

PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**BIOEQUIVALENCE TRIAL INFORMATION*****General Instructions:***

Please review all the instructions thoroughly and carefully prior to completing the bioequivalence trial information form (BTIF). Neither the format nor the content of the document (text and tables) should be changed. New tables can be inserted but it should maintain the format of the tables in the 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 state the exact Common Technical Document (CTD) location (Modular number, Annex number, Page number) of appended documents in the relevant sections of the BTIF. This procedure must be followed throughout the entire document where location of annexed documents is requested.

Before submitting the completed BTIF, kindly check that you have provided all requested information and enclosed all requested documents.

Should you have any questions regarding this Form, please contact us at registration@nafdac.gov.ng with the subject prefix "BTIF-...".

A properly filled out BTIF in MSWord format along with all its annexes must be placed in Module One of the Common Technical Document (CTD) 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 the BTIF 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

BIOEQUIVALENCE TRIAL INFORMATION**1 SUMMARY****1.1 Summary of bioequivalence studies performed**

(Provide a brief description of each comparative bioavailability study included in the submission)

1.2 Tabulation of the composition of the formulation(s) proposed for marketing and those used for bioequivalence studies

(State the location of the master formulae in the quality part of the submission)

(Tabulate the composition of the biobatch using the table below. For solid oral dosage forms the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any.

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

Composition of the batches used for bioequivalence studies					
Batch number					
Batch size (number of unit doses) ¹					
Comments, if any					
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)					
Ingredients (and quality standard)	Function	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
Total					
Equivalence of the compositions or justified differences					
Maximum intended commercial batch size					

¹ Bioequivalence batches should be at least of pilot scale (10% of production scale or 100,000 capsules/tablets whichever is the greater) and manufacturing method should be the same as for production scale.

2 CLINICAL STUDY REPORT

- a) Study number:
- b) Study title:
- c) Location of study protocol:
- d) Start and stop dates for each phase of the clinical study:
- e) Dates of product administration:

2.1 ETHICS

- a) State the name of review committee, date of approval of protocol and consent form and the location of approval letter in the submission
- b) State location of a reference copy of the informed consent form

2.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

- a) Name of principal investigator(s) (State location of c.v. in the submission)
- b) Clinical Facility (Name and full mailing address)
- c) Clinical Laboratories (Name and full mailing address)
- d) Analytical Laboratories (Name and full mailing address)
- e) Company performing pharmacokinetic/statistical analysis (Name and full mailing address)

2.3 STUDY OBJECTIVES

Briefly state the study objectives.

2.4 INVESTIGATIONAL PLAN**2.4.1 Overall study design and plan —description**

(Describe the type of study design employed in 1-2 sentences)

2.4.2 Selection of study population

2.4.2.1 Inclusion Criteria

(List the inclusion criteria applied to subjects)

2.4.2.2 Exclusion Criteria

(List the exclusion criteria applied to subjects)

2.4.2.3 Health Verification

(State location of the individual data included in the submission)

- a) List criteria used and all tests performed in order to judge health status
- b) Indicate when tests were performed
- c) Study site normal values
- d) *(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)*
- e) Report any results that were outside of study site normal values
- f) *(State location in submission of the summary of anomalous values)*

2.4.2.4 Removal of Trial subjects from Trial or Assessment

- a) Number of subjects enrolled in the study
(All subjects including alternates, withdrawals, and dropouts)
- b) Alternates
(Please note: Generally all subjects enrolled in the study should be included in the data set i.e., alternate subjects are strongly discouraged. However, in cases where there are alternate subjects, describe the procedure of including/excluding the alternates and whether alternates have been included in the study)
- c) Withdrawals/dropouts
(Identify each withdrawal/dropout by subject and provide the reason for withdrawal/dropout and at what point in the study the withdrawal/dropout occurred)

2.4.3 Products Administered

2.4.3.1 Test Product

- a) Batch number, size, date of manufacture and expiry date for the test product
- b) Potency (measured content) of test product as a percentage of label claim as per validated assay method
- c) *(This information should be cross-referenced to the location of the certificate of analysis in the submission)*

2.4.3.2 Comparator (Reference) Product

(Append to this template a copy of product labelling (snap shot of the box, on which the name of the product, name and address of the manufacturer, batch number, and expiry date are clearly visible on the labelling)

- a) Name and manufacturer of the comparator product and market where the comparator product was purchased
- b) Batch number and expiry date for the comparator product
- c) Purchase, shipment, storage of the comparator product
(Indicate from which company/pharmaceutical distributor the comparator product has been obtained. Clearly indicate in chronological order the steps and dates of shipment/transport from company of purchase to the study site. In addition, the storage conditions should be given. This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)
- d) Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product
- e) *(This information should be cross-referenced to the location of the certificate of analysis in the submission)*
- f) Justification of choice of comparator product
- g) *(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)*

2.4.4 Selection of doses in the study

- a)
- State dose administered

(Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets)

2.4.5 Selection and Timing of Dose for Each Subject

- a)
- State volume and type of fluid consumed with dose

- b)
- Interval between doses (i.e., length of washout)

- c)
- Protocol for the administration of food and fluid

- d)
- Restrictions on posture and physical activity during the study

2.4.6 Blinding**2.4.6.1 Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so**

- a) study
- monitors
- : Yes
-
- / No
-
- If No, justify:

- b)
- subjects
- : Yes
-
- / No
-
- If No, justify:

- c)
- analysts
- : Yes
-
- / No
-
- If No, justify:

2.4.6.2 Identify who held the study code and when the code was broken

2.4.7 Drug Concentration Measurements**2.4.7.1 Biological fluid(s) sampled****2.4.7.2 Sampling protocol**

- a) Number of samples collected per subject
- b) Volume of fluid collected per sample
- c) Total volume of fluid collected per subject per phase of the study
- d) List the study sampling times
- e) Identify any deviations from the sampling protocol
- f) *(State location of summary in the submission)*
- g) *(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analysis)*

2.4.7.3 Sample Handling

- a) Describe the method of sample collection
- b) Describe sample handling and storage procedures

2.5 Comments from review of Section 2 – NAFDAC use only

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3 TRIAL SUBJECTS

3.1 Demographic and other baseline characteristics

- a) Identify study population (i.e., normal, healthy adult volunteers or patients)
- b) Summary of ethnic origin and gender of subjects
- c) Identify subjects noted to have special characteristics and state notable characteristics
- d) Range and mean age \pm SD of subjects
- e) Range and mean height and weight \pm SD of subjects
- f) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

3.2 Subjects who smoke

- a) Number of smokers included in the study
- b) Indicate how many cigarettes smoked per day per subject
- c) Comment on the impact on study

3.3 Comments from review of Section 3 – NAFDAC use only

4 PROTOCOL DEVIATIONS

4.1 Protocol deviations during the clinical study

(Describe any such deviations and discuss their implications with respect to bioequivalence)

4.2 Comments from review of Section 4 – NAFDAC use only

5 SAFETY EVALUATION**5.1 Identify adverse events observed**

(List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State location of this summary in the submission.)

(Discuss the implications of the observed adverse events with respect to bioequivalence.)

5.2 Comments from review of Section 5 – NAFDAC use only**6 EFFICACY EVALUATION****EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL TRIAL SUBJECTS DATA****6.1 Presentation of data**

- a) State location in submission of tables of mean and individual subject concentrations
- b) State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

6.2 Pharmacokinetic (PK) parameters

- a) State how the pharmacokinetic parameters were calculated/obtained for AUC_{0-t} , AUC_{0-inf} , C_{max} , t_{max} , the elimination rate constant, and $t_{1/2}$ (indicate location of description in protocol)
- b) State whether actual sampling time points were used for estimation of the pharmacokinetic parameters
- c) Complete the table below

Test				Reference		
Parameter	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)
AUC_{0-t} (units)						
AUC_{0-inf} (units)						
C_{max} (units)						
t_{max} (units)						
$t_{1/2}$ (units)						

- d) Ratio of AUC_{0-t} to AUC_{0-inf}
(State mean ratio for both test and reference, state location in submission where individual ratios can be found)

6.3 Statistical analysis

(State the method of calculation of the 90% confidence intervals for the ratio of test formulation over the reference formulation and indicate how treatment, period, sequence and subjects within sequence were included as factors in the ANOVA. Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC_{0-t} and C_{MAX} and other relevant parameters. State software used for computing ANOVA.)

a) Geometric means, results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-subject)

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						

b) Comparison of the results

(Compare the results, including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs, etc), and copies of the references used should be appended to this document)

6.4 Discussion of results

(State location of the discussion of the results in the submission)

6.5 Comments from review of Section 6 – NAFDAC use only

7 ANALYTICAL VALIDATION REPORT**7.1 Analytical technique****7.1.1 Validation protocol**

(State the location of the validation protocol)

7.1.2 Identify analyte(s) monitored**7.1.3 Comment on source and validity of reference standard****7.1.4 Identify internal standard****7.1.5 Comment on source and validity of internal standard****7.1.6 Identify method of extraction****7.1.7 Identify analytical technique or method of separation employed****7.1.8 Identify method of detection****7.1.9 Identify anticoagulant used *(if applicable)*****7.1.10 If based on a published procedure, state reference citation****7.1.11 Identify any deviations from protocol****7.2 Selectivity**

(Address the methods to verify selectivity against endogenous/exogenous compounds & results)

7.3 Sensitivity

(Address the methods to verify sensitivity & results)

7.4 Carry-over

(Summarize the method to verify carry-over & results)

7.5 Standard curves

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

- a) List number and concentration of calibration standards used
- b) Describe the regression model used including any weighting
- c) List the back-calculated concentrations of the calibration standards of the validation runs *(highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)*

7.6 Quality control samples

- a) Identify the concentrations of the QC samples and the storage conditions employed prior to their analysis

7.7 Precision and accuracy during validation

- a) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay validation
- b) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay re-validation
(If applicable)
- c) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay validation
- d) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay re-validation
- e) *(If applicable)*

7.8 Dilution integrity

(Summarize the method to verify dilution integrity & results)

7.9 Matrix effect (in case of MS detection)

(Summarize methods to verify the matrix effect & results)

7.10 Stability

(For each section provide the location of the raw data, a description of the methodology employed and a summary of the data.)

a) Summarize data on long-term storage stability

b) Summarize data on freeze-thaw stability

c) Summarize data on bench top stability

d) Summarize data on auto-sampler storage stability

e) Summarize data from any other stability studies conducted

f) *(e.g. long-term stock solution and working solution stability, short-term stock solution and working solution stability, dry-extract stability, wet-extract stability, stability in blood before sample processing)*

7.11 Re-injection reproducibility

(Summarize the method to verify re-injection reproducibility& results)

7.12 Comments from review of Section 7 – NAFDAC use only

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8 BIOANALYTICAL STUDY REPORT

(State the location of the bioanalytical report for the analysis of the study subject samples)

8.1 Analytical technique

(Confirm whether the method is the same as the validated method and whether the same equipment was employed. Identify any differences between the validated method described above in Section 7 and the method employed for subject sample analyses)

8.1.1 Analytical protocol

(State the location of the analytical protocol)

8.1.2 Identify any deviations from protocol**8.1.3 Dates of subject sample analysis****8.1.4 Longest period of subject sample storage**

(Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis)

8.1.5 State whether all samples for a given subject were analysed together in a single analysis run**8.2 Standard curves**

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

- a) List number and concentration of calibration standards used
- b) State number of curves run during the study (*valid and failed runs, including reasons of failure*).
- c) Summarize descriptive data including slope, intercept, correlation coefficients
- d) List the back-calculated concentrations of the calibration standards of the study runs (*highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ*)

8.3 Quality control samples

- a) Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis

- b) State the number of QC samples in each analytical run per concentration
- c) List the back-calculated concentrations of the QC samples of the study runs (*highlight the values outside of the acceptance range, e.g., 15%*)
- d) Discuss whether the concentrations of the QC sample concentrations are similar to the concentrations observed in the study samples
- e) State the percentage of QC samples per run with respect to the total number samples assayed in each run

8.4 Precision and accuracy

- a) Summarize inter-day precision of back-calculated standards and inter-day and intra-day precision and accuracy of QC samples analysed during subject sample analysis

8.5 Repeat analysis (re-analysis, re-injection and re-integration)

- a) List re-analysed samples by sample identification and include the following information for each re-analysis: initial value; reason for re-analysis; re-analysed value(s); accepted value; and reason for acceptance
- b) Report the number of re-analysis as a percentage of the total number samples assayed
- c) List re-injected samples by sample identification and include the following information for each re-injection: initial value; reason for re-injection; re-injected value; accepted value; and reason for acceptance
- d) Report the number of re-injections as a percentage of the total number samples assayed
- e) List re-integrated chromatograms by sample identification and include the following information for each re-integration: initial value; reason for re-integration; re-integrated value(s); accepted value; and reason for acceptance
- f) Report the number of re-integrated chromatograms as a percentage of the total number of samples assayed

8.6 Incurred sample reanalysis

(State location in the submission and summarize the results of incurred sample reanalysis, including the number of subject samples included in ISR and the total number of samples analysed in the study)

8.7 Chromatograms

(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)

8.8 Comments from review of Section 9 – NAFDAC use only

9 QUALITY ASSURANCE**9.1 Internal quality assurance methods**

(State locations in the submission where internal quality assurance methods and results are described for each of study sites (see 3.2 b-d.)

9.2 Monitoring, auditing, inspections

(Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in the submission of the respective reports for each study site (see 3.2 b-d.)

9.3 Comments from review of Section 10 – NAFDAC use only

10.0 CONCLUSIONS AND RECOMMENDATIONS – NAFDAC use only