South African Health Products Regulatory Authority
Building A
Loftus Park
Arcadia
Pretoria

ADDITIONAL STRENGTH BIOWAIVER APPLICATION FORM[1]

Date of submission	
Application number	Master: Duplicate:
Product (proprietary) name	Master: Duplicate:
Active Pharmaceutical Ingredient API(s)	
Applicant (name and address)	
FPP Manufacturer(s) used for biowaiver batch(es) (name and address)	
FPP Manufacturer(s) applied for (name and address)	
API manufacturer(s) used in biowaiver test product(s) (name and address)	
API manufacturer(s) applied for (name and address)	
Pharmaceutical form and strength(s)	
Batch number and size (test product –lower strength)	
Date of manufacture (test product – lower strength)	
Study Protocol/SOP number and	
Study Report /Reference number	
Test product (bio batch) Batch Number & Expiry date	
Study date/s	
Dissolution testing laboratory (name and address)	
For SAHPRA use only Biowaiver assessment outcome	

Disclaimer

This document is adopted from the WHO 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 WHO-PQ.

[1] Report format adapted from WHO Application form: Application for biowaiver: additional strength https://extranet.who.int/prequal/content/bioequivalence-0

This application form is designed to facilitate information exchange between the applicant and SAHPRA if a biowaiver is requested for additional strength(s) of the submitted product(s**). This form is not to be used, if the applicant seeks to waive bioequivalence studies, based on the Biopharmaceutics Classification System (BCS),** in which situation a separate SAHPRA's *Biopharmaceutics Classification System (BCS) Based Biowaiver Application Form* should be used.

A request for a waiver from the requirement for conducting bioequivalence studies on additional strengths of the product submitted for assessment to SAHPRA can be made based on the proportionality of the formulations of the series of strengths. If additional strengths are proposed and a biowaiver for these strengths is sought, the information requested from page 3 onwards of this document should be provided.

For further guidance, please consult:

- SAHPRA Guidelines

Employing the dissolution conditions described in the guidelines referenced above, in vitro dissolution data comparing the different strengths of the submitted product, one of which is the reference strength, must be provided.

The format of the dissolution study report(s) provided in support of this waiver request should be consistent with the format employed as a part of a BCS-based biowaiver application.

Final assessment of the proportionality of the proposed formulations and the acceptability of the comparative dissolution data will be made during evaluation of the Quality part of the dossier.

General instructions:

- Please review all the instructions thoroughly and carefully prior to completing the current Application Form.
- Provide as much detailed, accurate and final information as possible.
- Please include a cross-reference to the exact location of the documentation in the CTD. For example, in section 2.4 indicate in which section of the CTD the Certificate of Analysis can be found.
- **Please include the application form in both MS Word and signed pdf format in the working documents folder.**
- Before submitting the completed application form, kindly check that you have provided all requested information and enclosed cross-references to the exact location of all requested documents.
- Should you have any questions regarding this procedure, please contact SAHPRA via e-mail, enquiries@sahpra.org.za.

Signed Attestation		
I, the undersigned, certify that the information provided in this application and the attached documents is correct and true		
Name of Responsible Pharmacist / Pharmacist Authorised to Communicate with the Health Authority	Signature:	Date:
Title, Company:	Email Address:	Telephone Number:

1 TEST PRODUCT

1.1 Tabulation of the composition of formulation proposed for marketing

- Please state the location of the master formulae in the quality part of the submission.
- For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating or hard capsule, if any.
- Biowaiver batches should be at least of pilot scale (10 % of production scale or 100 000 capsules or tablets, whichever is greater) and manufacturing method should be the same as for production scale.

Composition of the batch used for comparative dissolution studies				
Batch number for biowaiver batch				
Batch size (number of unit doses)				
Date of manufacture				
Expiry date				
Comments, if any				
Unit dose compositions and FPP batch composition				
Ingredients (Quality standard)	**Unit dose (mg)**	**Unit dose (%)**	**Biowaiver batch (kg)**	**Biowaiver batch (%)**

1.2 Potency (measured content) of test product as a percentage of label claim as per validated assay method

This information should be cross-referenced to the location of the Certificate of Analysis in the submission.

<< Please enter information here >>

1.3 Pharmacokinetics

- State whether the drug displays linear or non-linear pharmacokinetics
- Provide literature-based support for your response and append all references cited in the response and state the location of these references in the dossier.
- State concentrations at which non-linearity occurs and any known explanations. Particular attention should be paid to absorption and first-pass metabolism

<< Please enter information here >>

Comments from review of *Section 1.1 - 1.3 – For SAHPRA use only*
Reviewer's comments:

2 REFERENCE STRENGTH

2.1 Reference strength

In this context, the reference strength is the strength of the FPP that was compared to the SAHPRA Comparator product in an in vivo bioequivalence study.

2.2 Tabulation of batch information for the reference strength

The biobatch of the reference strength (batch employed in the in vivo bioequivalence study) should be employed in the comparative dissolution studies.

Batch information for batch used for comparative dissolution studies				
Batch number				
Batch size (number of unit doses)				
Date of manufacture				
Expiry date				
Comments, if any				
Unit dose compositions and FPP batch composition				
Ingredients (Quality standard)	**Unit dose (mg)**	**Unit dose (%)**	**Batch (kg)**	**Batch (%)**

2.3 Batch confirmation

If the batch of reference strength employed in the comparative dissolution studies was not the biobatch of the reference strength (batch employed in the in vivo bioequivalence study), the following information should be provided:

- Batch number of biobatch
- Justification for use of a batch other than the biobatch
- Comparative dissolution data for batch employed vs. (historical data for) biobatch
- Indicate the exact location of the executed batch manufacturing records (BMRs) for batch employed in dissolution studies in the submission

<< Please enter information here >>

2.4 Potency (measured content) of reference product as a percentage of label claim as per validated assay method

This information should be cross-referenced to the location of the Certificate of Analysis in the submission.

<< *Please enter information here* >>

Comments from review of *Section 2.1 - 2.4 – For SAHPRA use only*
Reviewer's comments:

3. COMPARISON OF TEST AND REFERENCE STRENGTHS

3.1 Tabulation of batch information for the test and reference strengths

For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating or hard capsule, if any.

Component and Quality Standard	**Function**	**Strength (label claim)**			
		XX mg		**XX mg**	
		Quantity per unit	**% ***	**Quantity per unit**	**%***
TOTAL					

each ingredient expressed as a percentage of the total core

3.2 Confirmation of proportionality

The applicant should confirm that the test and reference strength formulations are directly proportional. Any deviations from direct proportionality should be identified and justified in detail.

<< *Please enter information here* >>

Comments from review of *Section 3.1 - 3.2 – For SAHPRA use only*
Reviewer's comments:

4. COMPARATIVE IN VITRO DISSOLUTION: STUDIES COMPARING DIFFERENT STRENGTHS OF THE TEST PRODUCT

- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- **As per the quality and dissolution guidelines (SAHPRA Quality and Bioequivalence Guideline and Dissolution Guideline), comparative dissolution studies should be conducted in pH 1,2, 4,5, and 6,8 media. If the proposed dissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.**
- Summary information regarding the comparative dissolution studies should be included below to provide a complete summary of the data supporting the biowaiver request.

State the exact location of the following documents:

- the dissolution study protocol or SOP in the submission
- the dissolution study report(s) in the submission
- the analytical method validation report in the submission

<< Please confirm the location of the documents in the CTD dossier >>

4.1 Summary of the dissolution conditions and method described in the study report(s)

Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported.

4.1.1 Dissolution study dates

Please indicate dates when the dissolution study was conducted

4.1.2 Dissolution media: Composition, temperature, volume, and method of de-aeration

<< *Please enter information here* >>

4.1.3 Type of apparatus and agitation speed(s) employed

<< *Please enter information here* >>

4.1.4 Number of units employed

<< *Please enter information here* >>

4.1.5 Sample collection: method of collection, sampling times, timing and method of filtration, sample handling, and storage

<< *Please enter information here* >>

4.1.6 Deviations from sampling protocol

<< *Please enter information here* >>

4.2 Summarize the results of the dissolution study(s)

Please provide a tabulated summary of individual and mean results with % CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.

<< *Please enter information here* >>

4.3 Summarize conclusions taken from dissolution study(s)

Please provide a summary statement of the studies performed.

<< Please enter information here >>

Comments from review of *Section 4.1 - 4.3 – For SAHPRA use only*
Reviewer's comments:

5 COMPARATIVE *IN VITRO* DISSOLUTION:

STUDIES COMPARING EACH STRENGTH OF THE TEST PRODUCT TO EQUIVALENT STRENGTH OF COMPARATOR PRODUCT; ONLY TO BE SUBMITTED IN CASE IN VITRO DISSOLUTION DATA BETWEEN DIFFERENT STRENGTHS OF TEST PRODUCT (see Section 4) ARE NOT SIMILAR

- This section is applicable in cases where, due to low solubility of the active pharmaceutical ingredient, similar comparative dissolution between differing strengths is difficult to achieve. The SAHPRA comparator product as per the requirements in the Quality and Bioequivalence guideline [2.02] should be employed.
- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- **As per the Quality and Dissolution guidelines (Quality and Bioequivalence Guideline and Dissolution Guideline), comparative dissolution studies should be conducted in pH 1,2, 4,5, and 6,8 media. If the proposed dissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.**
- Summary information regarding the comparative dissolution studies should be included below to provide a complete summary of the data supporting the biowaiver request.

5.1 Purchase, shipment and storage of the comparator product

As per the documentation requirements for comparator products, please attach relevant copies of documents (e.g. receipts) proving the stated conditions

<< *Please enter information here* >>

5.2 Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory under the same conditions as the test product.

This information should be cross-referenced to the location of the Certificate of Analysis in the submission.

<< *Please enter information here* >>

5.3 Please state the location of:

- the dissolution study protocol or SOP in the dossier,
- the dissolution study report(s) in the dossier
- the analytical method validation report in the dossier

<< *Please enter information here* >>

5.4 Summary of the dissolution conditions and method described in the study report(s)

Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported.

5.4.1 Dissolution media: Composition, temperature, volume, and method of de-aeration

<< *Please enter information here* >>

5.4.2 Type of apparatus and agitation speed(s) employed

<< *Please enter information here* >>

5.4.3 Number of units employed

<< *Please enter information here* >>

5.4.4 Sample collection: method of collection, sampling times, method of filtration, sample handling and storage

<< *Please enter information here* >>

5.4.5 Deviations from sampling protocol

<< *Please enter information here* >>

5.5 Summarize the results of the dissolution study(s)

Please provide a tabulated summary of individual and mean results with % CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.

<< *Please enter information here* >>

5.6 Summarize conclusions taken from dissolution study(s)

Please provide a summary statement of the studies performed.

<< *Please enter information here* >>

Comments for Review of Section 5.1-5.6 – *For SAHPRA use only*

Conclusions and recommendations – *For SAHPRA use only*

Date	**Reason for update**	**Version and publication**
July 2019	First publication: WHO Additional Strength 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, general instructions and wording in sections 1.2, 2.3, 2.4, 4 & 5 to comply with SAHPRA's requirements. Addition of form number. Released for comments	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	Version 3, November 2020

	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, Expansion of General Instructions; Clarification of some of the information required in sections 1.3, 2.2, 2.3, 2.4, 2.5, 4.1, 4.3, 5.1, 5.2 & 5.3. Released for implementation	