



**DRAFT GUIDANCE FOR INDUSTRY**  
Preparation of Comparative Bioavailability Information  
for Drug Submissions in the CTD Format

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**Health Products and Food Branch**  
**Guidance Document**

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:</p> <ul style="list-style-type: none"> <li>• Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li> <li>• Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li> </ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

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## SECTION 1

### 1. INTRODUCTION

The purpose of this guidance is to define the Common Technical Document (CTD) format of drug submissions which rely on comparative bioavailability studies to establish safety and efficacy. This guidance also references some of the technical requirements related to the conduct and analysis of such studies.

Frequently, the safety and efficacy of a given drug product is established on the basis of a “pivotal” comparative bioavailability (bioequivalence) study or studies. Examples of such situations include but are not limited to:

- the introduction of new dosage forms (e.g., tablet to capsule) or new strengths of a product;
- changing the formulation or manufacturing procedures for a product;
- “bridging” between the to-be-marketed formulation and the formulation(s) used in clinical trials; and
- the introduction of a new subsequent-entry drug product on the basis of “equivalency” with a marketed reference product.

As the majority of submissions of this type are Abbreviated New Drug Submissions (ANDS) for presentation to the Therapeutic Products Directorate (TPD) in compliance with the requirements of Division 8 of part C of the *Food and Drug Regulations*, this guidance is oriented towards submissions of this type. Nevertheless, it should also be used in the preparation of submissions for other dosage forms (e.g., oral solutions, suppositories) as well as for Supplemental Abbreviated New Drug Submissions (SANDS), New Drug Submissions (NDS), and Supplemental New Drug Submissions (SNDS) involving comparative bioavailability studies.

When preparing such submissions, it is also necessary to consult other related Health Canada (HC) guidances respecting the conduct and analysis of bioavailability and bioequivalence studies as well as labelling. For a complete list of HC guidances, policies, templates, and forms, the TPD website should be consulted.

Deviations, additions, or omissions from existing guidelines must be explained, either by introductory remarks or within each relevant Module of the submission, whichever is more appropriate.

## 1.1 Definitions

### 1.1.1 ANDS Eligibility

Subsection C.08.002.1 (1) of the *Food and Drug Regulations* defines the eligibility criteria for an ANDS as stated below:

“A manufacturer of a new drug may file an abbreviated new drug submission for the new drug where, in comparison with a Canadian reference product,

- a. the new drug is the pharmaceutical equivalent of the Canadian reference product;
- b. the new drug is bioequivalent with the Canadian reference product, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;
- c. the route of administration of the new drug is the same as that of the Canadian reference product; and
- d. the conditions of use for the new drug fall within the conditions of use for the Canadian reference product.”

Generally, subsequent market entry products which satisfy the above criteria would be eligible for filing as an ANDS.

### 1.1.2 Canadian Reference Product

Canadian reference product is defined in C.08.001.1 of the *Food and Drug Regulations* as:

- “a. a drug in respect of which a notice of compliance is issued pursuant to section C.08.004 and which is marketed in Canada by the innovator of the drug,
- b. a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued pursuant to section C.08.004 cannot be used for that purpose because it is no longer marketed in Canada, or

- c. a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph a ”.

The TPD policy on *Canadian Reference Product* outlines acceptance criteria for the use of a Canadian reference product purchased outside of Canada, pursuant to paragraph c above.

### ***1.1.3 Pharmaceutical Equivalence***

As stated in the section C.08.001.1 of the *Food and Drug Regulations*, pharmaceutical equivalent means "a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients".

### ***1.1.4 Declaration of Equivalence***

As stated in the subsection C.08.004 (4) of the *Food and Drug Regulations*, "a Notice of Compliance issued in respect of a new drug on the basis of information and material contained in a submission filed pursuant to section C.08.002.1 shall state the name of the Canadian reference product referred to in the submission and shall constitute a declaration of equivalence for that new drug."

### ***1.1.5 Bioequivalence***

Bioequivalence is defined in the TPD guidance *Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A* as "a high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse reactions, or both."



## SECTION 2

### 2. SUBMISSION PRESENTATION

This section outlines the Canadian requirements for providing an ANDS in the CTD paper format.

#### 2.1 Format

An ANDS should be presented with a modular structure as outlined in section 3.0 (Submission Structure) of this guidance. Section 4.0 (Structure and Content of New Drug Submissions in the CTD Format) of the *Guidance for Industry - Preparation of New Drug Submissions in the CTD Format* should be consulted for guidance on the filing of Supplements and Notifiable Changes (NCs).

#### 2.2 Language / Legibility and Size / Volume Binding and Labelling / Number of Copies / Pagination

An ANDS should be presented in accordance with the physical specifications for submitting paper submissions in the CTD format as outlined in section 5.0 (Presentation of the Submission) of the *Guidance for Industry - Preparation of New Drug Submissions in the CTD Format*<sup>1</sup>.

## SECTION 3

### 3. SUBMISSION STRUCTURE

In using the CTD format for ANDSs, the dossier should be organized similarly to a NDS, although certain CTD modules will not normally need to be submitted.

The majority of ANDSs are supported by one or more pivotal comparative bioavailability studies. When filing an ANDS in the CTD format, it is anticipated that *only* the following relevant modules will normally be required.

- Module 1: Administrative Information and Prescribing Information
  - 1.1 Table of Contents (Modules 1-5)
  - 1.2 Application Information
  - 1.3 Product Labelling

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<sup>1</sup> This guidance and accompanying notice should also be consulted regarding general considerations on the filing of submissions in the CTD format.

- 1.4 Health Canada Summaries
  - 1.5 Environmental Assessment Statement
  - 1.6 Electronic Review Documents
  - Module 2: Common Technical Document Summaries
    - 2.1 Overall CTD Table of Contents (Modules 2-5)
    - 2.2 Introduction
    - 2.3 Quality Overall Summary
  - Module 3: Quality
  - Module 5: Clinical Study Reports
    - 5.1 Table of Contents for Module 5
    - 5.2 Tabular Listing of all Clinical Studies
    - 5.3 Clinical Study Reports
      - 5.3.1 Biopharmaceutic Studies
        - 5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports
        - 5.3.1.3 In vitro-In vivo Correlation Study Reports
        - \*5.3.1.4 Reports of Bioanalytical and Analytical Method for Human Studies
      - 5.3.7 Case Report Forms and Individual Patient Listings
    - 5.4 Literature References
- \* Bioanalytical or analytical methods for BA/BE or *in vitro* dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

### 3.1 Module 1: Administrative Information and Prescribing Information

Module 1 is to include regional administrative documents and proposed labelling for use in the region.

An outline of Module 1 for ANDSs is provided below. The information to be included in Module 1 is identified in section 4.1 of the *Guidance for Industry - Preparation of New Drug Submissions in the CTD Format*. However, it is important to note that additional guidance for some sections is provided within the outline below.

## **1.1 Table of Contents (Modules 1-5)**

### **1.2 Application Information**

1.2.1 Drug Submission Application Form (HC/SC 3011)

1.2.2 Submission Fee Application Form

1.2.3 Submission Certification Form

1.2.4 Patent Information

1.2.5 Good Manufacturing Practices (GMP) and Establishment Licensing (EL)  
Information

1.2.6 Letters of Access

1.2.7 International Registration Status

1.2.8 Other Application Information

This section serves as a placeholder for other administration information that may be filed by the applicant in relation to the submission. Examples include the following.

#### **a. Canadian Reference Product Confirmation**

Confirmation that the Canadian reference product was used in the comparative bioavailability study may be provided in the form of a purchase receipt(s), signed confirmation in writing that the reference was purchased in Canada, or a photocopy of the product label(s) which clearly shows the trade name, product strength, lot #, expiry date, and Drug Identification Number (DIN) of the product administered in the biostudy.

Pursuant to paragraph (c) of section C.08.001.1 of the *Food and Drug Regulations*, the use of a Canadian reference product purchased outside of Canada, must be supported by a justification statement that should be provided in this section. The justification should address all of the criteria outlined in the TPD *Canadian Reference Product* policy and will include supporting data (e.g., comparative dissolution) which should be provided in the relevant modules of the CTD submission (i.e., Modules 2-5).

## **b. Waiver Requests**

Generally, results from comparative bioavailability studies should be provided in support of the safety and efficacy of each proposed product and of each proposed strength included in an ANDS. In the absence of such studies, a justification supporting a waiver of this requirement should be provided in this section for each product and each strength.

For example, if there are several strengths of the proposed product, and comparative bioavailability data has not been submitted for all strengths, the sponsor should provide a scientific justification for not conducting studies on each strength. This justification may address issues such as the nature of the kinetics of the drug (e.g., linear versus non-linear), and the proportionality of the strengths for which a waiver is sought to the strength on which a comparative bioavailability study was conducted.

The statement of justification for waiver will include supporting data (e.g., comparative dissolution data) which should be provided in the relevant module(s) of the CTD submission (i.e., Modules 2-5). For example, comparative dissolution profiles should be provided in Module 3, section 3.2.P.2 (Pharmaceutical Development).

## **c. Certificates of Analyses**

Certificates of Analyses should be provided in this section in order to verify the potency (as a percent of the label claim) for both the Test and Reference products.

## **1.3 Product Labelling**

### **1.3.1 Product Monograph**

The Product Monograph for second and subsequent market entry products must provide information directly relevant to the safe and effective use of the new drug. Please note that the conditions of use for the new drug must fall within the conditions of the use of the Canadian reference product. A copy of the current labelling and Product Monograph for the reference product must be included in the submission (in this section). Any differences between the Product Monographs must be annotated to supporting data. Copies of data or references to support such differences must be included in the submission. Please note that the labelling must be current at the time the NOC is issued.

The Product Monograph must include the Summary Table(s) of the Comparative Bioavailability Data (the format and content of which is presented in Appendix A). The location of the summary table(s) within the Product Monograph is outlined in the most current TPD guidance document(s).

#### *1.3.2 All Inner and Outer Labels*

#### *1.3.3 Non-Canadian Package Inserts*

### **1.4 Health Canada Summaries**

#### *1.4.1 Certified Product Information Document*

#### *1.4.2 Comprehensive Summary: Bioequivalence*

A completed paper copy of the Comprehensive Summary: Bioequivalence (CS-BE) for pivotal bioequivalence studies is to be included in this module. The electronic copy is to be provided in Module 1.6.

**Note that if the Comprehensive Summary: Bioequivalence (CS-BE) is completed for submissions that rely solely on pivotal comparative bioavailability studies to establish safety and efficacy, Modules 2.4-2.7 of the CTD do not need to be completed.**

If the dossier includes a pivotal comparative bioavailability study(ies) as well as other types of safety and efficacy studies, Modules 2.4-2.7 must be completed, as applicable, irregardless of whether or not the CS-BE was completed for the pivotal comparative bioavailability study(ies).

If the submission involves only a solution for parenteral use, and the Product Monograph has been provided as described above, and data concerning the pharmaceutical equivalency and characteristics of the formulation have been provided in the Chemistry and Manufacturing portion of the submission, then no additional information under Module 5 of this guidance is required.

The CS-BE is pivotal in the review process. It should provide a comprehensive, integrated summary of the overall content of information in the submission as it pertains to the comparability of the product with the Canadian reference product of proven safety and effectiveness under the proposed conditions of use. This should include a scientific rationale and justification for the study design used, the parameters assessed and the standards applied. It must also be cross-referenced to the supporting documents provided in Module 5 (Clinical Study Reports).

The CS-BE template provides placeholders for the following information (which may not necessarily be a component of the clinical study report(s) submitted in Module 5).

### **Physicochemical Characteristics**

This section should provide information characterizing the physicochemical properties of the drug, e.g.,  $pK_a$ , molecular weight, solubility in water (g/mL), chirality and polymorphism.

### **Pharmacology**

This section should include a concise synopsis of the salient features of the drug's pharmacologic actions, e.g., site and mechanism of action.

### **Pharmacokinetics**

Information on the absorption, distribution, metabolism and elimination of the drug should be presented here. The nature and extent of any first pass effect, whether plasma concentrations are directly related to dose (i.e., are the pharmacokinetics linear), and values of half-life ( $T_{1/2}$ ), clearance, volume of distribution and fraction excreted should be established on the basis of the information summarized in this section. This information, together with that provided under **Drug Product Classification**, is important in establishing the type and number of studies to be conducted in support of each ANDS.

- **Absorption-** information characterizing the following properties of the drug is required; area under the curve (AUC), time of maximum observed concentration ( $T_{max}$ ), maximum observed concentration ( $C_{max}$ ), time of onset of action and food effect on absorption. Other characteristics of absorption kinetics (e.g., stereospecificity and dose or concentration dependence of absorption) must also be reported.
- **Distribution-** degree of protein binding, information identifying sites of distribution is required, including reference to whether the drug crosses the blood-brain barrier.
- **Metabolism-** identify the site(s) and pathway(s) of metabolism. Metabolites should be characterized as to biological/pharmacological activity and whether or not drug metabolizing enzymes are induced. Specify the degree of first-pass metabolism and whether metabolism is capacity limited.

- **Elimination-** identify the route(s), percent of elimination and terminal half-life ( $T_{1/2}$ ).

### **Drug Product Classification**

On the basis of the scientific and medical information summarized above, the drug product is to be characterized as one of the following:

- i. conventional (immediate) release formulation with uncomplicated or non-variable pharmacokinetics
- ii. modified release formulation with uncomplicated or non-variable pharmacokinetics
- iii. conventional release formulation with complicated or variable pharmacokinetics
- iv. modified release formulation with complicated or variable pharmacokinetics

The study design, pharmacokinetic parameters and standards of bioequivalence to be used for a declaration of equivalence must be appropriate for the drug product characteristics. In this regard, characteristics of the medicinal ingredient (active drug substance) and the drug product (dosage form) must be taken into consideration. For a description of the characteristics to be used to classify the drug product refer to the TPD guidances *Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B, and the Expert Advisory Committee on Bioavailability -- Report C*.

### **Summary of the Bioavailability/Bioequivalence Studies**

This portion of the CS-BE should include summaries of each study performed to establish the bioavailability and bioequivalence of each formulation and be cross-referenced to the supporting documents provided in Module 5 (Clinical Study Reports).

All requests for waivers and justification statements should be included in Module 1.2.8 (Other Application Information).

For example, when a product is to be marketed in more than one strength, if the formulation of each strength contains the same medicinal and non-medicinal ingredients in the same proportion, the results of a single comparative bioavailability study may be extrapolated to all strengths in the series. In this regard, refer to the TPD policy on *Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms*. In all cases, however, if comparative bioavailability data is not provided for each formulation, the sponsor must provide a scientific justification for waiver of this requirement.

Similarly, if the submission involves a solution (e.g., oral solution, syrup, topical) which the sponsor believes should not require a comparative bioavailability study, a scientific justification must be presented for the waiver of this requirement (e.g., TPD policy: *Waiver of Comparative Bioavailability Requirements for Oral Solutions, Submissions for Generic Topical Drugs, Submissions for Generic Parenteral Drugs*).

### **1.5 Environmental Assessment Statement**

### **1.6 Electronic Review Documents**

Electronic review documents that are to be filed in addition to the paper copies are to be provided here, including but not limited to the proposed Product Monograph, Quality Summaries, Comprehensive Summary: Bioequivalence (CS-BE), and the BE data sets (\*.inf and \*.dat files provided in ASCII format). The required datasets should be provided in computer readable form described in Appendix B.

Section 4.1 of the *Guidance for Industry - Preparation of New Drug Submissions in the CTD Format* should be consulted for further guidance respecting electronic review documents filed in conjunction with a CTD-formatted submission.

## **3.2 Module 2: Common Technical Document Summaries**

The format of the table of contents for Module 2 is provided in the ICH M4 guidance, *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*.

### **2.1 CTD Table of Contents (Modules 2-5)**

This document provides an overall table of contents for Modules 2, 3, 4 (if applicable), and 5.



## **2.2 Introduction**

## **2.3 Quality Overall Summary**

### **2.4-2.7 Clinical/Nonclinical Overviews and Summaries**

**Note that if the Comprehensive Summary: Bioequivalence (CS-BE) is completed for submissions that rely solely on pivotal comparative bioavailability studies to establish safety and efficacy, Modules 2.4-2.7 of the CTD do not need to be completed.**

If the dossier includes a pivotal comparative bioavailability study(ies) as well as other types of safety and efficacy studies, Modules 2.4-2.7 must be completed, as applicable, irregardless of whether or not the CS-BE was completed for the pivotal comparative bioavailability study(ies).

## **3.3 Module 3: Quality**

The information in this part of the submission is to be presented in accordance with relevant HC guidances and policies respecting Quality.

## **3.4 Module 4: Nonclinical Study Reports**

Generally, Module 4 is not expected to be applicable.

## **3.5 Module 5: Clinical Study Reports**

### **5.1 Table of Contents for Module 5**

This section should include the table of contents of Module 5 only. The table of contents for Module 5 should be presented in accordance with *ICH M4: Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*.

### **5.2 Tabular Listing of all Clinical Studies**

### **5.3 Clinical Study Reports**

#### **5.3.1 Biopharmaceutic Studies**

##### **5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports**

Clinical study reports are to be structured in accordance with ICH E3: *Structure and Content of Clinical Study Reports*.

This section of the submission should include a detailed description of each study performed to establish the relative bioavailability and therefore, bioequivalence of each formulation. The reports should be based on raw quantitative and qualitative data. The reports will require the compilation of summary tables and graphs that should be presented as described in the TPD guidances *Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B*.

The clinical study report must include factual and concise descriptions of the methods and materials used, presentation of the results and critical evaluation of the study design, analytical methodology and statistical analysis of data.

It should be presented in sufficient detail to allow an independent evaluation of the drug. It is important that the bioequivalence report state, clearly and unambiguously, the chemical and pharmaceutical formulations used in the study of the drug.

Detailed accounts of, and reasons for, all protocol modifications, deviations, or violations must be highlighted, explained and cross-referenced to the original study protocol.

Generally, it is unlikely the clinical study report for a comparative bioavailability or bioequivalence trial will include all of the sections outlined in the ICH E3 guidance document. It is anticipated that some specific issues within various sections will not be applicable. For example, within section 11.4 (Efficacy Results and Tabulations of Individual Patient Data), it is unlikely that the following sections will be applicable.

Section 11.4.2	
Section 11.4.2.1	Adjustments of Covariates
Section 11.4.2.3	Interim Analyses and Data Monitoring
Section 11.4.2.4	Multicentre Studies
Section 11.4.2.5	Multiple Comparison / Multiplicity
Section 11.4.2.6	Use of an "Efficacy Subset" of Patients
Section 11.4.2.7	Active-Control Studies Intended to Show Equivalence
Section 11.4.2.8	Examination of Subgroups

- Section 11.4.3 Tabulation of Individual Response Data
- Section 11.4.4 Drug Dose, Drug Concentration, and Relationships to Response
- Section 11.4.5 Drug-Drug and Drug-Disease Interactions
- Section 11.4.6 By-Patient Displays

However, section 11.4.2.2 (Handling of Dropouts or Missing Data) and 11.4.7 (Efficacy Conclusions) will be applicable and should be addressed.

Sections of the clinical study report (E3) that are not applicable should appear in the table of contents for the clinical study report with the words “not applicable”; however, it is not necessary to include tabs for these non-applicable sections in the body of the report. If the table of contents for Module 5 of the dossier identifies the sections of the clinical study report (E3), sections that are “not applicable” should be handled in the same manner as described for the table of contents for the report.

The outline for a clinical study report for a comparative bioavailability study has been provided below. All sections are to be addressed unless identified as “not applicable”. For applicable sections, the ICH E3: *Structure and Content of Clinical Study Reports* guidance document should be followed with respect to structure and content unless otherwise specified below.

1. TITLE PAGE
2. SYNOPSIS
3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
5. ETHICS
  - 5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
  - 5.2 Ethical Conduct of the Study
  - 5.3 Patient Information and Consent

## 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This section of the report, in addition to the information detailed in ICH E3, should include the geographic location of the study facility(ies) as well as the name, address, telephone, and fax numbers of individuals responsible for the performance of the study.

## 7. INTRODUCTION

## 8. STUDY OBJECTIVES

## 9. INVESTIGATIONAL PLAN

### 9.1 Overall Study Design and Plan - Description

This section should provide a concise description of the study design (in 2-3 sentences) as outlined in the ICH E3 guidance document.

### 9.2 Discussion of Study Design, Including the Choice of Control Groups

This section is intended to be a detailed discussion of study design issues. With reference to the TPD guidance on the *Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A, and Part B*, the following are examples of issues which merit discussion in this section.

- potential problems associated with the use of a cross-over design, e.g., carry-over effects of treatment during study and duration of the study (likelihood of spontaneous change in subject health status)
- selection of patients versus healthy subjects
- if randomisation was not used, how other techniques, if any, guarded against systemic selection bias
- washout periods
- rationale for dose chosen
- dose interval selection for a multiple-dose study should be explained
- handling of endogenous levels of the analyte of interest

### 9.3 Selection of Study Population

#### 9.3.1 Inclusion Criteria

#### 9.3.2 Exclusion Criteria

#### 9.3.3 Removal of Patients from Therapy or Assessment

## 9.4 Treatments

### 9.4.1 Treatments Administered

### 9.4.2 Identity of Investigational Product(s)

The following information is to be summarized with respect to the test and reference products used in the study.

- i. the strengths available for the test and reference products
- ii. strengths compared
- iii. for the test product(s), in tabular format for each strength, the proportion (percent) of excipient and drug of total core weight (w/w)
- iv. the source of the reference product (with cross-referencing to the Canadian reference product confirmation documentation submitted in Module 1.2.8\*).
- v. lot number, potency (measured drug content), and the date of manufacture for the test and the expiry date for the reference products (cross-referenced to the Certificate of Analysis in Module 1.2.8).

\* Concerning the reference product, as differences in the excipient and/or the manufacturing process can lead to differences in product bioavailability, the comparative bioavailability study should be performed using the product marketed in Canada by the innovator as the reference standard. In this regard, proof of purchase indicating that the product was purchased in Canada, Drug Identification Number (DIN), expiry date and lot number are to be submitted in Module 1 (section 1.2.8). Exceptions to the use of a reference product purchased in Canada may be considered in accordance with the criteria outlined in the TPD policy on *Canadian Reference Product*. If a reference product purchased outside of Canada is used, data must be presented (in Module 1, section 1.2.8) to address each of the criteria specified in the policy.

### 9.4.3 Method of Assigning Patients to Treatment Groups

Usually, for comparative bioavailability studies, the selection of the treatment is by random assignment.

A detailed description of the randomisation method, including how it was executed, should be given in Appendix 16.1.7, with references cited as necessary. A table exhibiting the randomisation codes, patient identifier, and treatment assigned should also

be presented in the appendix. For a multicentre study, the information should be given by centre. The method of generating random numbers should be explained.

#### 9.4.4 Selection of Doses in the Study

#### 9.4.5 Selection and Timing of Dose for Each Patient

The timing (time of day, interval), of dosing should be described, and if it was not specified, this should be noted.

Information with respect to how a dose was taken should be described. For example, the volume, type, and temperature of fluid consumed with each dose should be described.

#### 9.4.6 Blinding

#### 9.4.7 Prior and Concomitant Therapy

#### 9.4.8 Treatment Compliance

### 9.5 Efficacy and Safety Variables

#### 9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

#### 9.5.2 Appropriateness of Measurements

Usually, blood is the biological fluid sampled to measure concentrations of the analyte in serum or plasma. However, there may be circumstances where other biological fluids may be sampled. Alternatives to blood sampling should be discussed in this section including a rationale for the biological sample collected.

The total volume of fluid collected per subject per phase of the study should be discussed with respect to subject safety and the potential impact on plasma concentration data.

In light of advances in analytical methodology it is expected that allowances made in the past for basing a bioequivalence assessment on the metabolite (rather than the parent compound) may no longer be valid. Therefore, in most cases, the bioequivalence assessment should be based on the parent compound.

If the assessment is to be based on the metabolite, a rationale for doing so should be provided in this section.

#### 9.5.3 Primary Efficacy Variable(s)

Not applicable.

#### 9.5.4 Drug Concentration Measurements

### 9.6 Data Quality Assurance

### 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

#### 9.7.1 Statistical and Analytical Plans

This section should be addressed as outlined in the ICH E3 guidance. In general terms, this section provides a description of the analyses planned in the protocol.

This section emphasizes the analyses, comparisons and statistical tests that were planned whereas section 11.4.2 emphasizes the statistical analyses that were actually used.

#### 9.7.2 Determination of Sample Size

With reference to section 3.3 of the TPD guidance document, *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects*, a discussion of sample size, including a subject sample size calculation should be provided.

The actual number of subjects enrolled, and the number completing the study should be provided under section 10.1 (in accordance with ICH E3).

### 9.8 Changes in the Conduct of the Study or Planned Analyses

## 10. STUDY PATIENTS

### 10.1 Disposition of Patient

### 10.2 Protocol Deviations

## 11. EFFICACY EVALUATION

### 11.1 Data Sets Analysed

Generally, this section (as described in ICH E3) is not applicable to comparative bioavailability studies.

### 11.2 Demographic and Other Baseline Characteristics

With reference to the TPD guidance on the *Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B*, where appropriate the following information should be summarized.

- i. choice of study subjects,
- ii. subject characteristics (e.g., age, height/weight ratio, health, ethnicity),
- iii. general medical history and physical examination results
- iv. blood clinical chemistry results
- v. haematology results
- vi. urinalysis clinical screen results
- vii. urinalysis screen of drugs of abuse results
- viii. study site normal values for items (iv) - (vii)

With reference to items iii to viii above the following information should be addressed as follows.

- a. Identification of medical examinations and clinical tests that were conducted pre- and/or post-study should be provided in section 9.5.1 (Efficacy and Safety Measurements Assessed and Flow Chart) in accordance with ICH E3.
- b. All results that were outside of study site normal values, the cause of abnormal values and the impact on study outcome should be addressed in section 12.4.1. A by-patient listing of all abnormal laboratory values are to be provided in section 14.3.4 using the format described in section 12.4.1.

### 11.3 Measurements of Treatment Compliance

Not applicable.

### 11.4 Efficacy Results and Tabulations of Individual Patient Data

#### 11.4.1 Analysis of Efficacy



## 11.4.2 Statistical/Analytical Issues

This section should be addressed as outlined in the ICH E3 guidance.

For a description of the data that should be recorded, the pharmacokinetic parameters, the statistical analyses to be performed, and the format that should be used to present the results, refer to TPD guidances *Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B, and the Expert Advisory Committee on Bioavailability -- Report C*.

Briefly, the measured individual and mean analyte concentrations for each formulation should be tabulated (and provided in Appendix 16.2.6). Any differences from the submitted study protocol must be identified and explained. These data should also be provided in the computer readable form described in Appendix B.

Mean and individual linear as well as semi-log concentration-time profiles for each formulation should be provided in Appendix 16.2.6. The regression lines, based upon at least four points during the terminal log-linear phase of the curve, used to estimate the terminal disposition rate constant ( $\lambda$ ) should also be displayed. The pharmacokinetic parameters should be tabulated for each subject by formulation. Their method of estimation should also be provided.

The submitted analyses of variance (ANOVA) should include the appropriate statistical tests of all effects in the model. The ANOVA should include all data from all subjects. Exclusion of data points or subjects must be justified. An ANOVA should be carried out on the raw (nontransformed)  $T_{\max}$  and  $\lambda$  data and on the logarithmically (natural) transformed  $AUC_T$ ,  $AUC_1$  and  $C_{\max}$  data. Results should be summarized in tabular form, including the information specified in the aforementioned guidances.

Results for  $AUC_T$  and  $C_{\max}$  ratios for test vs reference product, and the confidence interval about the mean AUC (and about the mean  $C_{\max}$ , when required), must be expressed as both uncorrected and corrected for measured content (potency).

If alternate statistical approaches are used, a discussion should be provided including a justification statement.

### 11.4.2.1 Adjustments for Covariates

Generally, this section is not applicable to comparative bioavailability studies.

#### 11.4.2.2 Handling of Dropouts or Missing Data

Each subject withdrawal and the reason for the withdrawal should be provided. The timing of the decision to withdraw the subject should be identified (e.g., before sample analysis). If the protocol for handling dropouts or withdrawals was not followed, a rationale for violating the protocol should be provided.

The procedure for dealing with missing data (e.g., a given subject was a “no show” for one or more of the ambulatory sampling time points) should be described.

With reference to section 3.4 of the TPD Guidance, *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Solid Oral Dosage Forms*, plasma concentration data for subjects withdrawn due to adverse drug reaction(s) should be provided in Appendix 16.2.5.

#### 11.4.2.3 Interim Analyses and Data Monitoring

Not applicable.

#### 11.4.2.4 Multicentre Studies

Not applicable

#### 11.4.2.5 Multiple Comparison/Multiplicity

Not applicable

#### 11.4.2.6 Use of an "Efficacy Subset" of Patients

Not applicable.

#### 11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

#### 11.4.2.8 Examination of Subgroups

Not applicable.

#### 11.4.3 Tabulation of Individual Response Data

This section should be addressed as outlined in the ICH E3 guidance document, as appropriate. In general terms, this section provides a brief description of the data presented in tables and figures in Appendix 16.2.6.

#### 11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

#### 11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

#### 11.4.6 By-Patient Displays

Not applicable.

#### 11.4.7 Efficacy Conclusions

A discussion of the efficacy findings should be provided in this section.

## 12. SAFETY EVALUATION

### 12.1 Extent of Exposure

Not applicable.

### 12.2 Adverse Events (AES)

#### 12.2.1 Brief Summary of Adverse Events

This section should include a brief summary of adverse reactions and side effects. For comparative bioavailability studies, this summary may combine the information that is applicable from sections 12.2.2 (Display of Adverse Events), 12.2.3 (Analysis of Adverse Events), and 12.2.4 (Listing of Adverse Events by Patient) in lieu of providing each of these sections (i.e., section 12.2.1-12.2.4) separately.

The adverse events should be provided in tabular format in section 14.3.1. The table(s) should include subject identification, period, treatment group, adverse event, how reported, duration of treatment required, frequency, outcome, severity, and relationship to study drug.

#### 12.2.2 Display of Adverse Events

See section 12.2.1 above.

#### 12.2.3 Analysis of Adverse Events

See section 12.2.1 above.

#### 12.2.4 Listing of Adverse Events by Patient

See section 12.2.1 above.

### 12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

#### 12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

- 12.3.1.1 Deaths
- 12.3.1.2 Other Serious Adverse Events
- 12.3.1.3 Other Significant Adverse Events

#### 12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

#### 12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

### 12.4 Clinical Laboratory Evaluation

#### 12.4.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)

#### 12.4.2 Evaluation of Each Laboratory Parameter

Generally, this section (i.e., sections 12.4.2.1 - 12.4.2.3) is not applicable.

- 12.4.2.1 Laboratory Values Over Time
- 12.4.2.2 Individual Patient Changes
- 12.4.2.3 Individual Clinically Significant Abnormalities

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

12.6 Safety Conclusions

### 13. DISCUSSION AND OVERALL CONCLUSIONS

### 14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

This section should be completed as described in the ICH E3 guidance document.

14.1 Demographic Data

14.2 Efficacy Data

Some examples of summary tables that may be included in this section are as follows.

- Definition of pharmacokinetic parameters
- Summary tables of comparative bioavailability data (see Appendix A)
- Summary of results of statistical analysis (i.e., the percent ratios with their respective geometric confidence intervals (CI) about the means for both measured and potency corrected data)
- Summary of individual and mean pharmacokinetic parameters for the Test
- Summary of individual and mean pharmacokinetic parameters for the Reference

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each patient)

### 15. REFERENCE LIST

## 16. APPENDICES

### 16.1 STUDY INFORMATION

- 16.1.1 Protocol and protocol amendments
- 16.1.2 Sample case report form (unique pages only)
- 16.1.3 List of IECs or IRBs (plus the name of the committee Chair) - Representative written information for patient and sample consent forms
- 16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
- 16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer.
- 16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.
- 16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)
- 16.1.8 Audit certificates (if available) (see Annex IVa and IVb of the guidance)
- 16.1.9 Documentation of statistical methods  
  
The statistical report should be provided in this appendix. See also ICH E3 Annex VIII (Guidance for section 11.4.2 - Statistical/Analytical Issues and Appendix 6.1.9).
- 16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used
- 16.1.11 Publications based on the study
- 16.1.12 Important publications referenced in the report

## 16.2 PATIENT DATA LISTINGS

### 16.2.1 Discontinued patients

### 16.2.2 Protocol deviations

### 16.2.3 Patients excluded from the efficacy analysis

### 16.2.4 Demographic data

### 16.2.5 Compliance and/or drug concentration data (if available)

### 16.2.6 Individual efficacy response data

Examples of tables and figures which may be included in this appendix are as follows.

- Individual and mean measured plasma concentrations of the test at each sampling time
- Individual and mean measured plasma concentrations of the reference at each sampling time
- Cumulative AUC of the test
- Cumulative AUC of the reference
- Individual and mean linear concentration-time profiles for the test and reference
- Individual and mean semi-logarithmic concentration-time profiles for the test and reference

### 16.2.7 Adverse event listings (each patient)

### 16.2.8 Listing of individual laboratory measurements by patient.

## 16.3 CASE REPORT FORMS

### 16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE

See Module 5.3.7.

### 16.3.2 Other CRFs submitted

See Module 5.3.7.

## 16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)

See Module 5.3.7.

## 16.5 ANALYTICAL STUDY REPORT

See “Measurement Methodology” in section 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies).

## 16.6 ANALYTICAL VALIDATION REPORT

See “Measurement Methodology” in section 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies).

### 5.3.1.3 In vitro-In vivo Correlation Study Reports

*In vitro* dissolution studies that provide BA/BE information, including studies used in seeking to correlate *in vitro* data with *in vivo* comparisons, should be placed in this section. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD formatted submission.

Please note that at the present time the TPD does not accept *in vitro-in vivo* correlation studies as evidence of safety and efficacy in lieu of pivotal *in vivo* studies. This Module is included in the outline only as a placeholder for future use should such correlation studies be developed and considered acceptable.

### 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

- \* Bioanalytical or analytical methods for BA/BE or *in vitro* dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

### **Measurement Methodology**

Evidence that the analytical method used is suitable, reliable and reproducible must be submitted. Without being limited to the following, the submitted information should include:



- i. standard operating procedures (SOPs)\*\* for those aspects of analysis that are critical to the assessment of the validity of the methodology used, such as sample preparation and stability, criteria for the acceptance/rejection of data (e.g., repeat analysis, QC's, standards curves, etc.), etc.
- ii. a description of the methodology,\*\*
- iii. copies of literature references cited, and
- iv. details of the specific attributes of the method as used by the analytical facility as described below.

\*\* Note: In general, it is not necessary to provide information of a proprietary nature. Should such information be required it can be submitted, in confidence, directly to the TPD.

In order to determine that the analytical method has yielded reliable and reproducible results, it must be characterized and validated. Validation comprises both pre-study (see A below) and during study (see C below) performance. For a previously validated analytical method not used on a regular basis, the continued validity of the method should be confirmed before sample analysis (see B below). Having confirmed the continued validity of the method, for routine analysis, the study parameters identified in (C) below should be provided. Furthermore, if analysis is conducted at more than one facility, interlaboratory reliability must be established (see D below). For a definition and detailed description of the parameters to be characterized, refer to TPD guidances *Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B*.

- A. Parameters for Pre-Study Method Validation: When developing a new method (or modifying a previously developed method) or introducing a published method in the laboratory, the following parameters should be addressed.
  - i. Specificity (Selectivity)
  - ii. Limit of Quantitation
  - iii. Limit of Detection
  - iv. Standard (calibration) Curves
  - v. Accuracy
  - vi. Precision
  - vii. Recovery
  - viii. Stability

The data generated for the above parameters should be used to establish specifications for the study parameters (see C below).

- B. Parameters for Method Revalidation: For methods not used on a regular basis, in order to confirm that the characteristics of the method have not changed relative to previous validation results, the parameters specified above are relevant. However, as a minimum, 3 standard curves with new quality control (QC) samples should be generated. The intra- and inter-day variabilities in standard curves and of QC determinations must be reported. These attributes will be used to determine the acceptability of the method.
- C. Study Parameters: The parameters that should be addressed during the ongoing (routine) analysis of study samples are specified below.
  - i. Standard (Calibration) Curves
  - ii. Quality Controls
- D. Parameters for Interlaboratory Reliability: When analysis is conducted at more than one facility or a previously validated method is being introduced into a new facility, in order to determine that the characteristics of the method are the same, the parameters specified in (A) above should be addressed.
- E. Repeat Analysis: A table including sample i.d., initial value, reason for repeat, repeat value(s), accepted value, reason for acceptance; and the number of repeats expressed as a percentage of the total number of samples assayed should be provided. The protocol used to establish *a priori* the reasons for repeat analysis must also be submitted.
- F. Chromatograms of the analysis of the unknown samples, including all associated standard curves and QC chromatograms, should be submitted for one-fifth (20%) of chromatograms (maximum of 5 subjects), chosen at random. These chromatograms should be obtained from a minimum of two analytical runs (two batches) and should include data for each period. The chromatograms for the applicable standard curves should include chromatograms for all calibration standards, including a zero standard (matrix sample processed with internal

standard) and a standard blank (matrix sample processed without internal standard). Chromatograms should be labelled as follows:

- i. date of analysis
- ii. subject ID number
- iii. period and sampling time
- iv. analyte (drug or metabolite)
- v. standard or QC, with concentration,
- vi. analyte and internal standard peaks and
- vii. peak heights and/or areas

### **Retention of Samples**

It is recommended that samples of the test and reference drug products used in the comparative bioavailability study(ies), and the biological samples collected, including QC samples, be retained until the submission is either cleared or withdrawn.

#### *5.3.7 Case Report Forms and Individual Patient Listings*

When paper copy alone is available the data listed in ICH E3 Study Report Appendices 16.1, 16.2 and 16.3.1 are to be included in the submission. Appendices 16.3.2 (Other Case Reports Forms (CRFs)) and 16.4 Individual Patient Data Listings), are to be sent only upon request. If requested, appendices should be delivered promptly (normally within two working days).

When all CRFs (i.e., including 16.3.2) are available in PDF file format on CD ROM, applicants are encouraged to provide one copy at the time of filing in Module 1.6 - Electronic Review Documents. In such instances, applicants are not required to provide the paper copy of the CRFs.

### **5.4 Literature References**

## 6. APPENDICES

### Appendix A: Summary Tables of the Comparative Bioavailability Data

[Table for single dose studies]

Analyte Name  ( __ x __ mg) From measured data  Geometric Mean Arithmetic Mean (CV%)
--

Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval‡
AUC <sub>T</sub> ‡ (units)				
AUC <sub>I</sub> (units)				
C <sub>max</sub> (units)				
T <sub>max</sub> § (h)				
T <sub>1/2</sub> € (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 AUC<sub>T</sub> should be replaced with AUC<sub>0-72</sub>.

§ 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 the AUC<sub>T</sub>, AUC<sub>I</sub>, and C<sub>max</sub> (if required).

**[Table for multiple dose studies]**

Analyte Name  ( ___ x ___ mg) From measured data  Geometric Mean Arithmetic Mean (CV%)
--

Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval#
AUC <sub>tau</sub> (units)				
C <sub>max</sub> (units)				
C <sub>min</sub> (units)				
T <sub>max</sub> § (h)				

\* 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.

# Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for the AUC<sub>tau</sub> and C<sub>max</sub> (if required).

## Appendix B: Computer Format for the Submission of Data for Comparative Bioavailability Studies

### 1. Introduction

In order to streamline the review of bioequivalence studies, sponsors should submit the drug concentration versus time data in a standard format that can be loaded directly into the TPD computers for review. The primary goal in providing the data in this format is to eliminate the time consuming task of re-entering the data into the computer for evaluation.

### 2. Detailed Specifications

The data should be submitted in electronic format. It should be formatted as an ASCII data file. The electronic copy should be labelled to identify the company, the drug and the date. Two files are required:

- a. an information file; and
- b. a concentration data file.

File names should differ only in their extensions. It is suggested that the file name identify the company, drug, and formulation.

- i. The information required in the **first file** (suggested extension .inf) is,
  - a. A list of the sampling time points for the study (these are the first entries in the file to facilitate access by SAS<sup>®</sup>).
  - b. The drug name, strength, dosage form, potency and dose given.
  - c. Limit of quantitation (LOQ) of the analytical method.
  - d. Lowest and highest nominal concentrations of the standard curve.
  - e. Study Period.
  - f. Treatment (formulation) labelling.
  - g. The sponsor company's name and the name of the firm that performed the study.
  - h. The name and telephone number of a person to whom inquiries concerning the electronic data set can be addressed.
  - i. The date the file was generated.
  - j. A description of the record layout in the data file (see 2 below).

- ii. The **second file** (suggested extension .dat) contains the measured (uncorrected) drug concentrations.

There is a record for each subject in each study period (ie. the total number of records = number of subjects x number of periods). The records should be grouped by treatment (formulation) and within each group by subject in numerical or alphabetical order. An example of the detailed format for each record is as follows;

<b>Descriptor</b>	<b>Position</b>	<b>Length</b>	<b>Type</b>	<b>Example</b>
subject number	1-2	2	alphanumeric	09
sequence	4-5	2	alphanumeric	AB or BA
study period	7-11	5	alphanumeric	1 or 2
treatment	13-13	1	alphanumeric	A or B
conc (0)	15-21	7	numeric	
conc (1)	23-29	7	numeric	
...	...	7	numeric	
conc (t)	114-120	7	numeric	

- Where t=the total number of time points (in this example t=14).
- All entries are delimited with a space.
- Missing data should be entered as a period (.).
- Concentrations below the limit of quantitation (LOQ) should be entered as 0.0.

See Attachments for examples of the two files.

A hard copy of the data should also be provided.

Please note that the above format is not inflexible, it represents a basic minimum required as a starting point.

The electronic copy should be submitted in Module 1.6.

## Attachment 1: Example of First File

**FILE NAME:** companydrugformulation.inf

- i. SAMPLING TIMES: 0 / 0.5 / 1.0 / 1.5 / 2.0 / 2.5 / 3.0 / 3.5 / 4.0 / 5.0 / 7.0 / 9.0 (N=12)
- ii. (a) DRUG NAME: Noname  
(b) DRUG STRENGTH COMPARED: 50 mg  
(c) DOSAGE FORM: tablets  
(d) POTENCY: 97.8% (A = test) and 98.1% (B = reference)  
(e) DOSE ADMINISTERED: 50 mg
- iii. LIMIT OF QUANTITATION (LOQ): 10 ng/mL
- iv. STANDARD CURVE RANGE: 10 ng/mL to 150 ng/mL
- v. STUDY PERIOD: STUDY PERIOD 1: May 14, 1989.  
STUDY PERIOD 2: May 21, 1989.
- vi. TREATMENT LABELLING: A = test product; B = reference product
- vii. (a) SPONSOR COMPANY'S NAME: Bioequivalence Inc.  
(b) FIRM PERFORMING STUDY: Biostudy Inc.
- viii. CONTACT PERSON: Dr. A. Noname (phone and fax number)
- ix. DATE FILE GENERATED: October 9, 1993



## Attachment 2: Example of Second File

**FILE NAME:** companydrugformulation.dat

DESCRIPTOR	POSITION	LENGTH	TYPE	EXAMPLE
subject number	1-2	2	alphanumeric	09
sequence	4-5	2	alphanumeric	AB or BA
study period	7-11	5	alphanumeric	1 or 2
treatment	13-13	1	alphanumeric	A or B
concentration 1	15-20	6	numeric	
concentration 2	22-27	6	numeric	
concentration 3	29-3	6	numeric	
concentration 4	36- 1	6	numeric	
concentration 5	43-48	6	numeric	
concentration 6	50-55	6	numeric	
concentration 7	57-62	6	numeric	
concentration 8	64-69	6	numeric	
concentration 9	71-76	6	numeric	
concentration 10	78-83	6	numeric	
concentration 11	85-90	6	numeric	
concentration 12	92-97	6	numeric	

The following provides an example of a hard copy of the data set and should be included with the submission:

```
01 AB 1 A 000.00 000.002 052.0123 095.03 122.204. 065.15 046.24 019.20 014.99 000.00 000.00
02 BA 2 A
03 BA 2 A
04 AB 1 A
05 BA 2 A
06 AB 1 A
07 BA 2 A
08 AB 1 A
09 BA 2 A
10 AB 1 A
11 AB 1 A
12 BA 2 A
13 BA 2 A
01 AB 2 B
02 BA 1 B
03 BA 1 B
04 AB 2 B
```

<sup>2</sup> Concentrations below the limit of quantitation (LOQ) should be entered as 0.0.

<sup>3</sup> The entered drug concentrations must be the measured (uncorrected) concentration and should not be below the lowest or above the highest nominal concentrations of the standard curve.

<sup>4</sup> Missing data must be entered as a period (.).