SUMMARY OF SUBMITTED DATA

Newfoundland and Labrador Interchangeable Drug Product Formulary

To be completed by sponsor:

Product Name:	
Active Ingredient(s):	
Dosage Form:	
Strength(s):	
Contact Person:	
Telephone:	
Facsimile:	
Is a Copy of Notice of Compliance Attached?	
Approved by: (Title and Signature)	

1.0 Information On Test Product

1.1 Tabulate the composition of the formulation(s)

(Tabulate the composition of the each product strength using the table below. 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 any.

Master Formula Number						
	mg	**%***	**mg**	**%***	**mg**	**%***
Ingredient Name **(include compendial standard)**						
TOTAL						

*** Each ingredient expressed as a percentage of the total core or coating weight, as applicable.**

1.2 Biostudies performed

(Provide a brief description of each comparative bioavailability study included in the submission. If no bioavailability study is included then the reason(s) for not having performed such studies)

(Provide data on studies used to compare test and reference products if no biostudies are performed)

1.3 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. Issues such as the proportionality of formulations included in the submission should be addressed)

2.0 Information On Reference Product

2.1 Name and manufacturer of the reference product

2.2 List dosage form(s) and strength(s) marketed in Canada by the manufacturer of the reference product

2.3 Justification for use of non-Canadian reference product

(If a non-Canadian reference product was used, provide a justification which addresses all the criteria outlined in the Therapeutic Products Programme Policy entitled Canadian Reference Product.)

3.0 Identification of Drug Characteristics and Dosage form Properties:

Determination of Applicable Standards

3.1 Identify the type(s) of formulation included in the submission

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

3.2 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.)

3.3 Common name or compendial name of the active ingredient(s)

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

(If the assessment is to be based on metabolite a justification should be provided as to why the parent compound cannot be used)

3.5 Aqueous Solubility

3.5.1 Comparative dissolution profiles of test and reference product. Include data for at least three production batches of test product.

3.6 Pharmacokinetic characteristics

(Please cite the sources for all information in this section)

3.6.1 Absorption

i. Identify primary site(s) of absorption

ii. Summarize reported information on rate and extent of absorption from pertinent dosage forms ***(Include reported values for AUC, T_{MAX}, and C_{MAX})***

iii. Identify any reported effect of food on absorption

3.6.2 Distribution

i. Identify site(s) of distribution

ii. State the extent of protein binding ***(as a percentage of total drug)***

3.6.3 Elimination

i. Identify the route(s) and the percentage of drug elimination attributable to each route

ii. State the reported terminal elimination half-life of the drug

3.6.4 Metabolism

i. Identify the sites(s) and pathway(s) of metabolism

ii. Identify extent of first-pass metabolism

3.6.5 Other pharmacokinetic considerations

i. State whether genetic polymorphism affects the pharmacokinetics of this drug ***(List affected route(s) of metabolism and any toxicologic concerns)***

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

(Pay particular attention to stereospecific absorption and metabolism)

a) If the substance is chiral, was a stereospecific assay used? If not, please justify.

iii. **State whether the drug displays non-linear kinetics within the usual dosage range. Particular attention should be paid to absorption and first-pass metabolism** ***(State concentrations at which non-linearity occurs and any known explanations)***

iv. **State whether the metabolism is capacity limited**

(If so, provide information on doses affected by capacity limitations.)

3.7 Therapeutic and toxicity concerns

3.7.1 **Identify the site(s) and mechanisms of action**

3.7.2 **State whether the time to onset of action is important**

3.7.3 **State the normal therapeutic range of the drug**

3.7.4 **Identify the minimum drug concentrations at which toxic effects are observed**

3.7.5 **State whether the drug is considered to be highly toxic**

3.7.6 **State whether the drug is considered to have a narrow therapeutic range**

FOR EACH BIOSTUDY CONDUCTED

4.0 Study Specific Product Information

4.1 Strength of product (label claim)

4.2 Batch number and date of manufacture for test product

4.3 Potency (measured content) of the test formulation as a percentage of label claim

(State location of certificate of analysis in submission) (Volume: pages:)

4.4 Batch number and expiry date for reference product

4.5 Potency (measured content) of the reference formulation as a percentage of label claim

(State location of certificate of analysis in submission) (Volume: pages:)

5.0 Bioavailability Study Background Information

5.1 Name of principal investigator(s)

(State location of C.V. in submission) ***(Volume: page(s):)***

5.2 Clinical facility

(Name and full mailing address)

5.3 Clinical laboratories

(Name and full mailing address)

5.4 Analytical laboratories

(Name and full mailing address)

5.5 Company performing statistical/pharmacokinetic analysis

(Name and full mailing address)

5.6 Institutional review board

(Name of review committee, date of approval and location of approval in submission) (Volume: page(s):)

6.0 Summary of Study Design and Subject Information

6.1 Briefly state study objectives

6.2 Describe the type of study design employed

6.4 Number of subjects enrolled in the study

(All subjects including withdrawals and dropouts)

6.5 Withdrawals

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

6.6 Identify study population

(i.e., normal healthy adult volunteers or patients)

6.6.1 Summary of ethnic origin and gender of subjects

6.6.2 Identify subjects noted to have special characteristics and state notable characteristics

(e.g., fast acetylators of debrisoquine)

6.6.3 Range and mean age ± SD of subjects

6.6.4 Range and mean height and weight ± SD of subjects

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

6.8 Number of smokers included in the study

6.8.1 Indicate how many cigarettes smoked per day per subject

6.8.2 Comment on Impact on Study

6.9 List the exclusion criteria applied to subjects

6.10 Blinding

6.10.1 Identify which of the following were blinded. If any of the groups were not blinded, please provide a justification for not doing so

i. study monitors

ii. subjects

iii. ***analysts***

6.10.2 ***Identify who held the study code and when the code was broken***

6.11 Describe protocol for the administration of food and fluid

6.12 Dosing

6.12.1 ***State dose administered***

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

6.12.2 ***State volume and type of fluid consumed with dose***

6.13 Restrictions on posture and physical activity during study

6.14 Interval between doses

(I.e., length of washout)

6.15 Biological fluid(s) sampled

6.16 Sampling protocol

6.16.1 Number of samples collected per subject

6.16.2 Volume of fluid collected per sample

6.16.3 Total volume of fluid collected per subject per phase of the study

6.16.4 List the study sampling times

6.16.5 Identify any deviations from the sampling protocol

(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)

6.17 Sample handling

6.17.1 Describe method of sample collection

6.17.2 Describe sample handling and storage procedures

6.18 Identify adverse reactions observed

(List any adverse reactions by subject number. State whether a reaction occurred following administration of 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 reactions with respect to bioequivalence)

6.19 Other protocol deviations during clinical segment of study

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

7.0 Information on the Analytical Methodology and Analysis of Subject Samples

7.1 Analytical technique

7.1.2 Identify analyte(s) monitored

7.1.3 Identify analytical technique employed

7.1.4 Identify method of detection

7.1.5 Identify internal standard

7.1.6 If based on a published procedure, state reference citation

7.1.7 Identify any deviations from protocol

7.2 Provide start and stop dates for each phase of the clinical segment of the study

7.3 Dates of subject sample analysis

7.4 State whether all samples for a given subject were analyzed together in a single analysis run

7.5 Standard curves

7.5.1 List number and concentration of calibration standards used

7.5.2 State number of curves run during the study

7.5.3 Summarize descriptive data including slope, intercept, correlation coefficients

7.6 Describe the regression model used including any weighting

7.7 State the limit of quantitation (LOQ)

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

7.8 State the limit of detection (LOD)

7.9 Quality control samples

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

7.9.2 State the number of QC samples tested on each analysis day per concentration

7.10 Precision and accuracy

7.10.1 Summarize inter-day and intra-day accuracy and precision during assay validation

7.10.2 Summarize inter-day and intra-day accuracy and precision during assay re-validation

7.10.3 Summarize inter-day and intra-day accuracy and precision of QC samples analyzed during subject sample analysis and inter-day precision of back-calculated standards

7.11 Stability

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

7.11.1 Summarize data on long-term storage stability

7.11.2 Summarize data on freeze-thaw stability

7.11.3 Summarize data on bench top stability

7.11.4 Summarize data on autosampler storage stability

7.11.5 Summarize data from any other stability studies conducted

7.12 Specificity

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

8.0 Summary of Drug Disposition and Pharmacokinetic Analysis

8.1 Presentation of data

***8.1.1** State location in submission of tables of mean and individual subject concentrations (Volume: page(s):)*

***8.1.2** State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots: (Volume: page(s):)*

8.2 Pharmacokinetic (PK) Parameters

(Complete the following tables for uncorrected and potency corrected data, modify the units if required. A set of tables is provided for both a single-dose and a steady-state study. Please delete the unused set of tables.)

The following parameters have been derived:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA FOR SINGLE DOSE STUDIES

Analyte Name
(Amount of product administered - number/volume and strength)
From measured and log transformed data
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	***TEST***	***REFERENCE***	***% RATIO OF GEOMETRIC MEANS***

AUC_T (µg.h/mL)			
AUC_I (µg.h/mL)			
C_{MAX} (µg/mL)			
T_{MAX}^{*} (h)			
$T_{½}^{*}$ (h)			

** expressed as arithmetic mean (CV%) only.*

Geometric Mean

PARAMETER	*TEST*	*REFERENCE*	*% RATIO OF GEOMETRIC MEANS*
AUC_T (µg.h/mL)			
AUC_I (µg.h/mL)			
C_{MAX} (µg/mL)			

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA FOR STEADY STATE STUDIES

Analyte Name
(Amount of product administered - number/volume and strength)
From measured and log transformed data
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	***TEST***	***REFERENCE***	***% RATIO OF GEOMETRIC MEANS***
AUC (µg.h/mL)			
C_{MAX} ***(µg/mL)***			
C_{MIN} ***(µg/mL)***			
T_{MAX}^{*} ***(h)***			
FL* ***(%)***			

**** expressed as arithmetic mean (CV%) only.***

Geometric Mean

PARAMETER	***TEST***	***REFERENCE***	***% RATIO OF GEOMETRIC MEANS***
AUC (µg.h/mL)			
C_{MAX} (µg/mL)			
C_{MIN} (µg/mL)			

8.2.1 Ratio of AUC_T to AUC_I

(State mean ratio for both test and reference)

8.2.2 Other parameters calculated

(Identify and provide mean for both test and reference)

8.3 Statistical analysis

(Provide the following results from the ANOVA on the logarithmically transformed AUC_T and C_{MAX} and other relevant parameters, e.g. in the case of steady-state designs, AUC , C_{MAX} , and C_{MIN})

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

8.3.2 ***For the test to reference, state the percent ratios with their respective geometric confidence intervals (CI) about the means for both measured and potency corrected data***