

DRUGS DIRECTORATE GUIDELINES

PREPARATION OF

**DRUG IDENTIFICATION NUMBER
SUBMISSIONS**

*Health Protection Branch
Health Canada*

February 22, 1995

Table of Contents

Introduction	1
Section I Change in Manufacturer's Name and/or Address; Change in Product Name; or Cross-Referenced Drug Product	4
Section II Homeopathic Preparations	4
Section III Traditional Herbal Medicines	5
Section IV Disinfectant Drugs	5
Section V Nonprescription Products Subject to a Category IV Monograph	6
Section VI Nonprescription Products Subject to a Labelling Standard (LS)	6
Section VII Solid Oral Dosage Forms, Oral Suspensions, Powder/Granules for Oral Suspension, and Oral Solutions, Intended for Systemic Effect	7
Section VIII Modified-Release Oral Dosage Forms	10
Section IX Solutions for Inhalation	12
Section X Injectable Preparations (Aqueous and Non-Aqueous Solutions, Powders for Injection, Suspensions and Emulsions)	14
Section XI Peritoneal Dialysis Solutions	16
Section XII Hemodialysis Solutions	17
Section XIII Ophthalmic Preparations	18
Section XIV Rectal Suppositories that Deliver Drugs for Systemic Absorption	20
Section XV Topical Preparations, Dental Topical, Vaginal and Nasal Preparations Intended for Local Effect	22
Section XVI Otic Preparations	24
Section XVII Other Products	27

Appendices

- A** *Drug Submission Application*, Health Canada form HPB 3011
- B** *Application for a Numbered Certificate of Registration as a Proprietary Medicine*, Health Canada form HC/SC-XXZ 4093 (7-94)
- C** *DIN Submission Certification* form
- D** *Category IV Drug Submission Certification*
- E** Factors to be Addressed in Assessing Bioequivalence Requirements
- F** Drugs Directorate Publications
- G** *Drugs Directorate Policy, Animal Tissues: Evaluation Procedures*
- H** Health Protection Branch Notes No. 12, *Add-Vantage Drug Delivery System*
- I** Guidance: Computer Format for the Submission of Data for Bioavailability Studies
- J** Glossary of Terms

Introduction

Under the provisions of section C.01.014 of the *Food and Drug Regulations*, no manufacturer shall sell a drug in dosage form unless a drug identification number (DIN) has been assigned for that drug and the assignment of the number has not been cancelled pursuant to section C.01.014.6. In the case of a new drug, a new drug submission filed pursuant to Division 8 of the Food and Drug Regulations is regarded as an application for a DIN. When a product is not subject to Division 8, the application is called a DIN submission.

Prior to issuing drug identification numbers, the Drugs Directorate requires the submission of sufficient data to evaluate the safety and efficacy of a drug for its intended use. This is in keeping with the requirements of subsection 9(1) of the *Food and Drugs Act*:

"No person shall label, package, treat, process, sell or advertise any drug in any manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety."

It is in the interest of public health for the Drugs Directorate to determine that a drug product is of sufficient quality not to be injurious to the Canadian public, and to perform in the expected manner.

The Guideline for Preparation of DIN Submissions outlines the information normally needed to establish quality, safety and efficacy of drug products according to product type. In addition to the basic application and certification requirements, the applicant need only refer to that section of this guideline that applies to the product type.

DIN Submission Definition

A Drug Identification Number (DIN) is an eight (8) digit numerical code assigned to each drug product marketed under the *Food and Drugs Act and Regulations*.

A DIN identifies the following product characteristics:

- manufacturer
- brand name
- medicinal ingredient(s)
- strength of medicinal ingredient(s)
- pharmaceutical form
- route of administration

Where any of the product characteristics differ, a separate DIN submission is required.

New Drug Status Decision

A New Drug Status decision will be made on all DIN submissions. Where the drug product is considered to be in New Drug Status, the applicant will be so informed, otherwise the DIN submission evaluation will proceed.

A list of products currently regulated as New Drugs has been prepared. Although the list **will not** be all-encompassing due to the complexity of Division 8 of the *Food and Drugs Regulations*, it is intended to assist applicants in identifying many new drugs. This list is accessible on the Electronic Bulletin Board.

Presentation of the Submission

A submission for a DIN should contain the following information for review:

- a) a completed *Drug Submission Application*, Health Canada HPB form 3011, (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable
- b) a completed *DIN Submission Certification* (Appendix C) or *Category IV Drug Submission Certification* (Appendix D) as appropriate
- c) specific product type information as specified in Sections I - XVII.

Review of the information submitted may result in the request for additional material to respond to a particular concern.

The Sections that follow the Introduction outline the minimum presentation and content requirements for a DIN submission by product type. The Sections consists of two parts:

- A - information requirements and
- B - conditions under which the requirements apply

Applicants need only consult those Sections which apply to their particular product type for identification of the data requirements.

A post-market audit procedure will be implemented. This audit will include such aspects as compliance with good manufacturing practices (GMP), and verification of data submitted to support DIN issuance. A detailed mechanism to support this audit is being developed. The provision of the information outlined in the Guideline will enable the Drugs Directorate to evaluate the DIN submission in an effective and efficient manner. This will expedite the review process. The Management of Drug Submissions Policy will continue to apply to DIN submissions.

Scope

This guideline is applicable to all pharmaceutical products for human use with the exception of Schedules C (radiopharmaceutical) and D (biological) drugs and GP products not subject to a Category IV Monograph or Labelling Standard.

Changes After DIN Issuance

For product changes after the DIN has been issued, the provisions of Section C.01.014.4 of the *Food and Drugs Regulations* apply. Additionally, Section C.01.014.5 of the *Food and Drugs Regulations* states that "every manufacturer of a drug shall, annually before the first day of October, and in a form authorized by the Director, furnish the Director with a notification signed by the manufacturer or by a person authorized to sign on his behalf, confirming that all the information previously supplied by the manufacturer with respect to that drug is correct."

For DINs issued on the basis of a demonstration of bioequivalence, comparative pharmacodynamic/clinical studies or pharmaceutical equivalence, any change which would have an impact on these parameters would cause the previously filed information to be no longer correct (ref. C.01.014.5 of the *Food and Drugs Regulations*). For this reason, such changes would require notification and approval prior to implementation. A working group has been established to develop clear guidelines to cover all aspects of changes post-DIN issuance.

Section I

Change in Manufacturer's Name and/or Address; Change in Product Name; or Cross-Referenced Drug Product

Section I-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. a letter signed by the company representative stating that all aspects of the application, with the exceptions itemized in **Section I-B Conditions** are identical to that of the original submission; and
3. for cross-referenced submissions, a letter from the company holding the DIN for the marketed product authorizing HPB to access their data to support the submission for the second product.

Section I-B Conditions

The DIN will be processed in an expedited manner, provided there is no change in the site of manufacture or packaging **and** provided that all other aspects of the application are identical to the original submission with the exception of:

1. manufacturer's name and/or address
2. product name **or**
3. product name and manufacturer for cross-referenced DIN submissions

No other sections apply

Section II

Homeopathic Preparations

Section II-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A)
2. completed *DIN Submission Certification* (Appendix C)

3. labelling (proposed Canadian labels and prescribing information or a package insert where applicable) in conformity with the *Drugs Directorate Guidelines: Homeopathic Preparations: Application for Drug Identification Numbers*

Sections X (Injectables) and XIII (Ophthalmics) may apply

Section III

Traditional Herbal Medicines

Section III-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A)
2. completed *DIN Submission Certification* (Appendix C)
3. labelling (proposed Canadian labels and prescribing information or a package insert where applicable) in conformity with the *Drugs Directorate Guidelines: Traditional Herbal Medicines*.

Further data may be requested should evaluation of the information raise concerns.

Sections VIII (Modified-Release), XIII (Ophthalmics), XIV (Rectal), XV (Topicals) and XVI (Otics) may apply

Section IV

Disinfectant Drugs

Section IV-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A)
2. completed *DIN Submission Certification* (Appendix C) or *Category IV Drug Submission Certification* (Appendix D) as appropriate
3. labelling (proposed Canadian labels and prescribing information or a package insert where applicable) in conformity with the *Drugs Directorate Guidelines: Disinfectant Drugs*

4. efficacy data, if applicable, as outlined in *Drugs Directorate Guidelines: Disinfectant Drugs* (except for Category IV Drugs)

Section XIII (Ophthalmics) may apply

Section V

Nonprescription Products Subject to a Category IV Monograph

Section V-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), or *Application for a Numbered Certificate of Registration as a Proprietary Medicine*, form HC/SC-XXZ 4093 (Appendix B) as appropriate, including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *Category IV Drug Submission Certification* (Appendix D)
3. for proprietary medicine products, all data required as per Division 10 of the *Food and Drugs Regulations*.

No other sections apply

Section VI

Nonprescription Products Subject to a Labelling Standard (LS)

Section VI-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), or *Application for a Numbered Certificate of Registration as a Proprietary Medicine*, form HC/SC-XXZ 4093 (Appendix B) as appropriate, including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. a letter quoting the name and date of the LS referenced; indicating compliance with or outlining any discrepancies from the LS, with supporting rationale. In the case of discrepancies, further data may be requested.

4. for proprietary medicine products, all data required as per Division 10 of the *Food and Drugs Regulations*.

Sections VII through XVII (including Oral, Modified-Release, Inhalation, Ophthalmics, Rectal, Topical, Otic) may apply

Section VII

Solid Oral Dosage Forms, Oral Suspensions, Powder/Granules for Oral Suspension, and Oral Solutions, Intended for Systemic Effect

Section VII-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. subject to **Section VII-B Conditions**, a justification for waiver of the requirements **or**
 - a) for bioequivalence:
 - i) the complete description and data (hard copy) pertaining to the bioequivalence study
 - ii) body fluid concentration versus time data on disk as outlined in *Computer Format for the Submission of Data for Comparative Bioavailability Studies* (Appendix I)

Refer to HPB document entitled *Conduct and Analysis of Bioavailability and Bioequivalence Studies, part A: Oral Dosage Formulations Used for Systemic Effects*, Health Protection Branch (HPB), Health Canada (Cat.No. H42-2-56-1992). For drugs having complicated or variable pharmacokinetics, refer to *Draft Report on Bioavailability of Oral Dosage Formulations of Drugs Used for Systemic Effects, Report C: Report on Bioavailability of Oral Dosage Formulations, Not in Modified-Release Form, of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics*, Health Protection Branch, December 1992.

- b) for comparative pharmacodynamic/clinical studies:
 - i) justification that a bioequivalence study is not possible
 - ii) the complete description and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between the applicant's drug product and the Canadian reference product. Include justification for the appropriateness of the study design for the clinical endpoints

measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies.

- c) the name and address of the study facilities used for the bioequivalence, or pharmacodynamic/clinical studies
- d) the following information for the test and reference products used in the bioequivalence, or pharmacodynamic/ clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

- 4. for all prescription drug products and for those nonprescription drugs products assessed as requiring bioequivalence data:
 - a) Chemistry and Manufacturing - General Requirements (all product types):
 - i) the complete quantitative formulation of the product
 - ii) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
 - iii) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
 - iv) *Certificate of Analysis* for one lot of the finished product (the lot used in the bioequivalence or pharmacodynamic/ clinical study, if applicable)
 - v) the name and address of the fabricator (and importer, if applicable) of the product
 - b) Chemistry and Manufacturing Data - Specific Requirements for Products Assessed as Requiring Bioequivalence, Pharmacodynamic/Clinical Studies:
 - i) the name and address of the fabricator of the medicinal ingredients
 - ii) the Master Formula for a typical batch size and a detailed method of manufacture
 - iii) certification that the lot used to demonstrate equivalence was manufactured using the identical formulations as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in ii). If these conditions do not exist, all deviations should be reported and fully justified.

Section VII-B Conditions

Exclusions

Excluded from the assessment to determine bioequivalence requirements are:

1. Section II products: Homeopathic Preparations
2. Section III products: Traditional Herbal Medicines
3. Section V products: Nonprescription Products Subject to a Category IV Monograph
4. Vitamin, mineral or vitamin/mineral preparations

Nonprescription Products

The clinical consequences of variable bioavailability for solid oral dosage forms, oral suspensions, powder/granules for oral suspension, and oral solutions, intended for systemic effect containing nonprescription drugs are **generally** less significant in overall patient health outcomes. For this reason, the submission of bioequivalence data will only be required if, after consideration of all relevant factors outlined in Appendix E, it is determined that such studies would be required based on the risk(s) posed.

For nonprescription drugs an assessment by the applicant of the need for bioavailability data is required to be conducted, however, if the assessment is negative, submission of the assessment and justification are **not** required, except on request.

Prescription Products

Demonstration of bioequivalence is **generally** required for solid oral dosage forms, oral suspensions, powders/granules for oral suspension and oral solutions, intended for systemic effect containing prescription drugs. This is because of the nature of the ingredients, the conditions being treated and the clinical significance of differences in bioavailability.

The applicant may apply to waive demonstration of bioequivalence for prescription drugs. Justification based on scientific principles must be submitted.

Waiver of Bioequivalence Requirement

A waiver of bioequivalence may be granted for the following:

1. For different strength(s) of the same dosage form produced by the same manufacturer, if the product meets all of the following:
 - a) the bioequivalence of one of the strengths to the Canadian reference product has been demonstrated **and**

- b) the composition of the other strengths is proportionally similar in its medicinal and non-medicinal ingredients to that strength which underwent the acceptable bioequivalence study **and**
- c) all strengths of the drug product exhibit equivalent dissolution profiles.

Note: A waiver of bioequivalence would not normally be granted for additional strengths for medicinal ingredients with known non-linear pharmacokinetics.

- 2. Non-absorbable oral preparations; since non-absorbability is a relative term, determination of the bioequivalence requirements will be made on a case-by-case basis.
- 3. Oral solutions, elixirs, syrups or other similar solubilized forms containing the same medicinal ingredient(s) in the same concentration(s) as the Canadian reference product and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).
- 4. Justification provided by the applicant based on assessment to determine bioequivalence requirements.

Assessment to Determine Bioequivalence Requirements

All factors outlined in Appendix E should be addressed in assessing a product and should be included in any scientific justification submitted for a waiver of bioequivalence.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

Section VIII

Modified Release Oral Dosage Forms

Section VIII-A Information Requirements

- 1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
- 2. completed *DIN Submission Certification* (Appendix C)
- 3. subject to **Section VIII-B Conditions**, a justification for waiver of the requirements **or**:
 - a) complete description and data (hard copy) pertaining to bioequivalence studies carried out in accordance with the Drugs Directorate Guidelines; refer to *Conduct and Analysis of Bioavailability and Bioequivalence Studies, Part B: Oral Modified-Release Formulations Used for Systemic Effects*, 1992 (Cat. No. H42-2/56-1-1993)

- b) body fluid drug concentration versus time data on disk as outlined in *Computer Format for the Submission of Data for Comparative Bioavailability Studies* (Appendix I)
- c) In cases where the standards of bioequivalence can not be met, comparative pharmacodynamic/clinical studies between the applicant's product and the Canadian reference product should be conducted. The following data should be submitted:
 - i) justification for using pharmacodynamic/clinical studies
 - ii) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product
 - iii) justification for the appropriateness of the study design for the clinical endpoints measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies
- d) the name and address of the study facility for the bioequivalence, pharmacodynamic/clinical study
- e) the following information for the test and reference products used in the bioequivalence, or pharmacodynamic/ clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

- 4. Chemistry and Manufacturing - for modified release oral dosage forms assessed as requiring bioequivalence, pharmacodynamic/clinical studies:
 - a) the complete quantitative formulation of the product
 - b) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
 - c) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
 - d) *Certificate of Analysis* for one lot of the finished product (the lot used in the bioequivalence or pharmacodynamic/clinical study, if applicable)
 - e) the name and address of the fabricator (and importer, if applicable) of the product

- f) the name and address of the fabricator of the medicinal ingredients
- g) the Master Formula for a typical batch size and a detailed method of manufacture
- h) certification that the lot used to demonstrate equivalence was manufactured using the identical formulation as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in (g). If these conditions do not exist, all deviations should be reported and fully justified.

Section VIII-B Conditions

Excluded from the assessment to determine bioequivalence requirements are vitamins, minerals or vitamin/mineral products.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

Section IX

Solutions for Inhalation

Section IX-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. subject to **Section IX-B Conditions**:
 - a) results of comparative testing between the applicant's product and the Canadian reference product including chemical composition and appropriate physical properties, such as specific gravity, surface tension and refractive index
 - b) results of comparative droplet size distribution studies between the applicant's product and the Canadian reference product
 - c) dependant on the results of a) and b), if pharmacodynamic/clinical studies are required:
 - i) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product
 - ii) justification for the appropriateness of the study design for the clinical endpoints measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies

- iii) the name and address of the study facilities used for the pharmacodynamic/clinical study
- d) the following information for the test and reference products used in the comparative studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

- 4. For all products:
 - a) the complete quantitative formulation of the product
 - b) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
 - c) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
 - d) *Certificate of Analysis* for one lot of the finished product (the lot used in the pharmacodynamic/clinical study, if applicable)
 - e) the name and address of the fabricator of the medicinal ingredients
 - f) the name and address of the fabricator (and importer, if applicable) of the product
 - g) the Master Formula for a typical batch and a detailed method of manufacture including where applicable all steps critical in assuring the sterility of the product (e.g. filling and sterilization procedures, sterilization of packaging components, and in-process controls)
 - h) certification that the lot used to demonstrate equivalence was manufactured using the identical formulation as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in (g)). If these conditions do not exist, all deviations should be reported and fully justified.

Section IX-B Conditions

If the formulation (combination and proportion of medicinal and non-medicinal ingredients) of the applicant's product is the same as the Canadian reference product, comparative studies between the applicant's product and the Canadian reference product should be conducted.

If the formulation differs, the product is considered to be subject to Division 8 of the Food and Drug Regulations.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

Section X

Injectable Preparations (Aqueous and Non-Aqueous Solutions, Powders for Injection, Suspension and Emulsions)

Section X-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. subject to **Section X-B Conditions**, a justification for waiver of the requirements **or** :
 - a) evidence that the formulation of the applicant's product and the Canadian reference product are the same or pharmaceutically equivalent
 - or** b) comparative pharmacodynamic/ clinical studies:
 - i) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product
 - ii) justification for the appropriateness of the study design for the clinical endpoints measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies
 - iii) the name and address of the study facilities used for the pharmacodynamic/ clinical study

- iv) the following information for the test and reference products used in the pharmacodynamic/clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

4. For all injectable products:

a) Chemistry and Manufacturing - General Requirements (all product types):

- i) the complete quantitative formulation of the product
- ii) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
- iii) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
- iv) the manufacturing instructions and/or Master Formula to be used to manufacture the product. These should indicate all steps critical in assuring the sterility and apyrogenicity of the product, e.g. filling and sterilization procedures, sterilization and depyrogenation of packaging components, and in-process controls
- v) if the product is an injectable and packaged as to be in contact with an elastomeric closure, confirmation that the product meets the USP test <381> Elastomeric Closures for Injections. Furthermore, provide certification from the manufacturer of the closure that the closure is free of 2-mercaptobenzoimidazole (2-MCBT, 2-MBT) and its related substances (e.g. thiazoles, mercaptobenzoimidazoles) and that no nitrosamines or other known toxic additives are included in the formulation of the closure. Alternatively provide cross-reference and authorization for access to a Product Master File with the Health Protection Branch
- vi) for 'Add-Vantage' injectable drug delivery systems, the information as outlined in Health Protection Branch Notes No. 12 *Add-Vantage* Drug Delivery System (Appendix H)
- vii) *Certificate of Analysis* for one lot of the finished product (the lot used in the pharmacodynamic/clinical study, if applicable)
- viii) the name and address of the fabricator (and importer, if applicable) of the product

- b) Chemistry and Manufacturing - Specific Requirements for Products Assessed as Requiring Pharmacodynamic/Clinical Studies:
- i) the name and address of the fabricator of the medicinal ingredients
 - ii) certification that the lot used to demonstrate equivalence was manufactured using the identical formulations as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in 4(a)(iv)). If these conditions do not exist, all deviations should be reported and fully justified.

Section X-B Conditions

Unless the formulation (combination and proportion of medicinal and non-medicinal ingredients) is the **same** as the Canadian reference product or pharmaceutically equivalent, pharmacodynamic/clinical studies that establish the comparative safety and effectiveness of the applicant's product and the Canadian reference product should be conducted.

The applicant may apply to waive demonstration of equivalence. Justification based on scientific principles must be submitted. All relevant factors should be addressed in the justification.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

SECTION XI

Peritoneal Dialysis Solutions

Section XI-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. the complete quantitative formulation of the product
4. specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
5. specifications with limits including tests for sterility and apyrogenicity and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
6. the manufacturing instructions and/or Master Formula to be used to manufacture the product. These should indicate all steps critical in assuring the sterility and apyrogenicity of the product,

e.g. filling and sterilization procedures, sterilization and depyrogenation of packaging components, and in-process controls

7. *Certificate of Analysis* for one lot of the finished product

No other sections apply

SECTION XII

Hemodialysis Solutions

Section XII-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. the complete quantitative formulation of the product
4. specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
5. specifications with limits including tests for apyrogenicity (and sterility where applicable) and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
6. *Certificate of Analysis* for one lot of the finished product
7. the manufacturing instructions and/or Master Formula to be used to manufacture the product. These should indicate all steps critical in assuring the apyrogenicity (and sterility if applicable) of the product, e.g. filling and sterilization procedures, sterilization and depyrogenation of packaging components, and in-process controls.

No other sections apply

SECTION XIII

Ophthalmic Preparations

Section XIII-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable
2. completed *DIN Submission Certification* (Appendix C)
3. subject to **Section XIII-B Conditions**, a justification for waiver of the requirements **or**:
 - a) evidence that the formulation of the applicant's product and the Canadian reference product are the same or pharmaceutically equivalent
 - b) comparative pharmacodynamic/clinical studies:
 - i) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product. Include justification for the appropriateness of the study design for the clinical endpoints being measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies
 - ii) the name and address of the study facilities used for the pharmacodynamic/clinical study
 - iii) the following information for the test and reference products used in the pharmacodynamic /clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

4. For all ophthalmic products:
 - a) Chemistry and Manufacturing - General Requirements (all product types):
 - i) the complete quantitative formulation of the product

- ii) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
 - iii) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
 - iv) the manufacturing instructions and/or Master Formula to be used to manufacture the product. These should indicate all steps critical in assuring the sterility and apyrogenicity of the product, e.g. filling and sterilization procedures, sterilization and depyrogenation of packaging components, and in-process controls
 - v) *Certificate of Analysis* for one lot of the finished product (the lot used in the pharmacodynamic/clinical study, if applicable)
 - vi) the name and address of the fabricator (and importer, if applicable) of the product
- b) Chemistry and Manufacturing - Specific Requirements for Products Assessed as Requiring Pharmacodynamic/Clinical Studies:
- i) the name and address of the fabricator of the medicinal ingredients
 - ii) certification that the lot used to demonstrate equivalence was manufactured using the identical formulations as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in 4(a)(iv)). If these conditions do not exist, all deviations should be reported and fully justified.

Section XIII-B Conditions

Exclusions

Excluded from the assessment to determine equivalence requirements are:

1. Artificial tears
2. Eye washes
3. Contact lens solutions

Nonprescription Products

The clinical consequences of interproduct variability for ophthalmic products containing nonprescription drugs are **generally** less significant in overall patient health outcomes. For this reason, the submission of comparative pharmacodynamic/clinical studies will only be required if, after consideration of all relevant factors, it is determined that such studies would be required based on the risk(s) posed.

For nonprescription products an assessment by the applicant of the need for such data is required to be conducted, however, if the assessment is negative, submission of the assessment and justification are **not** required, except on request.

Prescription Products

Unless the applicant's product has the **same** formulation (combination and proportion of medicinal and non-medicinal ingredients) or is **pharmaceutically equivalent** to the Canadian reference product, pharmacodynamic/clinical studies should be conducted against the Canadian reference product.

The applicant may apply to waive demonstration of equivalence. Justification based on scientific principles must be submitted. All relevant factors should be addressed in the justification.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

SECTION XIV

Rectal Suppositories That Deliver Drugs for Systemic Absorption

Section XIV-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. subject to **Section XIV-B Conditions**, a justification for waiver of the requirements **or** :
 - a) for bioequivalence studies:
 - i) the complete description and data (hard copy) pertaining to the bioequivalence study
 - ii) body fluid drug concentrations versus time data on disk as outlined in *Computer Format for the Submission of Data for Comparative Bioavailability Studies* (Appendix I)
 - b) for pharmacodynamic/clinical studies:
 - i) justification for using pharmacodynamic/clinical studies
 - ii) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product
 - iii) justification for the appropriateness of the study design for the clinical endpoints measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies
 - c) the name and address of the study facility used for the bioequivalence or pharmacodynamic/clinical study

- d) the following information for the test and reference products used in the bioequivalence or pharmacodynamic/clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

4. For all rectal suppositories that deliver drugs for systemic absorption:
- a) Chemistry and Manufacturing - General Requirements:
- i) the complete quantitative formulation of the product
 - ii) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
 - iii) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
 - iv) *Certificate of Analysis* for one lot of the finished product (the lot used in the bioequivalence or pharmacodynamic/clinical study, if applicable)
 - v) the name and address of the fabricator (and importer, if applicable) of the product
- b) Chemistry and Manufacturing - Specific Requirements for Products Assessed as Requiring Bioequivalence, Pharmacodynamic/Clinical Studies:
- i) the name and address of the fabricator of the medicinal ingredients
 - ii) the Master Formula for a typical batch size and a detailed method of manufacture
 - iii) certification that the lot used to demonstrate equivalence was manufactured using the identical formulation as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in ii). If these conditions do not exist, all deviations should be reported and fully justified.

Section XIV-B Conditions

Bioequivalence, or pharmacodynamic/clinical studies between the applicant's drug product and the Canadian reference product are required unless the manufacturer can provide justification based on scientific principles as to why such data are not necessary. All relevant factors should be addressed in the justification.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

SECTION XV

Topical Preparations, Dental Topical, Vaginal and Nasal Preparations Intended for Local Effect**

Section XV-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. subject to **Section XV-B Conditions**, a justification for waiver of the requirements **or** :
 - a) for pharmacodynamic/clinical studies:
 - i) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product
 - ii) justification for the appropriateness of the study design for the clinical endpoints measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies
 - iii) the name and address of the study facilities used for the pharmacodynamic/ clinical study

- iv) the following information for the test and reference products used in the pharmacodynamic/clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

4. For all prescription drug products and for those nonprescription drugs products assessed as requiring pharmacodynamic/clinical studies:
- a) Chemistry and Manufacturing - General Requirements (all product types):
 - i) the complete quantitative formulation of the product
 - ii) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
 - iii) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
 - iv) *Certificate of Analysis* for one lot of the finished product (the lot used in the comparative pharmacodynamic/clinical study, if applicable)
 - v) the name and address of the fabricator (and importer, if applicable) of the product
 - b) Chemistry and Manufacturing - Specific Requirements for Products Assessed as Requiring Comparative Pharmacodynamic/Clinical Studies:
 - i) the name and address of the fabricator of the medicinal ingredients
 - ii) the Master Formula for a typical batch size and a detailed method of manufacture
 - iii) certification that the lot used to demonstrate equivalence was manufactured using the identical formulation as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in ii). If these conditions do not exist, all deviations should be reported and fully justified.

**

Dental Preparations intended to be applied topically to mucous membranes and to inner and outer dental surfaces

Section XV-B Conditions

Exclusions

Pharmacodynamic/clinical studies are not required for products of simple formulation such as a solution which contains the drug substance(s) in a solvent which does not include non-medicinal ingredients that may affect penetration/absorption of the drug.

Nonprescription Products

The clinical consequences of interproduct variability for these preparations containing nonprescription drugs are **generally** less significant in overall patient health outcomes. For this reason, the submission of pharmacodynamic/clinical studies will only be required if after consideration of all relevant factors, it is determined that such studies would be required based on the risk(s) posed.

For nonprescription products an assessment by the applicant of the need for such data is required to be conducted, however, if the assessment is negative, submission of the assessment and justification are **not** required, except on request.

Prescription Products

Pharmacodynamic/clinical studies between the applicant's drug product and the Canadian reference product are required for all prescription products unless the manufacturer can provide justification based on scientific principles as to why such data are not necessary. All relevant factors should be addressed in the justification. The clinical endpoints measured in the studies must be relevant to the claims of efficacy. Surrogate models may be considered in lieu of clinical studies in certain cases. At the present time there is only one accepted surrogate model. This is the Vasoconstrictor Assay used to compare topical steroid products.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

Section XVI

Otic Preparations

Section XVI-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)

3. subject to **Section XVI-B Conditions**, a justification for waiver of the requirements **or** :
- a) evidence that the formulation of the applicant's product and the Canadian reference product are the same or pharmaceutically equivalent

or b) for pharmacodynamic/clinical studies:

- i) the complete descriptions and results including statistical analysis of pharmacodynamic/clinical studies that establish the comparative safety and effectiveness between this drug product and the Canadian reference product. Include justification for the appropriateness of the study design for the clinical endpoints measured. The applicant should contact the appropriate Bureau at the Health Protection Branch for assistance in defining the requirements of these studies
- ii) the name and address of the study facilities used for the pharmacodynamic/ clinical study
- iii) the following information for the test and reference products used in the pharmacodynamic/clinical studies:

Identification of Study:

	Test Product	Reference Product
Manufacturer of Reference Product		
Lot Number		
Batch Size of test product		
Expiry Date		

4. For all prescription drugs and for those nonprescription products assessed as requiring comparative pharmacodynamic or clinical studies:

a) Chemistry and Manufacturing - General Requirements (all product types):

- i) the complete quantitative formulation of the product
- ii) specifications with limits and a description of the analytical methods for the medicinal ingredients (refer to pharmacopoeial standards where applicable)
- iii) specifications with limits and a description of the analytical methods for the finished product (refer to pharmacopoeial standards where applicable)
- iv) *Certificate of Analysis* for one lot of the finished product (the lot used in the pharmacodynamic/clinical study, if applicable)
- v) the name and address of the fabricator (and importer, if applicable) of the product

- b) Chemistry and Manufacturing - Specific Requirements for Products Assessed as Requiring Pharmacodynamic/Clinical Studies:
- i) the name and address of the fabricator of the medicinal ingredients
 - ii) the Master Formula for a typical batch size and a detailed method of manufacture
 - iii) certification that the lot used to demonstrate equivalence was manufactured using the identical formulation as, and using a method equivalent to (i.e. same process, equipment design and operating principles), that described above in ii). If these conditions do not exist, all deviations should be reported and fully justified.

Section XVI-B Conditions

Nonprescription Products

The clinical consequences of interproduct variability for otic preparations containing nonprescription drugs are **generally** less significant in overall patient health outcomes. For this reason, the submission of pharmacodynamic/clinical studies will only be required if, after consideration of all relevant factors, it is determined that such studies would be required based on the risk(s) posed.

For nonprescription products an assessment by the applicant of the need for such data is required to be conducted, however, if the assessment is negative, submission of the assessment and justification are **not** required, except on request.

Prescription Products

Unless the applicant's product has the **same** formulation (combination and proportion of medicinal and non-medicinal ingredients) or is **pharmaceutically equivalent** to the Canadian reference product, pharmacodynamic/clinical studies should be conducted against the Canadian reference product.

The applicant may apply to waive demonstration of equivalence. Justification based on scientific principles must be submitted. All relevant factors should be addressed in the justification.

Section VI (Nonprescription Products Subject to a Labelling Standard) may apply

Section XVII

Other Products

Section XVII-A Information Requirements

1. completed *Drug Submission Application* form, HPB 3011 (Appendix A), including proposed Canadian labels and prescribing information or a package insert where applicable.
2. completed *DIN Submission Certification* (Appendix C)
3. Additional requirements will be handled on a product-specific basis. These requirements, as identified, will be documented for incorporation into an update to the Guideline.

APPENDIX A

Drug Submission Application Health Canada form HPB 3011

The Drug Submission Application is posted on the Therapeutic Products Directorate Web Site.

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/hc3011_sc3011-eng.php

Telephone: 613-941-0838
Fax: 613-941-7284

Note : On January 24, 1998 a Notice of Intent to revoke Division 10 of the *Food and Drug Regulations* under the authority of which Certificates of Registration of Proprietary Medicines (GP numbers) are currently issued. (Schedule 979)

APPENDIX B

Application for a Numbered Certificate of Registration as a Proprietary Medicine Health Canada form HC/SC - XXZ 4093 (7-94)

Copies of the Application are available upon request from the:

Submission and Information Division
Drugs Directorate
1620 Scott Street
Unit 14
Ottawa, Ontario K1A 0L2

APPENDIX C

DIN Submission Certification form

DIN Submission Certification

We certify that:

Product Name: _____

1. The information and data provided in support of this DIN submission is complete and accurate and, where summarized, correctly represents the information and material to which it refers.
2. The product will be manufactured in accordance with Canadian Good Manufacturing Practices (GMP) as required under Division 2 of the Food and Drug Regulations.
3. Stability data will support the labelled expiration date of the product. In addition to the first two production batches of the product, stability will be monitored in accordance with Canadian GMP requirements.
4. For injectables and ophthalmic preparations, the container will meet the appropriate requirements for containers in either USP<661> or BP (Appendix XIX).
5. The product does **not** contain any of the following ingredients:
 - a) phenacetin in combination with any salt or derivative of salicylic acid
 - b) oxyphenisatin
 - c) oxyphenisatin acetate
 - d) phenisatin
 - e) strychnine or any of its salts
 - f) extracts or tinctures of:
 - i) *Strychnos nux vomica*
 - ii) *Strychnos Ignatii*
 - ii) a *Strychnos* species containing strychnine, other than those species mentioned in subparagraph i) and ii)
 - g) Methapyrilene or any of its salts
 - h) Echimidine or any of its salts
 - i) any of the following plant species or extracts or tinctures thereof:
 - i) *Symphytum asperum*
 - ii) *Symphytum X uplandicum*
 - iii) any other plant species containing echimidine
 - j) chloroform
 - k) arsenic or any of its salts or derivatives
 - l) methyl salicylate (as a medicinal ingredient in a drug for internal use)
 - m) mercury or a salt or derivative thereof, unless the drug is one of the following:
 - i) an ophthalmic drug or other drug to be used in the area of the eye
 - ii) a drug for nasal administration

- iii) a drug for otic administration
- iv) a drug for parenteral administration that is packaged in a multi-dose container

in which the mercury or the salt or derivative thereof is present as a preservative and the manufacturer or importer has submitted evidence to the Director demonstrating that the only satisfactory way to maintain the sterility or stability of the drug is to use that preservative.

6. The product does not contain any colouring agent, with the exception of those listed in Section C.01.040.2 of the Food and Drug Regulations (this does not apply to hard surface or instrument disinfectants).
7. If the product contains animal tissue or animal tissue was used as an intermediate during manufacturing, the required information has been submitted (refer to *Drugs Directorate Policy, Animal Tissues: Evaluation Procedures*, Appendix G).
8. The product has been assessed to determine the applicability of bioequivalence, pharmacodynamic/clinical studies or pharmaceutical equivalence requirements. Where applicable, the data have been submitted. Excluded from this assessment are:
 - homeopathic preparations
 - traditional herbal medicines
 - disinfectants
 - vitamin, mineral or vitamin/mineral preparations
 - nonprescription products subject to a standardized proprietary medicine monograph (SPMM)
 - nonprescription products subject to a labelling standard where the standard specifies that a bioavailability assessment for the purpose of a DIN application is not required
 - peritoneal dialysis
 - hemodialysis
 - contact lens solutions
 - artificial tears
 - eye washes
9. Signature of the responsible officer of the company certifying the accuracy of this document.

Signature

Date

Name

Position Title

Company

Product Name

APPENDIX D

Category IV Drug Submission Certification form

Category IV Drug Submission Certification

We certify that:

Product Name: _____

1. The information and data provided in support of this submission is complete and accurate and, where summarized, correctly represents the information and material to which it refers.
2. The product will be manufactured in accordance with Canadian Good Manufacturing Practices (GMP) as required under Division 2 of the Food and Drug Regulations.
3. Stability data will support the labelled expiration date of the product. In addition to the first two production batches of the product, stability will be monitored in accordance with Canadian GMP requirements.
4. The product does **not** contain any of the following ingredients:
 - a) phenacetin in combination with any salt or derivative of salicylic acid
 - b) oxyphenisatin
 - c) oxyphenisatin acetate
 - d) phenisatin
 - e) strychnine or any of its salts
 - f) extracts or tinctures of:
 - i) *Strychnos nux vomica*
 - ii) *Strychnos Ignatii*
 - ii) a *Strychnos* species containing strychnine, other than those species mentioned in subparagraph i) and ii)
 - g) Methapyrilene or any of its salts
 - h) Echimidine or any of its salts
 - i) any of the following plant species or extracts or tinctures thereof:
 - i) *Symphytum asperum*
 - ii) *Symphytum X uplandicum*
 - iii) any other plant species containing echimidine
 - j) mercury or a salt derivative thereof
 - k) chloroform
 - l) arsenic or any of its salts or derivatives
 - m) methyl salicylate (as a medicinal ingredient in a drug for internal use)

5. The product does not contain any colouring agent, with the exception of those listed in Section C.01.040.2 of the Food and Drug Regulations (this does not apply to hard surface or instrument disinfectants).
6. If the product contains animal tissue or animal tissue was used as an intermediate during manufacturing, complete the Animal Tissue Form attached to the relevant Category IV Monograph.
7. The product named in this application will comply in all respects with the requirements of Category IV Monograph

Titled: _____

Dated: _____

9. Signature of the responsible officer of the company certifying the accuracy of this document

Signature

Date

Name

Position Title

Company

Product Name

APPENDIX E

Factors to be Addressed in Assessing Bioequivalence Requirements

1. Is there a known or suspected bioavailability problem?
2. Does the drug product exert therapeutic activity in a narrow therapeutic range e.g. how wide is the margin between minimum effective and minimum toxic plasma concentrations?
3. Does the drug product require careful dosage titration and patient monitoring?
4. Is there pharmacokinetic evidence that:
 - a) the medicinal ingredient is absorbed in a particular segment of the gastrointestinal tract or is absorbed from a localized site?
 - b) the degree of absorption of the medicinal ingredient is poor e.g. less than 70%, ordinarily in comparison to an I.V. dose, even when it is administered in pure form e.g. in solution?
 - c) there is rapid metabolism of the medicinal ingredient i.e. >40% in the intestinal wall or liver during the process of absorption (first-pass metabolism) so that the therapeutic effect and/or toxicity of the drug product is determined by the rate as well as the degree of absorption?
 - d) the medicinal ingredient is rapidly metabolized or excreted so that rapid dissolution and absorption are required for effectiveness?
 - e) the medicinal ingredient is unstable in specific portions of the gastrointestinal tract and requires special coatings or formulations e.g. buffers, enteric coatings and film coatings, to ensure adequate absorption?
 - f) the drug is subject to dose dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to bioequivalence?
5. Is there physicochemical evidence that:
 - a) the medicinal ingredient has a low solubility in water, e.g. less than one percent, or if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose greatly exceeds the volume of fluids present in the stomach (taken to be 100 mL for adults and prorated for infants and children)?
 - b) the dissolution rate of the medicinal ingredient from the drug product is slow?
 - c) the particle size and/or surface area of the medicinal ingredient is critical in determining its bioavailability?
 - d) the medicinal ingredient exhibits certain physical structural characteristics which may lead to poor dissolution and thus may affect absorption, (e.g. polymorphic forms, solvates, complexes and crystal modifications)?
 - e) the drug product has a high ratio of excipients to medicinal ingredients, e.g. greater than 5 to 1?
 - f) hydrophilic or hydrophobic excipients and lubricants are present which may be required for absorption or may interfere with absorption of the drug?

APPENDIX F

Drugs Directorate Publications

The following publications are available from Health Canada and may assist applicants in preparing submissions for a DIN:

1. Chemistry and Manufacturing - New Drugs (Cat. No. H42-2/30-1990)
2. Product Monographs (Cat. No. H42-2/12-1989)
3. Food and Drugs Act and Regulations
4. Labelling of Drugs for Human Use (Cat. No. H42-2/12-1989)
5. Good Manufacturing Practices (Cat. No. H42-2/1-1989)
6. Toxicologic Evaluation (Cat. No. H42-2/15-1990)
7. Conduct and Analysis of Bioavailability and Bioequivalence Studies, Part A: Oral Dosage Formulations Used for Systemic Effects (Cat. No. H42-2-56-1992)
8. Conduct and Analysis of Bioavailability and Bioequivalence Studies, Part B: Oral Modified-Release Formulations Used for Systemic Effects (Cat. No. H42-2/56-1-1993)
9. Draft Report on Bioavailability of Oral Dosage Formulations of Drugs Used for Systemic Effects, Report C: Report on Bioavailability of Oral Dosage Formulations, not in modified release form, of drugs used for systemic effects, having complicated or variable pharmacokinetics, Health Protection Branch, December 1992
10. Disinfectant Drugs (Cat. No. H42-2-61-1994)
11. Homeopathic Preparations: Application for Drug Identification Numbers (Cat. No. H42-2/21-1990)
12. Traditional Herbal Medicines (Cat. No. H42-2/36-1990)
13. Drugs Directorate Policy: Change in Manufacturer's Name and/or Address (available on electronic bulletin board)
14. Drugs Directorate Policy: Management of Drug Submissions, May 3, 1993 (available on electronic bulletin board)
15. Canadian Drug Identification Code (Cat. No. H42-1/1-1992)

The previously mentioned items may be ordered from:

The Canadian Government Publishing Centre
Supply and Services Canada
45 Sacre-Coeur Blvd.
Hull, Québec
K1A 0S9

Order Desk Telephone: (819) 956-4802
 Facsimile: (819) 994-1498

APPENDIX G

Drugs Directorate Policy Animal Tissues: Evaluation Procedures

The Animal Tissues: Evaluation Procedures Policy may be accessed in the area called POLICY ISSUES - ENGLISH of the electronic bulletin board (file name: PRO_ANIM).

APPENDIX H

Health Protection Branch
Notes No. 12
Add-Vantage Drug Delivery System

A copy of Health Protection Branch Notes No. 12, *Add - Vantage Drug Delivery System* is available upon request from:

Drug Regulatory Affairs Division
Health Protection Branch Building
2nd Floor, Room 212
Tunney's Pasture
Ottawa, Ontario K1A 0L2

Telephone: 613-941-3184
Fax: 613-957-3989

APPENDIX I

Guidance: Computer Format for the Submission of Data for Bioavailability Studies

Computer Format for the Submission of Data for Bioavailability Studies

Introduction

In order to streamline the review of comparative *bioequivalence* studies, companies should submit their body fluid drug concentration versus time data in a standard format that can be loaded directly into the Drugs Directorate computers for review. The primary goal in providing the data in this format is to eliminate the time consuming task of reentering the data into the computer for use by the reviewer.

The format recommended here is for human abbreviated drug submissions.

For the purposes of this guidance an electronic submission will consist of a 3.5 inch (micro-floppy) diskette containing the raw blood (or other body fluid) level data for each subject and associated parameters derived from that data.

Detailed Specifications

Currently, IBM compatible personal computers, using DOS 3.3 as the Operating System and the SAS System for the analysis of data, are used. Because organizations use different SAS programs it is recommended that the data be formatted as an ASCII data file which can then be transposed into a SAS data set.

The data should be submitted on a 3.5 inch double sided high or low density micro-floppy disk which has been formatted on an IBM or compatible computer, using DOS 2.1 or greater. The disk should be labelled to identify the company, the drug and the date. **Three files** are required:

1. an information file
2. a data concentration file
3. a pharmacokinetic data file

File names should differ only in their extensions; of the 8 characters in the filename it is suggested that the first three characters be used to identify the company and the remaining five be used to identify the drug and formulation.

1. 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)
 - b) The drug name, strength, dosage form, potency and dose given for the drug
 - c) Limit of quantitation (LOQ) of the analytical method
 - d) Lowest and highest nominal concentrations of the standard curve
 - e) Treatment (formulation) labelling

- f) The sponsor company's name and the name of the firm that performed the study
- g) The name and telephone number of a person to whom inquiries concerning the electronic data set can be addressed
- h) The date the file was generated
- i) A unique number that identifies the file (the HPB Project ID and File Number, if known)
- j) A description of the record layout in the data file (typically as shown below in record layout)

2. The **second file** (suggested extension .dat) contains the drug concentrations.

There is a record for each subject in each period (i.e. the total number of records = number of subject X number of periods). The record should be grouped by treatment (formulation) and within each group by subject in numerical order. The detailed format for each record is as follows:

<u>Descriptor</u>	<u>Position</u>	<u>Length</u>	<u>Type</u>	<u>Example</u>
subject number	1-2	2	alphanumeric	09
sequence	4-5	2	alphanumeric	AB or BA
study period	7-11	5	alphanumeric	JUN08
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 (.)

! The entered concentrations cannot be below the lowest or above highest nominal concentrations of the standard curve. Concentrations at and below the limit of quantitation (LOQ) should be entered as 0.0

* In order that the ANOVA (PROC GLM in SAS) be applied in the correct fashion the reference product should be identified by a name that is alphabetically later than the test product (e.g. in a two way crossover the test treatment can be labelled A (experimental) and the reference B).

3. The **third file** (suggested extension .pkv) contains the pharmacokinetic variables for each subject and each formulation e.g.:

AUC	7	numeric
Cmax	7	numeric
Tmax	7	numeric

Hardcopy of the data should also be provided. The first file (.INF) may also explain the data set and any instructions necessary for downloading to a SAS data set (if required). This text file may be in an ASCII format and readable through the TYPE command. Hardcopy of this file should also be included.

This format is based on information obtained during discussions with industry and reviewers at the HPB. The intent is to streamline the reviews of abbreviated drug submissions. The format is not inflexible, it represents a basic minimum required as a starting point. Changes to the record layout should be clearly recorded in the first or information file (.INF).

It is recommended that if a computer ready submission is being tendered that reference be made to the fact in a cover letter.

The diskette should be submitted along with the complete printed copy of the study report. The diskette should be attached to the inside of the front cover of the bioequivalence report.

APPENDIX J

Glossary of Terms

Glossary of Terms

Add-Vantage injectable drug delivery system:

A Drug Delivery System comprised of a flexible container for diluents and a stoppered glass vial containing a drug, both of which have been especially designed to be joined together to form a unique drug delivery system. The vial content is reconstituted, diluted and mixed in one single operation to provide I.V. solution for infusion. The entire vial stopper with a plastic flange is totally immersed in the drug solution during activation.

Bioavailability

The rate and extent of absorption of a drug into the systemic circulation.

Bioequivalence:

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 effects, or both.

Bioequivalent means that test and reference products containing an identical drug or drugs, after comparison in an appropriate bioavailability study, were found to meet standards for rate and extent of absorption specified in HPB guidelines (consult Appendix F).

Canadian reference product:

A new drug that has been issued a notice of compliance pursuant to Section C.08.004 and is currently marketed in Canada by the innovator, or a drug acceptable to the Director.

Company representative:

A responsible officer of the Canadian manufacturer or importer of a drug in dosage form.

Comparative dissolution profiles:

At least six dosage units (eg: tablets, capsules) of each batch are tested individually and mean and individual results reported. The percentage of nominal content released is measured at a number of time points to provide a profile for each formulation. The formulations are tested using the same apparatus and if possible tested on the same day. Test conditions are normally those used in routine quality control.

Drug in Dosage Form:

A drug in a form in which it is ready for use by the consumer without requiring any further manufacturing.

Fabricator:

The company who manufactures the drug in dosage form.

Formulation:

A quantitative list of medicinal and nonmedicinal ingredients used in the course of manufacture for a drug in dosage form.

Good Manufacturing Practices (GMP):

Compliance with Division 2, Part C of the Food and Drugs Regulations, and including all GMP-related activities in the production and importation of drugs for human use.

Importer:

A person who imports into Canada a drug in dosage form for the purpose of sale.

Label:

"... includes any legend, word or mark attached to, included in, belonging to, or accompanying any food, drug, cosmetic, device or package" (Section 2 of the Food and Drugs Act) and is commonly understood to mean all packaging and product inserts.

Manufacturer:

A person who under his own name, or under a trade, design or word mark, trade name or other name, word or mark controlled by him sells a drug and includes a firm, partnership or corporation.

Package Insert:

A document included with the drug package and that contains information to complement that on the label affixed to the package. It may contain information for the patient and/or for the health practitioner.

Pharmaceutically equivalent:

The condition in which drug products contain identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that do not necessarily contain the same non-medicinal ingredients.

Pharmacopoeial standards:

A standard or specifications for an ingredient or a finished product as contained in a publication mentioned in Schedule B to the Food and Drugs Act.

Prescribing information:

Drug product information including clinical pharmacology, indications and clinical use, contraindications, warnings, precautions, adverse reactions, symptoms and treatment of overdose, dosage and administration and availability of dosage forms to be provided to professionals.

Product Master File:

A reference source that provides information about specific processes and components used in the manufacturing, processing and packaging of a drug meant for human use.

Surrogate Models:

In vitro and/or in vivo models used to compare drug products.