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).

Provide as much detailed, accurate and final information as possible. Note that the greyed areas are NOT to be filled in by the applicant but are for NMRC use ONLY!

Please state the exact location (Annex number) of appended documents in the relevant sections of the BTIF. For example, in ***section 3.4.3.1*** *under* ***point b)****, indicate in which Annex (number) the Certificate of Analysis can be found. 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 Registrar of Namibia Medicines Regulatory Council

A properly filled out and signed original copy of the BTIF with all its annexes (including a copy on CD-ROM) must be submitted to the NMRC together with the bioequivalence part of the dossier.

ASSESSMENT REPORT FOR MULTI-SOURCE (GENERIC)

FINISHED PHARMACEUTICAL PRODUCTS (FPPS)

BIOEQUIVALENCE PART OF A NEW DOSSIER

Date		
First assessor	Name	Signature
Second assessor	Name	Signature
Reference Number		
Date of the submission		
Number of binders		
Proprietary Product Name (if relevant)	*..	
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	*..	
Conclusion of the assessment	**ACCEPTED (no outstanding issues)** **ADDITIONAL DATA REQUESTED** **REJECTED** ***(please delete the wrong entries)***	
Name and complete address of the applicant	*..	
Name and address of the Contract Research Organisation(s) where the clinical studies proving efficacy and safety of the product were conducted. *(Add as much rows as necessary)*	*..	

This product assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment. The report should be completed by at least two evaluators

The assessment report should be typed with "Times New Roman 12" fonts. The format of tables must not be changed.

BIOEQUIVALENCE TRIAL INFORMATION

1.0 SUMMARY OF BIOAVAILABILITY/BIOEQUIVALENCE STUDIES PERFORMED

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

*…

2.0 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 each product strength 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)*

*…

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 or coating weight*

Composition of the batches used for clinical, bioequivalence or dissolution 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	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
Equivalence of the compositions or justified differences				

2.1 HAS COMPARATIVE BIOAVAILABILITY DATA BEEN SUBMITTED FOR ALL STRENGTHS?

(If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification for not submitting such data; append copies of all references cited in the justification. Justification should include – but is not limited to – argumentation related to dose-proportional composition, dose-linearity of pharmacokinetics (Cmax and AUC,), discriminatory (with regard to bioavailability differences) power of dissolution tests employed)

*…

Sections 3.0 – 11.0 below should be copied and completed separately for each bioequivalence study performed.

[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.

3.0 CLINICAL STUDY REPORT

Study #:
Study Title:
Location of Study Protocol:
Start and stop dates for each phase of the clinical study:

*…

3.1 ETHICS

(a) Name of review committee, date of approval of protocol and consent form, location of approval letter in the submission

*…

(b) State location of a reference copy of the informed consent form

*…

3.2 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)*

*…

3.3 STUDY OBJECTIVES

Briefly state the study objectives.

*…

3.4 INVESTIGATIONAL PLAN

3.4.1 Overall Study Design and Plan – Description

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

*…

3.4.2 Selection of Study Population

*…

3.4.2.1 Inclusion Criteria

*…

3.4.2.2 Exclusion Criteria

(List the exclusion criteria applied to subjects)

*…

3.4.2.3 Removal of Trial subjects from Trial or Assessment

*…

(a) Number of subjects enrolled in the study

(All subjects including alternates, withdrawals, and dropouts)

*…

(b) Withdrawals

(Identify each withdrawal by subject and provide the reason for withdrawal and at what point in the study the withdrawal occurred)

*…

3.4.2.4 Health Verification

(Individual data should be 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

(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)

*…

(d) Report any results that were outside of study site normal values

(State location in submission of the summary of anomalous values)

*…

3.4.3 Products Administered

3.4.3.1 Test Product

*…

(a) Batch number, size and date of manufacture for the test product

*…

(b) 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)

*…

3.4.3.2 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 reference product

*…

(b) Batch number and expiry date for the reference product

*…

(c) Purchase, shipment, storage of the reference product

(This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)

*…

(d) Potency (measured content) of the reference product as a percentage of label claim, as measured by the same laboratory and 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)

*…

(e) Justification of choice of reference product

(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)

*…

3.4.4 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)

*…

3.4.5 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

*…

3.4.6 Blinding

3.4.6.1 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:_____

*…

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

*…

3.4.7 Drug Concentration Measurements

*…

3.4.7.1 Biological fluid(s) sampled

*…

3.4.7.2 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

(State location of summary in the submission)

(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)

*…

3.4.7.3 Sample Handling

*…

(a) Describe the method of sample collection

*…

(b) Describe sample handling and storage procedures

*…

3.5 COMMENTS FROM REVIEW OF SECTION 3.0 – *NMRC USE ONLY*

4.0 TRIAL SUBJECTS

4.1 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

(e.g., fast acetylators of debrisoquine)

*…

(d) Range and mean age ± SD of subjects

*…

(e) Range and mean height and weight ± SD of subjects

*…

(f) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

*…

4.2 Number of smokers included in the study

*…

(a) Indicate how many cigarettes smoked per day per subject

*…

(b) Comment on the impact on study

*…

4.3 COMMENTS FROM REVIEW OF SECTION 4.0 – *NMRC USE ONLY*

5.0 PROTOCOL DEVIATIONS

5.1 Protocol deviations during the clinical study

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

*…

5.2 COMMENTS FROM REVIEW OF SECTION 5.0 – *NMRC USE ONLY*

6.0 SAFETY EVALUATION

6.1 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)

*…

6.2 COMMENTS FROM REVIEW OF SECTION 6.0 – *NMRC USE ONLY*

7.0 EFFICACY EVALUATION –

Efficacy Results and Tabulations of Individual Trial Subjects Data

7.1 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

*…

7.2 Pharmacokinetic (PK) Parameters

	Test			Reference		
Parameter	Arithmetic Mean	Standard deviation	Interindividual coefficient of variation (%)	Arithmetic Mean	Standard deviation	Interindividual coefficient of variation (%)
AUC_T (units)						
AUC_I (units)						
C_{max} (units)						
T_{max} (units)						
$T_{½}$ (units)						

(State method of AUC calculation and method of extrapolation. Indicate location of description in protocol)

*…

(b) Ratio of AUC_T to AUC_I ____

(State mean ratio for both test and reference, state location in submission where individual ratios can be found,)

*…

7.3 Statistical Analysis

(Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC_T and C_{MAX} and other relevant parameters, e.g. in the case of steady-state designs, AUC_τ , C_{MAX} , and C_{MIN} ; state software which has been used for computing ANOVA)

*…

(a) Geometric means, Results from ANOVA, Degrees of Freedom (DF) and derived CV (intraindividual)

Parameter	Test	Reference	% Ratio of Geometric Means	90 % Confidence Interval	DF	CV (%)
AUC_T (units)						
AUC_I (units)						
C_{max} (units)						

*…

(b) Period and/or sequence effects

(State whether any period- and/or sequence-effects have been found. If yes, provide short discussion of effects here, and state location in submission where comprehensive explanation is provided)

*…

7.4 DISCUSSION OF RESULTS

(State location of the discussion of the results in the submission. If the discussion currently included in the study report does not include comparisons of results, including inter- and intraindividual variability, of this study with published results (literature, product information of reference product (innovator), such a discussion should be provided here and copies of the references used should be appended to this document)

*…

7.5 COMMENTS FROM REVIEW OF SECTION 7.0 – *NMRC USE ONLY*

8.0 ANALYTICAL STUDY REPORT

8.1 Analytical Technique

*…

8.1.1 Analytical protocol

(State the location of the analytical protocol)

*…

8.1.2 Identify analyte(s) monitored

*…

8.1.3 Comment about source and validity of reference standard

*…

8.1.4 Identify analytical technique employed

*…

8.1.5 Identify method of detection

*…

8.1.6 Identify internal standard

*…

8.1.7 If based on a published procedure, state reference citation

*…

8.1.8 Identify any deviations from protocol

*…

8.1.9 Dates of subject sample analysis

*…

8.1.10 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)

*…

8.1.11 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

*…

(c) Summarize descriptive data including slope, intercept, correlation coefficients

*…

(d) Describe the regression model used including any weighting

*…

(e) State the limit of quantitation (LOQ)

(Summarize inter-day and intra-day precision and accuracy at the LOQ)

*…

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

*…

8.4 Precision and Accuracy

*…

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

*…

8.5 Repeat Analysis

(a) List repeats by sample identification and include the following information for each repeat: initial value; reason for repeat; repeat value(s); accepted value; and reason for acceptance

*…

(b) Report the number of repeats as a percentage of the total number samples assayed

*…

8.6 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)

*…

8.7 COMMENTS FROM REVIEW OF SECTION 8.0 – *NMRC USE ONLY*

9.0 ANALYTICAL VALIDATION REPORT

9.1 Precision and Accuracy

*…

(a) Summarize inter-day and intra-day accuracy and precision during assay validation

*…

(b) Summarize inter-day and intra-day accuracy and precision during assay re-validation

(If applicable)

*…

9.2 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 autosampler storage stability

*…

(e) Summarize data from any other stability studies conducted

(e.g., stock solution stability)

*…

9.3 Specificity

(Methods to verify specificity against endogenous/exogenous compounds & results)

*…

9.4 Matrix effect (in case of MS detection)

(Methods to verify the matrix effect & results)

*…

9.5 Recovery

(Method and results of assessment for analyte and internal standard including mean and CV%)

*…

9.6 COMMENTS FROM REVIEW OF SECTION 9.0 – NMRC *USE ONLY*

10.0 QUALITY ASSURANCE

10.1 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)

*…

10.2 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 of study sites (see 3.2 b-d)

*…

10.3 COMMENTS FROM REVIEW OF SECTION 10 – *NMRC USE ONLY*

11.0 CONCLUSIONS AND RECOMMENDATIONS – *NMRC USE ONLY*