Application for a Biowaiver: Additional Strength

This application form is designed to facilitate information exchange between the applicant and the NAFDAC 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 *Biowaiver Application Form: Biopharmaceutics Classification System (BCS)* 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 NAFDAC 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:

- NAFDAC Guideline on Registration Requirement to establish Interchangeability of Generic Pharmaceutical Products.
- NAFDAC Quality Guidelines for the Registration of Pharmaceutical Products for Human Use.

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. Note that the greyed areas are NOT to be completed in by the applicant but are for NAFDAC use only.
- Please enclose the required documentation in full and state in the relevant sections of the application form the exact location (annex number) of the appended documents.
- The appended electronic documents should be clearly identifiable by their file names, which should include the product name and annex number.
- Please provide the application form as an MS Word file.
- Before submitting the completed application form, kindly check that you have provided all requested information and enclosed all requested documents.
- Should you have any questions regarding this procedure, please contact us at registration@nafdac.gov.ng with the subject prefix "Additional Strength Form-..."

This form should be properly filled out in MSWord format and be placed in Module One of the Common Technical Document (CTD) along with all its annexes and submitted as CD-ROM to Registration and Regulatory Affairs Directorate, NAFDAC (detail of address provided below). A signed cover letter affirming the authenticity of the information provided in this form should be submitted along with the CD-ROM:

CONFIDENTIAL
Director General
Attention: The Director, Registration and Regulatory Affairs
Product Name:
NAFDAC
Plot 1 Isolo Industrial Area
Apapa-Oshodi Expressway
Isolo, Lagos

Administrative data

1. International Non-proprietary Name of active ingredient(s)	
	< Please enter information here >
2. Dosage form and strengths	
	< Please enter information here >
3. Product NAFDAC Reference numbers *(if available for any strengths of the product line, including the reference strength)*	
	< Please enter information here >

4. Name of applicant and official address	
	< Please enter information here >

5. Name of manufacturer of finished product and official address	
	< Please enter information here >

6. Name and address of the laboratory or contract research organization(s) where the biowaiver dissolution studies were conducted *(if applicable)*	
	< Please enter information here >

I, the undersigned, certify, that the information provided in this application and the attached documents is correct and true

Signed on behalf of:

<***Company***>

_____ (Date)

_____ (Name and title)

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 this biowaiver 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 >>

1.4 Comments from review of Section 1.1 - 1.3 – *NAFDAC use only*

2. REFERENCE STRENGTH

2.1 Reference strength

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

2.2 Tabulation of batch information for the reference strength

The bio batch 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 (%)

Batch confirmation

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

- Batch number of bio batch
- Justification for use of a batch other than the bio batch
- Comparative dissolution data for batch employed vs. (historical data for) bio batch
- As an Appendix, executed batch manufacturing records (BMRs) for batch employed in dissolution studies

<< Please enter information here >>

2.3 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 this biowaiver submission.

<< Please enter information here >>

2.4 Comments from review of Section 2.1 – 2.4 – *NAFDAC use only*

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

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 >>

3.2 Comments from review of Section 3.1 – 3.2 – *NAFDAC use only*

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 guideline (Guideline on Submission of Documentation for a Multi-source (Generic) Finished Pharmaceutical Product (FPP): Quality Part, Appendix 1), 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.

4.1 Please state the location of:

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

<< Please enter information here >>

4.2 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.

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

<< Please enter information here >>

4.2.1 Type of apparatus and agitation speed(s) employed

<< Please enter information here >>

4.2.2 Number of units employed

<< Please enter information here >>

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

<< Please enter information here >>

4.2.4 Deviations from sampling protocol

<< Please enter information here >>

4.3 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 >>

4.4 Summarize conclusions taken from dissolution study(s)

Please provide a summary statement of the studies performed.

<< Please enter information here >>

4.5 Comments from review of Section 4.1 – 4.4 – *NAFDAC use only*

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 WHO comparator product as identified on PQTm's website should be employed.
- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- **As per the Quality guideline *(NAFDAC Quality Guidelines for the Registration of Pharmaceutical Products for Human Use,* Appendix 1), 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 this biowaiver submission.

<< Please enter information here >>

5.3 Please state the location of:

- the dissolution study protocol(s) 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 >>

5.1 Comments from review of Section 5.1 – 5.6 – NAFDAC use only

CONCLUSIONS AND RECOMMENDATIONS – *NAFDAC USE ONLY*