*Form**: EVF03***

BIOEQUIVALENCE APPLICATION FORM

This application form is designed to facilitate information exchange between the Applicant and the MCAZ for bioequivalence studies.
You should refer to the MCAZ Guidelines on bioequivalence and WHO Guidelines for bioavailability/bioequivalence for the full requirements when submitting data for bioequivalence.

General Instructions:

- Please review all the instructions thoroughly and carefully prior to completing the Application Form.
- Provide as much detailed and accurate information as possible.
- Please enter the data and information directly following the shaded areas.
- 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. For example, in section 3.4.3.1(b) indicate in which Annex the Certificate of Analysis can be found.
- The appended electronic documents should be clearly identified with their file names, which should include the product name and Annex number.
- Before submitting the completed Application Form, ensure that you have provided all requested information and enclosed all requested documents.

The signed paper version of this Biowaiver Application Form together with Annexes (and their electronic copies in Microsoft Word in **CD format**) should be included to the bioequivalence part of the submitted dossier.

Administrative data

1. INN of active ingredient(s)
< *Please enter information here* >

2. Dosage form and strength
< *Please enter information here* >

3. Application number
< *Please enter information here* >

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

5. Name and address of manufacturer (s) of finished product
< *Please enter information here* >

6. Name and address of sponsor
< *Please enter information here* >

7. Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver dissolution studies were conducted.
< *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)

_____ (Signature)

_____ (Name and title)

BIOEQUIVALENCE TRIAL INFORMATION

1.0 SUMMARY OF BIOAVAILABILITY/BIOEQUIVALENCE STUDIES PERFORMED

(Insert a brief summary of the BE studies performed)

2.0 TABULATION OF THE COMPOSITION OF THE FORMULATION(S) PROPOSED FOR MARKETING AND THOSE USED FOR BIOEQUIVALENCE STUDIES

(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)*

Composition of bioequivalence, primary stability and production FPP batches									
Ingredients (Approved name)	Reason for inclusion	Unit		Bioequivalence (Batch number/Size)		Primary stability (Batch number/Size)		Production (Batch number/Size)	
		mg	%	kg	%	kg	%	kg	%
Core tablet / capsule contents (*Please delete / change which does not apply*)									
API 1									
API 2									
API 3									
Please add / delete as many rows as necessary									
Excipient 1									
Excipient 2									
Excipient 3									
Excipient 4									
Please add / delete as many rows as necessary									
Subtotal 1									
Film coat / capsule shell (*Please delete / change which does not apply*)									
Proprietary film-coating mixture*									
Please add / delete as many rows as necessary									
Subtotal 2									
Grand total									
Equivalence of compositions or justified differences									
* All components (……..) of the proprietary mixture are described in the …….. Pharmacopoeia.									

**each ingredient expressed as a percentage of the total core or coating weight*

2.1 HAS COMPARATIVE BIOAVAILABILITY DATA BEEN SUBMITTED FOR ALL STRENGTHS?

Yes ☐ **No** ☐
Not applicable ☐

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

3.0 CLINICAL STUDY REPORT

Study number:
Study Title:

Location of Study
Protocol in submission:

Start and stop dates for each phase of the clinical study

Period	**Start date**	**Stop date**
I		
II		

3.1 ETHICS

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

Name of review committee:
Date of approval:

Location of approval letter in submission:

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

Location of reference copy of the IC form in submission:

3.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

(a) Name of principal investigator(s) *(State location of C.V. in the submission)*

Name of PI:

Qualifications:

Location of CV in submission:

(b) Clinical Facility *(Name and full mailing address)*

Name of Clinical facility:

Full address:

(c) Clinical Laboratories *(Name and full mailing address)*

Name of Clinical Laboratories:

Full address:

(d) Analytical Laboratories *(Name and full mailing address)*

Name of Analytical Laboratories:

Full address:

(e) Company performing pharmacokinetic/statistical analysis *(Name and full mailing address)*

Name of Company performing PK/statistical analysis:
Full address:

3.3 STUDY OBJECTIVES

Objective 1:

Objective 2:

3.4 INVESTIGATIONAL PLAN

3.4.1 Overall Study Design and Plan – Description

3.4.2 Selection of Study Population

3.4.2.1 Inclusion Criteria

3.4.2.2 Exclusion Criteria

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

Batch number:

Manufacturing date:

Expiry date:

Batch size:

(b) Potency (measured content) of test product as a percentage of label claims 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 (summary of product characteristics), as authorised in country of purchase, and English translation if appropriate)

.

(a) Name and manufacturer of the reference product

.

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

Batch number:

Manufacturing date:

Expiry date:

Batch size:

(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

Test dose:

Reference dose:

(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 – *MCAZ 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 – *MCAZ 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 – *MCAZ 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 – *MCAZ 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	Inter-individual coefficient of variation (%)	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)
AUC_T (µgxhr/ml)						
AUC_I (µgxhr/ml)						
C_{max} (µg/ml)						
T_{max} (hours)						
$T_{½}$ (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 (non-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	P value
AUC_T (µgxhr/ml)					
AUC_I (µgxhr/ml)					
C_{max} (µg/ml)					

(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 – *MCAZ 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

Overall precision and accuracy for quality control samples

(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 – *MCAZ 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

.

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

.

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

.

9.5 COMMENTS FROM REVIEW OF SECTION 9.0 – *MCAZ 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 – *MCAZ USE ONLY*