A close up of a sign

AI-generated content may be incorrect.

**Veterinary Drugs Directorate (VDD)**

**Health Products and Food Branch (HPFB)**

**COMPREHENSIVE SUMMARY – BIOEQUIVALENCE (CS-BE)**

**FOREWORD**

The Comprehensive Summary – Bioequivalence (CS-BE) template is intended to assist sponsors in summarizing information regarding the conduct and analysis of pivotal comparative bioavailability (including bioequivalence) studies to support a veterinary drug regulatory submission. The template is not mandatory for an Abbreviated New Drug Submission (ANDS); however, it is a tool intended to support sponsors by providing a standardized approach for submitting bioequivalence study results to Health Canada.

Instructions are provided as part of the template in italics. If a section or field does not apply, this should be indicated by **“Not applicable”** or **“N/A”** in the appropriate area, with an accompanying explanatory note. The use of tabular summaries is encouraged, where possible. In addition, each section of the template should be cross-referenced to the location of supporting documentation or raw data within the submission.

This template provides for only a single study; however, if a submission includes more than one pivotal comparative bioavailability study, the sponsor should duplicate the relevant portions of the template and paste them into the original. A heading should be added to indicate what study the duplicated section(s) refer to.

Refer *to Guidance for Industry: Preparation of Veterinary Abbreviated New Drug Submissions (Generic Drugs) – Clinical and Human Safety Requirements* for additional information.

When completing the CS-BE, this **Foreword** page should be deleted prior to submitting.

**Comprehensive Summary – Bioequivalence (CS-BE)**

|  |  |
| --- | --- |
| **SUMMARY OF PRODUCT INFORMATION** | |
| Proprietary (brand) name of drug product |  |
| Non-proprietary (proper or common) name of drug product |  |
| Proper, Common or Non-Proprietary Name of Drug Substance (medicinal ingredient) |  |
| Manufacturer name (fabricator) |  |
| Manufacturer name (sponsor) |  |
| Dosage form(s) |  |
| Strength(s) |  |
| Drug Identification Number (DIN), if applicable |  |
| Route(s) of administration |  |
| Species |  |
| Canadian Reference Product (CRP) |  |
| Therapeutic classification |  |
| Type of submission |  |

|  |  |
| --- | --- |
| **ADMINISTRATIVE SUMMARY** | |
| Dossier ID number |  |
| Control number (DSTS number) |  |
| Sponsor’s date of preparation or revision |  |
| Revision number (for sponsor use) |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PRODUCT COMPOSITION / FORMULATION** | | | | | | |
| Location of the master formulae in the submission: | | | | | | |
| *Instruction – Tabulate the composition of EACH product strength using the table below, adjust and add lines as needed. For solid oral dosage forms, the table should contain only the ingredients in the product core. A copy of the table should be filled in for the coating ingredients, if applicable.* | | | | | | |
| Component | Quality Standard | Function | Strength (label claim) | | | |
| XX mg | | XX mg | |
| Quantity per unit | %\* | Quantity per unit | %\* |
| Medicinal ingredient(s): |  |  |  |  |  |  |
| 1 |  |  |  |  |  |  |
| 2 |  |  |  |  |  |  |
| NMI(s): |  |  |  |  |  |  |
| 1 |  |  |  |  |  |  |
| 2 |  |  |  |  |  |  |
| 3 |  |  |  |  |  |  |
| TOTAL | |  |  |  |  |  |

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

1. **REFERENCE PRODUCT OVERVIEW**

**1.1 Canadian Reference Product (CRP) Confirmation**

*Instruction – Information identifying the CRP used in any comparative studies conducted in connection with the submission (as per subsection C.08.002.1(2) of the regulations). For example, photos of the CRP labels of the product(s) purchased that clearly show the information outlined below.*

* Manufacturer name (market authorization holder):
* Product brand name:
* Product identifier (e.g. DIN, National Drug Code (NDC) number, etc.):
* Lot number:
* Expiry date:

**1.2 Justification for use of a CRP purchased outside of Canada (i.e. foreign-sourced reference product, FRP)**

*Instruction – If using an FRP in any comparative studies conducted in connection with the submission (as per subsection C.08.002.1(2) of the regulations), include information identifying the FRP. For example, photos of the FRP labels (including package inserts) of the product(s) purchased that clearly show the information outlined below. Also include supporting rationale for using the FRP.*

* Manufacturer name (market authorization holder):
* Product brand name:
* Product identifier (e.g. market authorization number, etc.):
* Lot number:
* Expiry date:
* Justification:

**1.3 Biowaiver Requests**

*Instruction – If comparative bioavailability/bioequivalence data has not been submitted for all strengths, the sponsor should provide a scientific justification for not submitting such data. Issues such as the proportionality of formulations included in the submissions should be addressed.*

* Justification:

**1.4 Certificates of Analysis**

* Location of the certificates of analysis in the submission for the test and reference products:

**1.5 Product Labelling**

* Location of the inner and outer labels and package insert in the submission:

1. **IDENTIFICATION OF DRUG CHARACTERISTICS AND DOSAGE FORM PROPERTIES**

**Determination of Applicable Standards**

*Instruction – Include information in every field of section 2.*

**2.1 Identify the type(s) of formulation included in the submission**

*(e.g., immediate release, enteric-coated modified release, etc.)*

**2.2 Indication(s) for use**

**2.3 State whether the dosage form is a combination product**

*(i.e., is there more than one drug substance in the formulation? If so, ensure that the remaining sections are completed with regard to both ingredients)*

**2.4 Proper, Common or Non-proprietary name of drug substance (medicinal ingredient)**

**2.5 Is the bioequivalence assessment to be based on the parent compound or metabolite?**

*Instruction – If the assessment is to be based on a metabolite, a justification should be provided as to why the parent compound cannot be used.*

**2.6 Physicochemical Characteristics**

* Solubility (if applicable)

**2.7 Pharmacokinetic Characteristics**

*Instruction – Cite the sources for all information in this section.*

2.7.1 Absorption

1. Identify primary site(s) of absorption
2. Summarize reported information on the rate and extent of absorption from pertinent dosage forms

*Instruction – Include reported values for AUC, Tmax, and Cmax.*

1. Identify any reported effect of food on absorption
   * 1. Distribution
2. Identify site(s) of distribution
3. State the extent of protein binding (as percentage of total drug)

2.7.3 Elimination

1. Identify the route(s) and the percentage of drug elimination attributable to each route
2. State the reported terminal elimination half-life of the drug
   * 1. Metabolism

##### Identify the site(s) and pathway(s) of metabolism

##### Identify the extent of first-pass metabolism

* + 1. Other Pharmacokinetic Considerations

1. State whether genetic polymorphism affects the pharmacokinetics of this drug

*Instruction – List affected route(s) of metabolism and any toxicologic concerns.*

1. State whether the substance is chiral. Identify the effects of the chirality on the activity and pharmacokinetics of the substance

*Instruction – Pay particular attention to stereospecific absorption and metabolism.*

1. If the substance is chiral, was a stereospecific assay used? If not, provide justification
2. State whether the drug display non-linear kinetics within the usual dosage range. Particular attention should be paid to absorption and first-pass metabolism

*Instruction – State concentrations at which non-linearity occurs and any known explanations.*

1. State whether metabolism is capacity limited

*Instruction – If so, provide information on doses affected by capacity limitations.*

* 1. **Therapeutic and Toxicity Concerns**

For each species:

1. Identify site(s) and mechanism(s) of action
2. State whether the time to onset of action is important
3. State the normal therapeutic range of the drug
4. Identify the minimum drug concentrations at which toxic effects are observed
5. State whether the drug is considered to be highly toxic
6. State whether the drug is considered to have a narrow therapeutic range
7. **BIOPHARMACEUTIC STUDIES**

**Comparative Bioavailability (BA) and Bioequivalence (BE)**

**3.1 Summary of Bioavailability/Bioequivalence Studies Performed**

*Instruction – Provide a brief description of each comparative study included in the submission.*

**3.2 Has comparative bioavailability data been submitted for all strengths?**

*Instruction – If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification. Issues such as the proportionality of formulations included in the submission should be addressed under Biowaiver Requests section above.*

***FOR EACH PIVOTAL COMPARATIVE BIOAVAILABILITY STUDY PERFORMED***

*Instruction – Sections 3.3-9 below should be copied and completed for each. Sections 1.1-1.4 should also be completed for each study.*

**3.3 Clinical Study Report**

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

**3.4 Investigators and Study Administrative Structure**

* Name of principal investigator(s):

Location of resume in the submission:

* Clinical Facility:

*Instruction – Name and full mailing address.*

* Clinical Laboratories:

*Instruction – Name and full mailing address.*

* Analytical Laboratories

*Instruction – Name and full mailing address.*

* Company performing pharmacokinetic/statistical analysis

*Instruction – Name and full mailing address.*

**3.5 Study Objectives**

*Instruction – Briefly state the study objectives.*

**3.6 Investigational Plan**

3.6.1 Overall Study Design and Plan – Description

*Instruction – Briefly describe the study design, 1-2 sentences.*

3.6.2 Selection of Study Population – Target species

*Instruction – If more than one target species, ensure all are covered in the sections below.*

3.6.2.1Inclusion Criteria

3.6.2.2 Exclusion Criteria

3.6.2.3 Removal of Subjects from Therapy or Assessment

* 1. Number of subjects enrolled in the study

*Instruction – All subjects including alternates, withdrawals and drop-outs. The number of subjects must be appropriate for statistical analysis, and an unequal number of subjects is not recommended.*

* 1. Withdrawals

*Instruction – Identify each withdrawal by subject and provide the reason for withdrawal and at what study phase (e.g., pre- or post-treatment) the withdrawal occurred.*

3.6.2.4 Health Verification

*Instruction – The intent is not to submit all the health records in the BA/BE studies conducted; the emphasis is to include such information when it is relevant to subject removal. Detailed information on health checks should be on file and made available upon request.*

* List criteria used and all tests performed in order to judge health status
* Indicate when tests were performed
* Study site normal values

Location in the submission of the study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen:

* Report any results that were outside of study site normal values

Location in the submission of the summary of anomalous values:

* + 1. Treatments Administered
  + **Test Product**
  1. Strength (label claim) of product(s) used in pivotal comparative bioavailability study:
  2. Lot number and date of manufacture for the test product:
  3. Potency (measured content) of test formulation as a percentage of label claim:

*Instruction – This information should be cross-referenced to the location of the certificate of analysis in the submission.*

* + **Reference Product**

1. Name and manufacturer of the reference product:
2. List of dosage form(s) and strength(s) marketed in Canada by the manufacturer of the reference product:
3. Strength (label claim) of product(s) used in pivotal comparative bioavailability study:
4. Lot number and expiry date for the reference product:
5. Potency (measured content) of the reference formulation as a percentage of label claim:

*Instruction – This information should be cross-referenced to the location of the certificate of analysis in the submission.*

* + 1. Selection of Doses in the Study
* Dose administered (in mg/kg, strength used):
* Route of administration:
  + 1. Selection and Timing of Dose for Each Subject

### Volume and type of fluid given with dose (fed studies):

### Interval between doses (length of washout):

### Protocol for the administration of food and fluid:

* + 1. Blinding

(a) Identify which of the following were blinded. If any of the groups were not blinded, provide a justification:

* Study monitors
* Subjects
* Analysts

### (b) Identify who held the study code and when the code was broken:

3.6.7 Drug Concentration Measurements

1. Biological fluid(s) sampled

1. Sampling Protocol

* Number of samples collected per subject:
* Volume of fluid collected per sample:
* Total volume of fluid collected per subject per phase of the study:
* List the study sampling times:
* Identify any deviations from the sampling protocol:

*Instruction – Describe and explain the reasons for deviations from sampling protocol. Comment on impact on the study. Indicate whether the deviations were accounted for in the pharmacokinetic analyses.*

* Location of the summary in the submission:

1. Sample Handling

* Describe the method of sample collection:
* Describe sample handling and storage procedures:

1. **STUDY SUBJECTS**

**4.1 Species/Breed and Other Baseline Characteristics**

a) Identify study population

*Instruction – Specify if normal, healthy or patients.*

b) Summary of species/breed and gender of subjects

*Instruction – Individual data should be included in the submission.*

c) Identify subjects noted to have special characteristics and state notable characteristics (such as stage of lactation, as applicable)

d) Range and mean age ± SD of subjects

*Instruction – Individual data should be included in the submission.*

e) Range and mean weight ± SD of subjects

*Instruction – Individual data should be included in the submission.*

1. **PROTOCOL DEVIATIONS**

**5.1 Protocol deviations during the clinical study**

*Instruction – Describe any such deviations and discuss their implications with respect to bioequivalence.*

1. **SAFETY EVALUATION**

**6.1 Identify adverse reactions observed**

Location of this summary in the submission:

*Instruction – List any adverse reactions 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. Also discuss the implications of the observed adverse reactions with respect to bioequivalence.*

1. **EFFICACY EVALUATION**

**Efficacy Results and Tabulations of Individual Subject Data**

**7.1 Presentation of Data**

* Location in submission of tables of mean and individual subject concentrations:
* Location in submission of mean and individual linear and semi-logarithmic subject drug concentration vs. time plots:

**7.2 Pharmacokinetic (PK) Parameters**

*Instruction – Complete the following tables. A set of tables is provided for both a single-dose and a steady-state study. Delete any unused set of tables.*

1. The following parameters have been derived:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

**[Table for single dose studies]**

| Analyte Name  (\_\_\_ x \_\_\_ mg)  From measured data  **uncorrected for potency**  Geometric Mean  Arithmetic Mean (CV %) | | | | |
| --- | --- | --- | --- | --- |
| Parameter | Test\* | Reference† | % Ratio of  Geometric Means | Confidence Interval# |
| AUCT‡  (units) |  |  |  |  |
| AUCI  (units) |  |  |  |  |
| Cmax  (units) |  |  |  |  |
| Tmax§  (h) |  |  |  |  |
| T½€  (h) |  |  |  |  |

\* Identity of the test product

† Identity of the reference product, including the manufacturer, and origin (country of purchase)

‡ For drugs with a half-life greater than 24 hours AUCT should be replaced with AUC0-72

§ Expressed as either the arithmetic mean (CV%) only or the median (range) only

€ Expressed as the arithmetic mean (CV%) only

# Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for AUCT, AUCI, and Cmax (if required)

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

**[Table for multiple dose studies]**

| Analyte Name  (\_\_\_ x \_\_\_ mg)  From measured data  **uncorrected for potency**  Geometric Mean  Arithmetic Mean (CV %) | | | | |
| --- | --- | --- | --- | --- |
| Parameter | Test\* | Reference† | % Ratio of  Geometric Means | Confidence Interval# |
| AUCtau  (units) |  |  |  |  |
| Cmax  (units) |  |  |  |  |
| Cmin  (units) |  |  |  |  |
| Tmax§  (h) |  |  |  |  |
| FL¶ (%) |  |  |  |  |

\* Identity of the test product

† Identity of the reference product, including the manufacturer, and origin (country of purchase)

§ Expressed as either the arithmetic mean (CV%) only or the median (range) only

¶ Expressed as the arithmetic mean (CV%) only

# Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for AUCtau and Cmax (if required)

b) Ratio of AUCT to AUCI

*Instruction – State mean ratio for both test and reference.*

c) Other parameters calculated

*Instruction – Identify and provide mean for both test and reference.*

**7.3 Statistical Analysis**

*Instruction – Provide the following results from the ANOVA on the logarithmically transformed AUCT and CMAX and other relevant parameters, e.g. in the case of steady-state designs, AUCτ , CMAX , and CMIN.*

**Mean Square Error, derived CV and associated degrees of freedom**

Location of tabulation in submission:

|  |  |  |  |
| --- | --- | --- | --- |
| PK Parameter | MSE | CV | DF |
| AUCT |  |  |  |
| AUCI |  |  |  |
| Cmax |  |  |  |

1. **ANALYTICAL STUDY REPORT**

**8.1 Analytical Technique**

8.1.1 Analytical protocol

Location of the analytical protocol in the submission:

8.1.2 Identify analyte(s) monitored – should be “parent”

8.1.3 Identify analytical technique employed

8.1.4 Identify method of detection

8.1.5 Identify internal standard

8.1.6 If based on a published procedure, state reference citation

8.1.7 Identify any deviations from protocol

8.1.8 Dates of subject sample analysis

8.1.9 Longest period of subject sample storage

*Instruction – Identify the time elapsed between the first day of the sample collection and the last day of the subject sample analysis.*

8.1.10 State whether all samples for a given subject were analysed together in a single analysis run

**8.2 Standard Curves**

Location in the submission of the tabulated raw data and back calculated data with descriptive statistics:

1. List number and concentration of calibration standards used (typically minimum 5 of concentrations)

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)

*Instruction – Summarize inter-day and intra-day precision and accuracy at the LOQ.*

f) State the limit of detection (LOD)

**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**

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 Analyses**

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**

Location in the submission where the sample chromatograms can be found:

1. **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**

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

1. Summarize data on long-term storage stability
2. Summarize data on freeze-thaw stability

1. Summarize data on bench top stability
2. Summarize data on autosampler storage stability
3. Summarize data from any other stability studies conducted

*(e.g., stock solution stability)*

**9.3 Specificity**

*Instruction – Methods to verify specificity against endogenous/exogenous compounds and results.*

**9.4 Recovery**

1. *Instruction – Method and results of assessment for analyte and internal standard including mean and CV%.*