

**Application for a Biowaiver:  
Biopharmaceutics Classification System (BCS)**

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

Some active pharmaceutical ingredients (APIs) have been identified as eligible for a BCS-based biowaiver application by Stringent Regulatory Authority (SRA) or WHO Prequalification Team (PQTm). For those APIs, you are only required to provide evidence of eligibility, it may not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e., data supporting the drug substance solubility or absorption/permeability class.

**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.
- Please provide the document as an MS Word file.
- Please do not paste snapshots into the document.
- The appended electronic documents should be clearly identifiable by their file names, which should include the product name and annex number.
- 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](mailto:registration@nafdac.gov.ng) with the subject prefix "BCS 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 (NAFDAC)

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)**

&lt;&lt; Please enter information here &gt;&gt;

**2. Dosage form and strength**

&lt;&lt; Please enter information here &gt;&gt;

**3. Product NAFDAC Reference number (if product dossier has been accepted for assessment)**

&lt;&lt; Please enter information here &gt;&gt;

**4. Name of applicant and official address**

&lt;&lt; Please enter information here &gt;&gt;

**5. Name of manufacturer of finished product and official address**

&lt;&lt; Please enter information here &gt;&gt;

**6. Name and address of the laboratory or contract research organization(s) where the BCS-based biowaiver solubility and dissolution studies were conducted**

&lt;&lt; Please enter information here &gt;&gt;

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)

**JUSTIFICATION FOR A BCS BIOWAIVER****Active pharmaceutical ingredient (API)**

Please confirm that the proposed product contains the same active substance (e.g. salt, ester, ether, isomer) as the comparator.

<< Please enter information here >>

**Therapeutic index of the API**

Please enclose a copy of the comparator product labelling and literature references employed to support that the drug does not exhibit a narrow therapeutic index for all authorized indications

<< Please enter information here >>

**Pharmacokinetic properties of the API**

Please enclose a copy of the literature references employed to document the pharmacokinetic (PK) properties (PK linearity or reasons for non-linearity).

<< Please enter information here >>

**Dosage form**

Please confirm that:

- the dosage form is an immediate release product for systemic action
- the posology is limited to oral administration
- the administration without water is not included in the proposed posology

<< Please enter information here >>

1.0 COMMENTS FROM REVIEW OF SECTION 1 – *NAFDAC USE ONLY*

**SOLUBILITY (COMPLETION OF THIS SECTION IS NOT NECESSARY IF THE API(S) ARE INCLUDED ON THE LIST OF BIOWAIVER-ELIGIBLE APIs BY AN SRA OR IN THE PQTM DOCUMENT *GENERAL NOTES ON BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)-BASED BIOWAIVER APPLICATIONS.*)**

**Maximum therapeutic dose of the API**

Please enclose a copy of the labelling of the comparator product to document the maximum single dose that can be administered in a single administration (e.g. two tablets together).

<< Please enter information here >>

**Stability of the drug in the physiological pH range**

Please discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract. Please discuss the ability of the analytical method to distinguish the API from its degradation products.

<< Please enter information here >>

**Method of solubility determination**

Please describe method and conditions (e.g. shake flask method at  $37\pm 1^{\circ}\text{C}$ ) Please indicate also location of the solubility study protocol.

<< Please enter information here >>

**Solubility study dates**

Please indicate dates of study protocol, study conductance and study report

<< Please enter information here >>

**Analytical method validation**

Please summarize the results and indicate location in the documentation.

<< Please enter information here >>

**Results**

Please indicate location of the solubility study report.

Please fill in the following table for the necessary pH values. Add as many rows as necessary to create a solubility – pH profile

Theoretical pH	Observed pH	Adjusted pH	Individual concentration at saturation (Cs) values	Cs (mean and CV (%))	Amount that can be dissolved in 250 ml
pH 1.2	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 4.5	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 6.8	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Other intermediate pH values (e.g. pKa, pKa-1, pKa+1)	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		

**Plot the solubility – pH profile**

Please attach the plot of the pH-solubility profile based on the above data

<< Please enter information here >>

2.0 COMMENTS FROM REVIEW OF SECTION 2 – NAFDAC USE ONLY

**ABSORPTION / PERMEABILITY (COMPLETION OF THIS SECTION IS NOT NECESSARY IF THE API(S) ARE INCLUDED ON THE LIST OF BIOWAIVER-ELIGIBLE APIs IN THE PQTM DOCUMENT *GENERAL NOTES ON BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)-BASED BIOWAIVER APPLICATIONS.*)**

**Human mass balance studies**

Summarize results of all studies found in the literature.

Please enclose a copy of the references describing human mass balance studies of the API.

<< Please enter information here >>

**Human absolute bioavailability studies**

Summarize results of all studies found in the literature.

Please enclose a copy of the references describing human absolute bioavailability of the API.

<< Please enter information here >>

**Supportive studies**

Summarize results of all studies found in the literature regarding in vivo or in situ intestinal perfusion animal models or in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) with a positive and negative control.

Please enclose a copy of the references.

<< Please enter information here >>

**3.0 COMMENTS FROM REVIEW OF SECTION 3 – NAFDAC USE ONLY**

**TEST PRODUCT****Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies**

- Please state the location of the master formulae in the quality part of the submission.
- Tabulate the composition of each product strength using the table below.
- 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/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.

**Please note:** If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation with clear identification in which study the respective formulation was used

Composition of the batches used for comparative dissolution studies				
Batch number				
Batch size (number of unit doses)				
Date of manufacture				
Comments, if any				
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)				
Ingredients (Quality standard)	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
Equivalence of the compositions or justified differences				

**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 >>

4.0 COMMENTS FROM REVIEW OF SECTION 4 – NAFDAC USE ONLY

**COMPARATOR PRODUCT****Comparator product**

Please indicate location in the documentation of the following documents that should be enclosed:

A copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

A copy of the comparator product carton outer box. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.

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

<< Please enter information here >>

**Name and manufacturer of the comparator product and official address**

<< Please enter information here >>

**Qualitative (and quantitative, if available) information on the composition of the comparator product**

Please tabulate the composition of the comparator product based on available information and state the source of this information.

Composition of the comparator product used in dissolution studies		
Batch number		
Expiry date		
Comments, if any		
Ingredients	Unit dose (mg)	Unit dose (%)



**Identify the source of the comparator product (where it was purchased), the method of shipment, and storage conditions of the comparator product from the time of purchase until completion of the comparative dissolution studies**

Please attach relevant copies of the following documents proving the stated conditions:

A copy of the invoice from the distributor or company from which the comparator product was purchased.

The address of the distributor must be clearly visible on the invoice.

Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.

<< Please enter information here >>

**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 >>

5.0 COMMENTS FROM REVIEW OF SECTION 5 – *NAFDAC USE ONLY*

**COMPARISON OF TEST AND COMPARATOR FORMULATIONS****Identify any excipients present in either product that are known to impact in vivo absorption processes**

A literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

<< Please enter information here >>

**Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products**

The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.

<< Please enter information here >>

**Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption**

<< Please enter information here >>

6.0 COMMENTS FROM REVIEW OF SECTION 6 – *NAFDAC USE ONLY*

**COMPARATIVE IN VITRO DISSOLUTION****Comparative in vitro dissolution**

Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.

Please state the location of:

- the dissolution study protocol(s) in this biowaiver application
- the dissolution study report(s) in this biowaiver application
- the analytical method validation report in this biowaiver application

<< Please enter information here >>

**Dissolution study dates**

Please indicate dates of study protocol, study conductance and study report

<< Please enter information here >>

**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, filtration and storage. Deviations from the sampling protocol should also be reported.

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

<< Please enter information here >>

**Type of apparatus and agitation speed(s) employed**

<< Please enter information here >>

**Number of units employed**

<< Please enter information here >>

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

<< Please enter information here >>

**Deviations from sampling protocol**

<< Please enter information here >>

**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 >>

**Summarize conclusions taken from dissolution study(s)**

Please provide a summary statement of the studies performed.

<< Please enter information here >>

**Dissolution specifications**

Please provide proposed dissolution specifications and discuss them in relation to the results obtained in the BCS biowaiver

<< Please enter information here >>

7.0 COMMENTS FROM REVIEW OF SECTION 7 – NAFDAC USE ONLY

**QUALITY ASSURANCE****Internal quality assurance methods**

Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites.

<< Please enter information here >>

**Auditing and inspections**

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites e.g. analytical laboratory, laboratory where dissolution studies were performed.

<< Please enter information here >>

8.0 COMMENTS FROM REVIEW OF SECTION 8 – *NAFDAC USE ONLY*

CONCLUSIONS AND RECOMMENDATIONS – *NAFDAC USE ONLY*