace the table with a table that you originally prepared for the submission, **if** the information in your table contains the **same** requested information in the template. The replaced table should **not** be an image or a picture.

3.6.3 - Dissolution results of additional strengths

Follow the instructions given previously for section 3.6.2 above to include the reference product dissolution results.

Section 5 - Applicant's response to the list of questions

Only complete this section if we have raised questions during the evaluation.

Our questions will be located in section 4 of this template under the space provided for 'TGA use only – List of questions'. You may also find a copy of the questions raised in the consolidated s31 request letter.

If you intend to attach any information as part of your answer to this section, refer to attaching information section above.

Version history

Version	Description of change	Author	Effective date
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