South African Health Products Regulatory Authority
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Pretoria

BIOEQUIVALENCE TRIAL INFORMATION 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 BE study test product (name and address)	
FPP Manufacturer(s) applied for (name and address)	
API manufacturer(s) used in BE study test product (name and address)	
API manufacturer(s) applied for (name and address)	
Pharmaceutical form & strength(s)	
Batch number and size (test product)	
Date of manufacture (test product)	
Contract Research Organisation (CRO) name	
IEC (Independent Ethics Committee) / IRB (Institutional Review Board) name	
Study Protocol Number	
Report number	
Study title	
Reference product (name) Batch Number & Expiry date Country of Procurement	
Study period (Clinical Study Dates)	
Principal investigator	
Sponsor	
Number of subjects enrolled in study (completed the study) e.g. n 24 (20)	
South African Innovator Product: Name, Batch Number & Expiry date Approved dose range and Administration in relation to food	
For SAHPRA use only Bioequivalence assessment outcome	

Disclaimer

This document is adapted from the WHO revised BTIF 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 from WHO revised BTIF *https://extranet.who.int/prequal/news/btif-revised* and TGA evaluation template

TABLE OF CONTENTS

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)[2]					
{Insert comments, if any}					
Comparison of unit dose compositions and of clinical FPP batches					
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					

1.3 Justification of the use of a foreign reference product i.e. Comparative Dissolution studies. Submit details of the study reference and OR SOP number as well as study results (individual data) comparing the dissolution profiles of the chosen reference product vs the SA innovator

[2]. Bioequivalence batches should be at least of pilot scale (10 % of production scale or 100 000 capsules / tablets whichever is greater). Manufacturing method should be the same as for production scale.

2. CLINICAL STUDY REPORT

Study number	
Study title	
Location of study protocol	
Start and stop dates for each phase of the clinical study	
Dates of product administration	

2.1 Ethics

State the name of review committee, date of approval of protocol and consent form and the location of approval letter in the submission.

State location in the dossier of a reference copy of the informed consent form.

2.2 Investigators and study administrative structure

Name of principal investigator(s)	
Clinical facility	
Clinical laboratories	
Analytical laboratories	
Company performing pharmacokinetic / statistical analysis	

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:

{List here.}

b) Indicate when tests were performed:

{Indicate here.}

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.

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

	Test product	Reference product
Batch number		
Batch size		
Potency (measured content)		
Manufacturing date		
Expiry		

Include a cross-reference to the location of the certificates of analysis for both reference and test in the submission, and potency should be within 5 % of each other; otherwise, apply potency correction.

2.4.3.1 Comparator (reference) product

Append to this template a copy of product labelling (snapshot 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

{Insert here.}

b) 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.

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

{Insert here.}

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

{Insert here.}

c) Protocol for the administration of food and fluid

{Insert here.}

d) Restrictions on posture and physical activity during the study

{Insert here.}

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:

Study monitors	Yes ☐	No ☐
Subjects	Yes ☐	No ☐
Analysts	Yes ☐	No ☐

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

{Insert here.}

2.4.7 Drug Concentration Measurements

2.4.7.1 Biological fluid(s) sampled

{Insert here.}

2.4.7.2 Sampling protocol

a) Number of samples collected per subject

{Insert here.}

b) Volume of fluid collected per sample

{Insert here.}

c) Total volume of fluid collected per subject per phase of the study (i.e. volume collected from screening to post-dose safety sampling e.g. pre - study, screening, PK samples)

{Insert here.}

d) List the study sampling times

{Insert here.}

2.4.7.3 Sample Handling

a) Describe the method of sample collection

{Insert here.}

b) Describe sample handling and storage procedures

{Insert here.}

Comments from review of Section 2 – *For SAHPRA use only*

3 TRIAL SUBJECTS

3.1 Demographic and other baseline characteristics for all enrolled subjects (information required in a) – f) may be provided in tabular form)

a) Identify study population (i.e., normal, healthy adult volunteers or patients)
{Insert here.}

b) Summary of ethnic origin and gender of subjects
{Insert here.}

c) Identify subjects noted to have special characteristics and state notable characteristics (e.g. fast acetylators of debrisoquine)
{Insert here.}

d) Range and mean age ± SD of subjects
{Insert here.}

e) Range and mean height and weight ± SD of subjects
{Insert here.}

f) Identify subjects whose ratio is not within 15 % of the values given on a standard height/weight table
{Insert here.}

3.2 Subjects who smoke

a) Number of smokers included in the study
{Insert here.}

b) Indicate how many cigarettes smoked per day per subject
{Insert here.}

c) Comment on the impact on study
{Insert here.}

Comments from review of Section 3 – *For SAHPRA 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.

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.

Comments from review of Section 4 – *For SAHPRA 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. Report any deaths. State location of this summary in the submission.

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

Comments from review of Section 5 – *For SAHPRA 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

{Insert here.}

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

{Insert here.}

6.2 Pharmacokinetic (PK) parameters

a) State how the pharmacokinetic parameters where calculated/obtained for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, the elimination rate constant, and $t_{½}$ (indicate location of description in protocol)

{Insert here.}

b) State whether actual sampling time points were used for estimation of the pharmacokinetic parameters

{Insert here.}

c) Complete the table below:

Parameter	Test			Reference		
	Arithmetic mean	**Standard deviation**	**Interindividual coefficient of variation (%)**	**Arithmetic mean**	**Standard deviation**	**Interindividual coefficient of variation (%)**
$AUC_{0\text{-}t}$ (units)						
$AUC_{0\text{-}inf}$ (units)						
C_{max} (units)						
t_{max} (units)						
$t_{½}$ (units)						

d) State whether actual sampling time points were used for estimation of the pharmacokinetic Ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$

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 AUC0-t and CMAX and other relevant parameters. State software used for computing ANOVA.] Confirm that a copy of the statistical output report (e.g. SAS ®) has been included

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 (%)
AUC_{0-t} (units)						
AUC_{0-inf} (units)						
C_{max} (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), 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.

Comments from review of Section 6 – *For SAHPRA 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

{Insert here.}

7.1.3 Comment on source and validity of reference standard

{Insert here.}

7.1.4 Identify internal standard

{Insert here.}

7.1.5 Comment on source and validity of internal standard

{Insert here.}

7.1.6 Identify method of extraction

{Insert here.}

7.1.7 Identify analytical technique or method of separation employed

{Insert here.}

7.1.8 Identify method of detection

{Insert here.}

7.1.9 Identify anticoagulant used (if applicable)

{Insert here.}

7.1.10 If based on a published procedure, state reference citation

{Insert here.}

7.1.11 Identify any deviations from protocol

{Insert here.}

7.2 Selectivity (at LLOQ)

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

{Insert here.}

7.7 Precision and accuracy during validation

a) Summarise inter-day/inter-run accuracy and precision of the calibration standards during assay validation

{Insert here.}

b) Summarise inter-day/inter-run accuracy and precision of the calibration standards during assay re-validation (if applicable)

{Insert here.}

c) Summarise inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay validation

{Insert here.}

d) Summarise inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay re-validation (if applicable)

{Insert here.}

7.8 Dilution integrity

Summarise the method to verify dilution integrity & results.

7.9 Matrix effect (in case of MS detection)

Summarise 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) Summarise data on long-term storage stability

{Insert here.}

b) Summarise data on freeze-thaw stability

{Insert here.}

c) Summarise data on bench top stability

{Insert here.}

d) Summarise data on auto-sampler storage stability

{Insert here.}

e) Summarise data from any other stability studies conducted

For example, 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

Summarise the method to verify re-injection reproducibility & results

Comments from review of Section 7 – *For SAHPRA use only*

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

{Insert here.}

8.1.3 Dates of subject sample analysis

{Insert here.}

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

{Insert here.}

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

{Insert here.}

b) State number of curves run during the study (valid and failed runs, including reasons of failure).

{Insert here.}

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

{Insert here.}

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)

{Insert here.}

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

{Insert here.}

b) State the number of QC samples in each analytical run per concentration

{Insert here.}

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 %)

{Insert here.}

d) Discuss whether the concentrations of the QC sample concentrations are similar to the concentrations observed in the study samples

{Insert here.}

e) State the percentage of QC samples per run with respect to the total number samples assayed in each run

{Insert here.}

8.4 Precision and accuracy

Summarise 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

{Insert here.}

b) Report the number of re-analysis as a percentage of the total number samples assayed

{Insert here.}

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

{Insert here.}

d) Report the number of re-injections as a percentage of the total number samples assayed

{Insert here.}

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

{Insert here.}

f) Report the number of re-integrated chromatograms as a percentage of the total number of samples assayed

{Insert here.}

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.

Comments from review of Section 8 – *For SAHPRA 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 table in section 2.2).

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 table in section 2.2).

Comments from review of Section 9 – *For SAHPRA use only*

Conclusions and recommendations – *For SAHPRA use only*

Date	Reason for update	Version and publication
July 2019	First publication: Bioequivalence Trial Information 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 new 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, expansion of the information required in sections 1.3, 2.4.3, units amended to be subscripts in section 6.2 & 6.3, spacing added between units in section 7.5, 8.2, 8.3 & 8.7 to comply with SAHPRA's requirements. Released for comments	Version 2, April 2020
October 2020	Comments from industry	Version 2, April 2020
November 2020	Third publication: Amendment of whole document: reformat margins to remove the unused space at the start of each 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; Removal of some instructions in section 2.4.3 as they were either duplicated elsewhere in the BTIF or for the attention of the evaluator / assessor only; Clarification and Expansion of some of the information required in sections 1.3, 2.4.3, 2.4.7, 3.1, 7.7, 8.1, 8.3 & 8.5 as per industry comments and in accordance with SAHPRA requirements. Released for implementation	Version 3, November 2020