GUIDANCE FOR INDUSTRY
PREPARATION OF VETERINARY NEW DRUG SUBMISSIONS

VETERINARY DRUGS DIRECTORATE
HEALTH CANADA

July 2006

FOREWORD

Guidance documents are meant to provide assistance to industry, and health care and food safety 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 Health Canada's 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, however, should be discussed in advance with the relevant program area oficers 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 define conditions not specifically described in this Guidance Document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a veterinary drug product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This Guidance Document should be read in conjunction with the relevant sections of other applicable guidelines and the applicable regulations.

This Guidance Document is dynamic in nature, and is offered without prejudice to future measures, which Health Canada might take in this area.

The drug manufacturers are encouraged to start using the guidelines given in this Document as soon as it is posted on Health Canada's web site. However, as of January 1, 2007, all submissions are to conform to the format given in this Document.

PREFACE

The Veterinary Drugs Directorate (VDD) is giving a notice of intent to undertake the following initiatives to expedite the review process by enabling evaluators to more efficiently spend their time on drug submission assessment. These initiatives will be undertaken to improve drug submission quality by way of a more thorough compilation and appraisal of data requirements by sponsors, to result in consistency of content and to facilitate the evaluation process.

1. **Quality Overall Summary of Chemical Entities (New Drug Submissions and Abbreviated New Drug Submissions) (*QOS-CE*)**

   Pursuant to Section C.08.005.1 of the *Food and Drug Regulations,* all new (NDS, ABNDS) and supplemental (SNDS and SABNDS) submissions to Health Canada should include a summary of the Chemistry & Manufacturing data (hereinafter Quality Overall Summary). The intent of this requirement is to facilitate the evaluation of the extensive experimental data and hence contribute toward a more effective and timely processing of drug submissions.

   The VDD is contemplating requiring drug sponsors to provide a QOS-CE for the Manufacturing and Chemical Evaluation portion of the drug submission. A QOS-CE prescribed format will be posted shortly on the HC website for consultation with the sponsors of the submissions for veterinary drugs.. With the completion of the QOS-CE (NDS and ABNDS), the Sponsors will share responsibility for the generation of the Manufacturing and Chemical Evaluation Reports.

   Paper and electronic versions of the Quality Overall Summary will be strongly recommended.

2. **Certified Product Information Document - Chemical Entities (CPID-CE)**

   VDD is contemplating requiring drug sponsors to provide a Certified Product Information Document on Chemical Entities (CPID-CE) for the Manufacturing and Chemical Evaluation portion of the drug submission. A CPID-CE prescribed format will be posted shortly on the HC website for consultation with VDD Sponsors. The CPID-CE will constitute part of the Notice of Compliance (NOC) package.

   The CPID-CE provides an accurate record of technical data in the drug submission at the time the NOC is issued, and is intended to serve as an official reference document during the course of post-approval inspections and post-approval change evaluations as performed by Health Canada. The CPID-CE template will represent a condensed version of the QOS-CE template and will be the final, agreed upon key data from the drug submission review (e.g., minimal data on manufacturer(s), drug substance/ drug product specifications, stability conclusions, etc.).

Paper and electronic versions of the CPID-CE will be strongly recommended.

3. **Drug Master File**

The VDD is currently developing Guidance for Manufacturers for providing information on its requirements for the Drug Master File for the Manufacturing and Chemical Evaluation portion of the drug submission. As soon as the draft Guidance Document outlining the requirements for drug substance from manufacturers is ready, it will be posted on the HC website for consultation. In the interim, requirements listed in the NDS Guidance Document apply.

4. **Evaluation Templates for Laboratory Animal Toxicity Studies for Drugs Intended for Use in Food-Producing Animals**

Evaluation templates for laboratory animal toxicity studies are being proposed for reviewing the scientific studies that are submitted to support applications for the registration of drugs intended to be used in food-producing animals. These templates capture specific toxicity data components and record the reviewer's conclusions and rationales that are based on each data set.

The VDD would encourage that the evaluation templates be used by the study directors during the conduct of the studies and creation of their study reports. The level of detail, however, should be the same as would normally be included in a study report. These templates (with slight modifications) are already available at the following web site of the Health Canada's Pest Management Regulatory Agency (PMRA): <http://eddenet.pmra-arla.gc.ca/9.0/9.5.asp> .

Paper and electronic versions of the Evaluation Templates will be strongly recommended.

5. **Electronic Submissions**

Currently, the VDD does not receive electronic drug submissions, but is contemplating moving towards such submissions. When the VDD develops a policy on electronic submissions and is ready to implement it, appropriate guidance document will be prepared for consultation with the industry.

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1. INTRODUCTION

This Guidance Document is to be used in the preparation of Veterinary Drug Submissions for presentation to Health Canada. Some sections of this Guidance Document are general in nature. Therefore, this Guidance Document should be used in conjunction with the complete *Food and Drugs Act and Regulations,* and with specific Health Canada Policies and Guidance Documents applicable to veterinary drugs. The manufacturers or those filing submissions on their behalf should ensure that all Veterinary Drug Submissions filed with the Veterinary Drugs Directorate of Health Canada (VDD) contain sufficient information in order to satisfy the requirements of the *Food and Drugs Act and Regulations.*

The purpose of this guidance is to assist the drug manufacturers (sponsors) with the preparation of a well structured veterinary drug submission to facilitate its screening and subsequent review by the VDD. It should be noted that all requirements in this guidance document may not necessarily apply to every product. Data requirements may vary depending on the drug and submission type for which a submission is filed.

Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by a satisfactory rationale and adequate scientific justification. Alternate approaches, however, should be discussed with the VDD, in advance in order to ensure compliance with all applicable statutes and *Regulations*.

It is important to note that the implementation and use of this guidance is a work in progress and thus subject to change or amendment. As such, it is expected that future updates to this guidance will continue to be necessary as a result of experience gained, as well as future development and implementation of new and updated related Health Canada policies and guidelines with respect to veterinary drugs. Drug manufacturers are encouraged to consult the VDD prior to undertaking studies not covered in these guidelines.

This guidance document partially supercedes Health Canada's 1991 *Preparation of Veterinary New Drug Submissions Guideline*.

The latest versions of Forms and Guidelines pertaining to veterinary drugs can be found on the following respective Web sites:
http://www.hc-sc.gc.ca/dhp-mps/vet/applic-demande/form/index_e.html
http://www.hc-sc.gc.ca/dhp-mps/vet/applic-demande/guide-ld/index_e.html

All references appearing in the document are identified by numbers in the superscript and are listed in SECTION 14, REFERENCES.

2. SCOPE

Division 8, Part C of the *Food and Drug Regulations* provides governance on the sale of new drugs in Canada and prohibits the sale of new drugs unless the manufacturer has filed a submission that is satisfactory to the Minister. The regulations do not define format requirements and therefore give the Minister the flexibility to accept submissions in various formats, provided they are deemed acceptable and that the information and data contained in these submissions comply with Division 8 Part C of the *Food and Drug Regulations*.

This guidance covers the preparation and filing of the following veterinary drug submissions, filed pursuant to Division 8, Part C of the *Food and Drug Regulations*:

- New Drug Submissions (NDSs) as per section C.08.002
- Abbreviated New Drug Submissions (ABNDSs) as per section C.08.002.1
- Supplemental New Drug Submissions and Supplemental Abbreviated New Drug Submissions (SNDSs, ABSNDSs) as per section C.08.003
- Notifiable Changes (NCs)

3. STRUCTURE OF NEW DRUG SUBMISSIONS

This section outlines filing considerations for New Drug Submissions. Table 1 below represents a quick reference guide for new drug submissions.

TABLE 1. OVERVIEW OF STRUCTURE OF VETERINARY NEW DRUG SUBMISSIONS.

PART NUMBER	PART TITLE	INCLUDED FOR SUBMISSION TYPE
I	MASTER VOLUME	ALL TYPES
II	MANUFACTURING AND QUALITY CONTROL	ALL TYPES
III	ANIMAL SAFETY	ALL TYPES
IV	EFFICACY	ALL TYPES
V	HUMAN SAFETY [1,2]	ALL EXCEPT NC
VI[3]	ENVIRONMENTAL IMPACT	ALL EXCEPT NC

(1) PART V is required for drugs intended for use in food-producing animals. When submissions for drugs intended for use in food-producing animals are filed, the data presented in this Part need not be duplicated in other Parts but cross-referenced and vice-versa.

(2) Under certain circumstances, the microbiological safety assessment may be required for veterinary antimicrobial products intended for use in non-food-producing animals.

(3) PART VI, of the Submission, will be forwarded to Healthy Environment and Consumer Safety Branch (HECSB) of Health Canada, as submitted.

4. PRESENTATION OF THE SUBMISSION

This section describes the physical specifications for filing NDS, ABNDS, SNDS, SABNDS and NC submissions. The paper submission is to serve as the official Central Registry copy until such time that the VDD is ready to accept submissions in electronic format.

4.1 Presentation

Every submission must:

4.1.1 be legible

All submissions should be bound on the left side of the document using standard 21.6 x 27.9 cm (8.5 x 11 inch) paper. The left margin should be sufficiently large that content is not obscured by the method of binding. Font sizes should be of a style and size that are large enough to be easily legible, even after photocopying. In general, it is suggested that each page be prepared in Times New Roman and 12-point font.

4.1.2 be easy to access

Information and material should be placed in three-ring binders. Binders should not be so thick or large that they become unwieldy; thus, the binders should be no more than 7.6 cm (3.0 inches) thick.

To facilitate review, different parts of the submission should be presented in separately bound binders to permit concurrent reviews of the submission by VDD's different scientific disciplines.

4.1.3 be properly paginated

Pagination must be sequential within each part of the submission. Every part should be numbered starting at page 1 and each binder should be sequentially numbered starting at Volume 1 for each part. It is strongly recommended that all pages of the submission include an unique header or footer to correspond to the Part (e.g., manufacturing and quality control, animal safety, efficacy) that the page belongs to.

If parts of the submission were taken from a foreign submission and already have pagination, the sponsor is required to clearly identify the page numbering that is specific for the submission filed. To facilitate the review, it is preferable that the sponsor add a clarification statement at the beginning of the submission. An example of this statement is listed as follows: "This submission is numbered sequentially by volume number within each part. Page numbers appear at the bottom right of the page in the format of "volume # and page #: 00010. All other page numbers should be disregarded."

4.1.4 be clearly identified

Data should be organized by parts and separated by volumes/binders as necessary. Each binder should be marked with the name of the drug, the name of the submission sponsor, the part and volume numbers and the filing date of the submission. An example of a binder label is shown below:

Product Name "ABC"
Sponsor Name "ABC Animal Health"
Part No.: "I, II, III, IV or V", Name of the Part [e.g., Manufacturing and Quality Control or Human Safety]
Volume "X" of "Y" [Y refers to the total number of volumes for that Part]
Filing date: Day, Month, Year

The above identifying information should appear on both the front cover and the spine of all binders. An actual example of the binder label is shown below:

Product Name: Super Drug for Dogs
Sponsor Name: ABC Animal Health
Part No.: Part II, Manufacturing and Quality Control
Volume 1 of 6
Filing Date: June 30, 2003
Binder type: Original

Every submission must contain a complete Table of Contents for the entire submission. The Table of Contents should contain all the sub-Tables of Contents prepared specifically for each part (e.g., Table of Contents for Part I, II, or V). The level of details for the sub-Table of Contents may vary depending on the data submitted. However, it should be detailed enough so that relevant sections of the submission can be easily and quickly located.

In order to facilitate screening and the review, cross reference should indicate part, page number, and should bear enough information for quick access, for example, "Part X", "Page 123".

4.1.6 contain tabs

Where applicable, tabs or separators should be used to facilitate the submission review. Tabs or separators should be used to the third level of the sub-Table of Contents within each part. For example, for Part II, Section 6.3, Drug Substance, tabs are required for the following sub-sections:

6.3.1 General information
6.3.1.1 Nomenclature
6.3.1.2 Structure
6.3.1.3 Physicochemical properties

In addition, individual clinical, residue or chemistry and manufacturing studies

should be separated by tabs or separators.

4.2 Language

Information in the submission should be prepared in either English or French. Materials in a different language should be accompanied by an English or French translation.

4.3 Submission Copies and Identification of Submission Volumes

For all original submissions (NDS, ABNDS, SNDS, SABNDS or NC), the number of paper copies required for each part of the submission is detailed below. For all copies received, one set will be an unadulterate copy used for archives and the rest will be used as review copies. The archival copy will be retained as VDD's official copy and historical record. Upon completion of the review of a submission, the review copy is usually destroyed in accordance with VDD's established procedure.

TABLE 2. NUMBER OF PAPER COPIES OF PARTS TO BE INCLUDED IN THE SUBMISSION.

PARTS TO BE INCLUDED IN THE SUBMISSION	NUMBER OF PAPER COPIES
PART I: MASTER VOLUME	4 (food-producing animals) 3 (non food-producing animals)
PART II: MANUFACTURING AND QUALITY CONTROL	2
PART III: ANIMAL SAFETY	2
PART IV: EFFICACY	2
PART V: HUMAN SAFETY	2 (see note 1)
PART VI: ENVIRONMENTAL IMPACT	2

[1] The binder/volume containing drug residue monitoring part of CFIA package is to be submitted in triplicate.

Whether two, three or four copies are required, all copies of the same part of the submission should contain the identical information and be prepared in the same format. The first copy of each volume should be identified as the original. This is particularly important for Part I, Master Volume where most administrative forms bear original signatures. All subsequent copies of the submission should be identified as the duplicate or triplicate copy.

For responses to all communications from VDD, the sponsor is required to submit sufficient separately bound copies to permit concurrent reviews of the sponsor's responses by VDD's different scientific disciplines. As indicated above, the copies should contain identical information and have the same format.

5. PART I: REQUIREMENTS FOR MASTER VOLUME

Every submission should include a Master Volume containing some or all of the following documents or information depending on the specific type of submission presented:

5.1 Cover letter

Every submission must be accompanied by a cover letter. The cover letter should include sufficient information such as the trade name and chemical name of the drug product, submission purpose, and the number of enclosures to facilitate the initial administrative processing of submissions.

If the name of the drug product proposed for marketing in Canada is different from that used during the product development stages and in the data submitted, clarification should be given in the cover letter to explain the difference.

5.2 Table of Contents

Every submission must contain a complete Table of Contents for the entire submission. The Table of Contents should contain all the sub-Tables of Contents prepared specifically for each part of the submission (e.g., Table of Contents for Part I, II, or V).

5.3 Submission Certification

Pursuant to Section C.08.005.1 of the *Food and Drug Regulations*, all initial and supplemental submissions should include an original, signed and dated version of the Submission Certification Form. It is strongly recommended that the submission sponsor print the Submission Certification on its corporate letterhead. As outlined in Section C.08.005.1 of the *Food and Drug Regulations*, the certification form must be signed and dated by the Senior Executive Officer of the manufacturer in Canada and the Senior Medical or Scientific Director of the manufacturer.

An original, signed and dated version copy of the Submission Certification is also required for all responses to VDD's screening or review letters as well as any unsolicited amendments to submissions under review.

5.4 Authorization Letter

The following information is to be provided, when applicable:

5.4.1 Authorization to act as a regulatory agent on behalf of the submission sponsor.

If the submission or any significant portion of the submission is prepared by a regulatory agent outside of the sponsor's company, an original, signed and dated authorization letter must be provided by the submission sponsor.

5.4.2 Authorization to access information submitted by another company/sponsor.

If the submission makes cross-references to a Drug Master File (DMF), Site Reference File (SRF) or any information submitted by a party other than the

submission sponsor, an original version of Letter of Authorization from the other party is required to permit VDD to refer to the third party information in support of the submission under review.

The Letter of Authorization should include the following elements:

(a) date of the letter; F, SRF or submission number;

(b) name of the DMF, SRF or submission information holder;

(c) corresponding Health Canada DM 4.1.5 contain a Table of Contents

(d) name of the persons authorized to make reference to information in the DMF, SRF or a third party submission in support of the submission under review;

(e) sections, volumes and page numbers to be referenced;

(f) signature of the authorizing official; and

(g) typed name and title of the official authorizing reference to DMF, SRF or a previously filed submission.

5.4.3 Authorization to share information with other agencies

If the sponsor has filed submissions with other regulatory agencies and agrees that Health Canada can share information with those other regulatory agencies, and obtain it from them, then a Letter of Authorization is required to authorize VDD to obtain the information from other regulatory agencies regarding the submission under review.

5.5 Drug Submission Application Form (HC/SC 3011)

A duly completed, original, signed, dated version of the HC/SC 3011 Form is required for all submissions.

5.6 Veterinary Drug Submission Fee Application Form

A completed *Veterinary Drug Submission Fee Application Form* is required where applicable. Details respecting fee assessment and payment schedule are outlined in the *Guidance Document on Veterinary Drug Submission Fees.*

5.7 Animal Ingredient Form

Pursuant to Section C.08.002(2) of the *Food and Drugs Act and Regulations*, all initial and

supplemental submissions should include an original signed and dated version of the Animal Ingredient Form (AIF). The manufacturer/sponsor can obtain an electronic copy of the AIF (available in HTML and PDF) on the Health Canada website http://www.hc-sc.gc.ca/dhp-mps/vet/applic-demande/form/index_e.html. Please complete the AIF either electronically or with a typewriter. The Guidance and Questions and Answers pertaining to the AIF are available at and http://www.hc-sc.gc.ca/dhp-mps/vet/faq/index_e.html, respectively. In addition, a draft Guidance for Industry, "Minimizing the Potential Risks of Transmission of the Transmissible Spongiform Encephalopathy (TSE) Agent Via Veterinary Therapeutic Products Containing Animal-Sourced Ingredients" is available at http://www.hc-sc.gc.ca/dhp-mps/vet/applic-demande/guide-ld/index_e.html

5.8 Draft Product Labels

Pursuant to Section C.01.014.1(1)(m) and C.08.002(2)(j) of the *Food and Drug Regulations*, draft copies of all product labels (inner and outer labels) and package inserts to be used in connection with the drug are required at the time of the initial filing of a submission.

Draft copies should be provided for each dosage form, strength, package format of the drug product and diluents. Information in product labeling should correspond to that displayed in the Drug Submission Application Form and that in the data submitted.

In order to distinguish the different versions of the labels that will be reviewed during the course of the review of a submission, it is recommended that the sponsor indicates the version number on each of the labelling that is submitted.

The labelling of the product may include instructions for general safety of the product in the feed mill, at the farm, in the animal hospital, at home and/or in the environment. Whenever necessary, the directions on labelling must include cautions, precautions and warnings against potential hazard to children and adult human beings exposed to the drug during its handling and use; to personnel involved in the disposal of the unused or expired product; and to workers involved in containment of accidental spills. In addition, first aid instructions and information to contact poison control centres must appear on the labelling when necessary.

Studies may be required to support the general safety statements appearing on the labelling. The studies will depend on the nature and extent of exposure of human adults and children, and may require testing in laboratory animals. Guidance on general safety of the product may be obtained from the current *Guide for the Labelling of Drugs for Veterinary Use*[14.4], as well as Workplace Hazardous Materials Information System (WHMIS) of Health Canada (website: http://www.hc-sc.gc.ca/ewh-semt/occup-travail/whmis-simdut/index_e.html) and Material Safety Data Sheets (MSDS, website:http://www.hc-sc.gc.ca/ewh-semt/occup-travail/whmis-simdut/applications/msds-fichs_signaletiques_e.html).

5.9 Patent Forms/Documents (if applicable)

The following forms and documents are required where applicable pursuant to *The Patented Medicines (Notice of Compliance) Regulations*:

- Form IV: Patent List - Pertaining to Patented Medicines (Notice of Compliance) Regulations - First Person Application
- Form V: Declaration Re: Patent List Patented Medicines (Notice of Compliance) Regulations - Second Person Application
- Letter of Allegations

The sponsor should refer to the document entitled: "Patented Medicines (Notice of Compliance) Regulations Guideline" for details respecting the requirement of all the above forms. The forms can be accessed from TPD's web site at:
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/patmedbrev/index_e.html
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/index_e.html

5.10 GMP Status Information and Establishment Licence Information

Where applicable, the sponsor should provide up-to-date GMP compliance status on the related sites that are involved in fabricating, packaging, labeling, testing, importing, storage or distribution of the product.

The sponsor should consult with the Health Products and Food Branch (HPFB) Inspectorate for further information on GMP compliance and Establishment Licence. The HPFB Inspectorate's Web site can be accessed at:http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index_e.html

5.11 Prior Submissions

To facilitate the review, the sponsor is encouraged to provide a list of previously filed submissions that are related to the submission under review. The list should include information such as submission type (e.g., NDS, SNDS, IND, ESC or NC), submission number, filing date and clearance date (if available).

When the information required under a section of the submission has been previously submitted in an approved submission in its entirety without any change, the relevant section should be cross- referenced to the prior drug submission. The name of the drug product, the sponsor's name, file number and submission number for the cross-referenced submission should be provided.

5.12 Submission and Product Summary

For NDS, ABNDS submissions, a brief summary should be provided to describe the manufacturing and quality control, animal safety, human safety (if applicable) and efficacy

aspects of the product. Appropriate references should be made to pivotal studies conducted in support of the NDS and ABNDS under review.

For SNDS, SABNDS and NC submissions, a brief summary of the submission should be provided and should contain the following elements:

- nature of the changes proposed in the supplemental submissions
  rationales for the changes
- discussion of potential impact that the proposed changes may have on the manufacturing and quality control, animal safety, human safety (if applicable) and efficacy aspects of the product
- list of studies conducted to support the changes proposed
- discussion of impact that the proposed changes may have on the information that was previously submitted.

5.13 Summary of Batch Information

When applicable, the sponsor should provide a summary of the batches of drug product and drug substance used in studies for generating data in support of the drug submission. The summary should be provided in a tabulated format as shown in the example given in Tables A-1, A-2 and A-3 in Appendix I.

5.13.1 For NDS and ABNDS

Pursuant to Section C.08.002(2)(m) and C.08.002.1(d) of the *Food and Drug Regulations*, the sponsor is required to provide evidence that all test batches of the new drug used in studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production. Although it is recognized that changes may have occurred throughout the developmental phase of the new drug, the drug product batches used to generate the data in support of a submission for a new drug should not have been produced according to a significantly different formulation and/or manufacturing process (including the manufacturing process of the drug substance) than what is proposed for the commercial production of the drug product.

All drug product and drug substance batches used in studies to generate the data provided in a NDS or ABNDS should be included with the appropriate information in Table A-1, Table A-2 and Table A-3 (Appendix I).

5.13.2 For SNDS, SABNDS and NC

A summary of batch information (Appendix I) should be provided for each lot of drug product and drug substance that were used to generate data provided in the submission in support of the proposed changes.

5.14 Summary of Qualification for an ABNDS or a SABNDS Submission

For sponsors who file ABNDS or SABNDS submissions, the following information is required pursuant to Section C.08.002.1 and C.08.003 of the *Food and Drug Regulations*:

- clear identification of a Canadian Reference Product (CRP) to which the new drug is compared to
- evidence that the new drug is the pharmaceutically equivalent of the CRP
- evidence that the route of administration is the same as that of a CRP
- evidence that the conditions of use for the new drug fall within the conditions of use for the CRP
- evidence that the new drug is bioequivalent with the CRP
- for a drug intended for administration to food-producing animals, evidence that the withdrawal period of the new drug is identical to that of the CRP

5.15 Information Package for the Canadian Food Inspection Agency (CFIA)

5.15.1 Drug Residue Monitoring Methods

For all NDSs, ABNDSs, SNDSs and SABNDSs for drugs intended for use in food producing animals, the methodology package for eventual inclusion and use in CFIA's residue monitoring programs, should be submitted for review, in triplicate: two copies for Health Canada and the third copy for CFIA.

This package should be in a separate binder and include information on the following characteristics of the method(s):

- specificity,
- accuracy,
- precision,
- limit of detection (LOD),
- limit of quantitation (LOQ),
- practicability,
- ruggedness and susceptibility to interference,
- stability of residues under the conditions of procedures employed or prolonged storage of samples,
- stability of standards, including storage conditions for standards and standard solutions, and
- the source of the material for internal standard (if applicable).

The regulatory analytical method(s) must be described in detail, be practical and be suitable for routine monitoring for veterinary drug residues in food. For further guidance on the suitability of methods for monitoring of veterinary drugs, please contact:

Director, Laboratories Directorate
Canadian Food Inspection Agency
59 Camelot Drive
Ottawa, Ontario
K1A 0Y9

The manufacturer shall appoint a contact person responsible for providing standards, assistance to analysts, if required, samples of incurred residue(s) and controls.

Standards and samples of incurred residue and controls should be submitted, when required by the appropriate CFIA laboratory.

Upon completion of review by the Human Safety Division, the CFIA copy of this package will be forwarded to the Director, Laboratories Directorate, CFIA.

5.15.2 Drug Premix Products

For all NDSs, ABNDSs, SNDSs or SABNDSs, filed for drug premix products, where applicable, the sponsor is required to submit an information summary document for validation of methods for analysis of feed premixes and medicated feeds directly to the CFIA for review. For specific data requirements concerning the actual information package, the sponsor should consult with the Chief, Drugs and Contaminants, CFIA, for guidance.

The information should be sent to the following address:

Chief, Drugs and Contaminants
Ottawa Laboratory (Carling) - Feed and Fertilizer
Canadian Food Inspection Agency
Building #22, CEF
960 Carling Avenue
Ottawa, ON K1A 0C6

Furthermore, when submitting a NDS, an ABNDS, a SNDS or an ABSNDS, the sponsor should provide a statement in this section to inform VDD whether or not an information package has been sent to the CFIA.

5.16 Foreign Registration Information

Where applicable, information on the registration status of the drug product in other countries should be provided. For ease of review, information such as the foreign filing date, approval date, intended use and species should be provided and the sponsor is encouraged to provide copies of the product labels that are approved by foreign regulatory agencies.

6. PART II: REQUIREMENTS FOR MANUFACTURING AND QUALITY CONTROL

6.1 NDS and ABNDS

When preparing Part II of NDS and ABNDS, all section headings and numbering as described in the sub-section 6.3 on the Drug Substance and sub-section 6.4 on the Drug Product, should be retained. In situations where a particular section or sub-section may not be applicable or not relevant to the particular type of submission or type of product for which the submission is filed, this section or subsection should still be included in Part II of the submission and should be marked "Not Applicable" or "Not Relevant". Whenever a section or subsection is marked as "Not Applicable" or "Not Relevant", it should be accompanied by a brief rationale explaining why it is not applicable or not relevant. It is not necessary, however, to include sub-section headings when an entire section is designated "Not Applicable".

6.2 SNDS, SABNDS and NC

For these types of submissions, the information and data requirements with respect to manufacturing and quality control may vary substantially depending on the nature of the changes proposed to the new drug in respect of which a NOC has been issued. Sponsors should only provide the new manufacturing and quality control information and data to support the proposed changes under the relevant sections and/or subsections affected by the proposed changes.

When preparing the SNDS, SABNDS or NC, sponsors should present Part II of the submission in one of the following ways:

a) As indicated in sub-section 6.1 above, all section headings and numbering as described in sub-sections 6.3 and 6.4, are retained and appear in Part II of the submission. Any section and/or subsection not affected by a proposed change should be marked as either, "Not Applicable", "Not Relevant" or "Not Changed", as appropriate. Whenever a section or subsection is marked as "Not Applicable" or "Not Relevant", it should be accompanied by a brief rationale explaining why it is not applicable or not relevant. Whenever a section or subsection is marked as "Not Changed", it should be accompanied by a reference to the new drug in respect of which a NOC has been issued including the submission type, control number, brand name, manufacturer/sponsor's name, Health Canada Central Registry file number and the date the NOC was issued

b) A general note should be included at the beginning of Part II regarding its content and the rationale for omissions of some of the sections and subsections as described in sub-section 6.1 of this Guidance Document.

6.3 DRUG SUBSTANCE

Some of the detailed information to be included under the drug substance section of the submission may not be available to the sponsor because it is of a proprietary nature (e.g., the detailed method of manufacture). In this case, the sponsor can make reference to a related Type I Drug Master File (DMF) which can be filed directly with Health Canada by the holder of the Type I DMF. The DMF will be held in strict confidence and will be used in support of the drug submission only upon receipt of written authorization from the DMF holder of the drug substance.

Sponsors should note the following with respect to the DMF:

- When a DMF is filed for the first time with Health Canada in support of a Veterinary Drug Submission, then the DMF should be filed with VDD.

- Cross reference to a DMF previously filed with the Therapeutic Products Directorate (TPD) of Health Canada in support of a human drug product is considered acceptable.

- Reference to the open part of a Type I DMF is not a substitute for providing the information regarding the drug substance as outlined in section 1 of this Guidance Document.

- The non-proprietary information contained in the open part of a Type I DMF should be incorporated into the drug submission. It is the responsibility of the sponsor to obtain that information from the DMF holder of the drug substance.

- Regardless of the information included in a Type I DMF, the sponsor is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the drug substance and results of batch analyses are provided by the drug product manufacturing facilities.

- Reference to a DMF filed with a foreign regulatory authority is not acceptable.

The proprietary information in the closed part of the DMF is reviewed in connection with a drug submission. The DMF holders will be contacted directly only when deficiencies are determined in the closed part of information of the DMF and comments regarding such deficiencies are sent directly to the DMF holder. In such a case, the sponsor will be notified in writing that a deficiency letter has been sent to the DMF holder but not informed of the specific comments contained in the letter. The comments on the deficiencies observed in any other part of information on drug substance in the submission, are sent to the sponsor of the drug submission.

For further information on the requirements for Drug Master Files, see Health Canada's guidance document: *Product Master Files*.

6.3.1 General Information

6.3.1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided. For example:

(a) Recommended International Non-proprietary Name (INN);

(b) Compendial name, if relevant;

(c) Chemical name(s);

(d) Company or laboratory code;

(e) Other non-proprietary name(s) (e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN); and

(f) Chemical Abstracts Service (CAS) registry number.

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling. Where several names exist, indicate the preferred name.

Where a chemical moiety is formed in-situ (e.g., by chemical reaction), both the starting and chemical moiety should be described.

6.3.1.2 Chemical Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in Section 6.3.1. For drug substances existing as salts or hydrates, the molecular mass of the free base or anhydrous form should also be provided.

6.3.1.3 Physicochemical Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

This information can be used in developing the specifications, in formulating dosage forms, and in the testing for release and stability purposes. Give the physical and chemical properties of the drug substance such as:

- physical description
- solubilities in common solvents (e.g., water, alcohols, chloroform, acetone, etc.)
- quantitative aqueous pH solubility profile (e.g., pH 1 to 8, dose/solubility volume)
- polymorphism
- particle size distribution
- pH and pKa values
- UV absorption maxima and molar absorptivity
- melting point
- refractive index (for a liquid)
- hygroscopicity
- partition coefficient
- optical rotation

This list is by no means exhaustive, but provides an indication as to the type of information that could be included.

Some of the more important properties to be considered for all drug substances are discussed below in greater detail.

6.3.1.3.1 Physical Description

The description should include appearance, colour, and physical state. Solid forms should be identified as being crystalline or amorphous. A simple statement such as "powder" is not considered satisfactory.

6.3.1.3.2 Solubilities/ Quantitative Aqueous pH Solubility Profile

The solubility should be provided in a number of common solvents (e.g., water, alcohols, chloroform, acetone, etc.). The solubilities over the physiological pH range (pH 1 to 8) in several buffered media should also be provided. Phrases such as "sparingly soluble" or "freely soluble" should be quantitatively defined or a literature reference can be provided (e.g., "as per USP"). If this information is not readily available (e.g., literature references, open part of the Drug Master File), it should be generated in-house.

The dose/solubility volume should be provided. The dose/solubility volume is calculated based on the minimum concentration of the drug (in mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37˚ ± 0.5˚C). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. For example, Compound A has as its lowest

solubility at 37˚ ± 0.5˚C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL).

6.3.1.3.3 Polymorphism

If solubility of the potential polymorphic forms is a concern, results from an investigation of several batches of the drug substance, recrystallized from several solvents, should be provided to determine if the drug substance exists in more than one crystalline form. The study should include the characterization of the batch(es) used in the clinical and/or comparative bioavailability studies, using a suitable method (e.g., X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR)). The absence of the potential for polymorphism can further be confirmed by providing the results of a literature search.

If the results of studies conducted on the physical and chemical properties of the various crystalline forms indicate that there is a preferred polymorph, criteria should be incorporated into the drug substance specification to ensure polymorphic equivalence of the commercial material to the batch(es) used in the clinical and/or comparative bioavailability studies. Generally, controls on polymorphism are not a concern for drug substances that are considered highly soluble or when there is no difference in solubility among polymorphic forms. Justification for the exclusion of the controls for polymorphism should be provided.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the drug substance is used in a solvated form, the following information should be provided:

(a) specifications for the solvent-free drug substance, if that compound is a synthetic precursor;

(b) specifications for the solvated drug substance including appropriate limits on the weight ratio of drug substance to solvent (with data to support the proposed limits); and

(c) a description of the method used to prepare the solvate.

6.3.1.3.4 Particle size distribution

For poorly soluble drug substances, the particle size distribution of the material can have an effect on the *in vitro* and/or *in vivo* behaviour of the drug product. Particle size can also be important in achieving uniformity of content in low-dose tablets (e.g., 2 mg or less), desired smoothness in ophthalmic preparations, and stability of suspensions. If particle size distribution is important (e.g., as in the above cases), results from an investigation of several batches of the drug substance should be provided, including characterization of the batch(es) used in the clinical and/or comparative bioavailability studies. If applicable, the acceptance criteria should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the clinical and/or comparative bioavailability studies (e.g., limits for d_{10} , d_{50} , and d_{90}). These criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following is provided for illustrative purposes as possible acceptance criteria for particle size limits:

- d_{10} NMT 10% of total volume less than *X* µm
- d_{50} *X* µm - *Y* µm
- d_{90} NLT 90% of total volume less than *Z* µm

Other controls on particle size, or the absence of controls, may be considered acceptable, if scientifically justified.

6.3.2 Method of Manufacture

If reference is made to a Type I DMF for certain proprietary information, the DMF number assigned by Health Canada should be provided. It should be ensured that the information included in the DMF is current (i.e., no more than two years old) and that the latest update of the DMF has been received by Health Canada. Copies of the letters of access should be provided. If an authorized agent is used by the DMF owner, a letter from the DMF owner should be submitted allowing the agent to act on their behalf, rather than the letter coming from the authorized agent.

6.3.2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing of the drug substance should be provided. This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the drug substance. If certain companies are responsible only for specific steps (e.g., milling of the drug substance), this should be indicated. The list of manufacturers should specify

the actual production or manufacturing site(s) involved, rather than the administrative offices.

6.3.2.2 Description of Manufacturing Process and Process Controls

A flow diagram of the synthetic process(es) should be provided from the open part of the DMF. It includes:

- molecular formulae, weights, yield ranges,

- chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry,

- identification of operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, all process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time). Alternate processes and reprocessing steps, if any, should be justified and described with the same level of detail as the primary process. Data generated to support this justification should be provided in Section 6.3.5.

The information on the manufacturing process should start from commercially available or well characterized starting materials. The manufacturing process for the batch(es) of drug substance used in the clinical and/or comparative bioavailability drug product lots should be representative of the commercial process (i.e., laboratory scale batches are *not* considered satisfactory).

If the drug substance is prepared as sterile, a complete description and validation data should be provided for the method used in the sterilization. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided.

In addition to the above information, the data provided for a drug substance produced by fermentation should include:

(a) source and type of micro-organism(s) used;

(b) composition of media;

(c) precursors;

(d) additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and

(e) name and composition of preservatives.

For drug substances of plant origin, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. It may be necessary to include limits for considerable residues resulting from such treatments in the drug substance specification. Absence of toxic metals and radioactivity may also have to be confirmed.

6.3.2.3 Control of Materials

Materials used in the manufacture of the drug substance (e.g., starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided.

Copies of the specifications for the materials used in the synthesis, fermentation, extraction, isolation, and purification steps should be provided in the drug submission and should meet standards appropriate for their intended use.

Generally, starting materials specifications would include tests and acceptance criteria for identity, purity, and potency, where applicable. Special consideration should be given to potential isomeric impurities in the starting material as such contaminants could be carried through the synthesis to the drug substance.

Drug substances of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) agents. For any material of animal origin used in the manufacture of the drug substance, information should be provided in accordance with the most stringent requirements set out in Schedule B compendial monographs (e.g., USP, Ph.Eur., B.P.) and the requirements of the AIF.

This information includes a list of all medicinal ingredients and non-medicinal animal-sourced ingredients (including excipients, auxiliary reagents, medium components used in culture/fermentation, raw and/or starting materials, and/or reagents used in synthesis/biosynthesis and processed materials used it the formulation of the drug product), their origin and use in the drug product, specifications, age of animal, country of origin,

geographical profile of the animal or herd, BSE status of the country of origin, TSE classification of animal-sourced material(s), measures taken to minimize TSE prions and cross-contamination, testing of the herd where available or required by the agricultural regulations, description of the testing performed and viral safety data. A TSE-Certificate of Suitability and/or a science-based risk assessment and/or other relevant documentation should be provided when appropriate (please refer to the AIF) so that the VDD may confirm that the drug substance of animal origin is free of BSE/TSE agents. This information should be included with the drug submission.

6.3.2.4 Controls of Critical Steps and Isolated Intermediates (applied to the NDS)

Isolated intermediates:

Information on the quality and control of intermediates isolated during the process should be provided. Copies of the specifications for isolated intermediates should meet standards appropriate for their intended use. Generally, intermediates specifications would include tests and acceptance criteria for identity, purity, and potency, where applicable. Special consideration should be given to potential isomeric impurities in the starting material, as such contaminants could be carried through the synthesis to the drug substance.

Critical steps:

Information on controls performed at the critical steps identified in section 6.3.2.2 (Description of Manufacturing Process and Process Controls) should be provided in the submission. This information should identify test(s) conducted and associated acceptance criteria, as well as provide suitable justification (including experimental data).

6.3.2.5 Process Validation and/or Evaluation (applied to the NDS)

Process validation and evaluation studies should be included for all drug substances produced using aseptic processing or sterilisation.

6.3.2.6 Manufacturing Process Development (applied to the NDS)

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, pilot, clinical, stability, comparative bioavailability, scale-up, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 6.3.4.

6.3.3 Structure Elucidation and Confirmation

Confirmation of structure based on synthetic route and spectral analyses should be provided. The submission should include a list of the studies performed and a conclusion from the studies (e.g., if the results support the proposed structure). The submission should also include copies of the legible spectra, peak assignments, and an interpretation of the data.

6.3.3.1 Non-chiral drug substances

The studies carried out to elucidate and confirm the chemical structure of the drug substance typically include:

For new chemical entities:

- Elemental analysis
- Infrared (IR)
- Ultraviolet (UV)
- Nuclear Magnetic Resonance (NMR)
- Mass Spectra (MS)
- X-ray diffraction (XRD)

For existing drugs (e.g., generics): Copies of the IR and UV spectra of the drug substance from the proposed suppliers run concomitantly with suitable reference standard. A suitable primary reference standard could be obtained from the Schedule B compendia (e.g., USP, Ph.Eur., BP, etc.) or from a batch of the drug substance that has been fully characterized (e.g., IR, UV, NMR, MS, etc.). See Section 6.3.6 for further details on Reference Standards.

It is recognized that some drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the drug substance. If a drug substance consists of more than one component, the physicochemical characterization of the components and their relative proportions should be submitted.

6.3.3.2 Chiral Drug Substances

In addition to the information required under 6.3.3.1, when a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

A discussion should be included of all possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the drug substance specification should include a test to ensure isomeric identity and purity.

For drug substances that contain a chiral centre, where there has not been any information provided regarding the manufacture of the starting material through which it has been introduced, results of chiral HPLC analyses should be submitted on enantiomeric purity/ratio of the drug substance.

If, based on the structure of the drug substance, there is no potential for isomerism, it may be sufficient to include a statement to this effect.

6.3.4 Impurities

Information on impurities should be provided. The study of impurities can be considered one of the most important aspects of the manufacturing and quality control portion of the drug submission.

In addition to the guidance outlined in this section, more detailed guidance regarding impurities is available in the VDD's adopted VICH guidance documents GL10 (drug substances)[14.1], GL11 (drug products)[14.2] and GL18 (residual solvents)[14.3].

6.3.4.1 Potential impurities

The sponsor should provide a discussion of those potential impurities most likely to arise from the synthesis, purification, and storage of the drug substance. These impurities can be drug related (e.g., starting materials, by-products, intermediates, enantiomeric impurities, degradation products) or process related (e.g., residual solvents, catalyst, reagents). The summarization of information about these impurities should include names, structures, origin,, etc. The origin refers to how the impurity can be introduced (e.g., "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis, potential residual solvent from recrystallization step.). It should also be indicated if the impurity is a metabolite of the drug substance.

6.3.4.2 Actual impurities detected

Analytical results for actual levels of impurities found in several batches of the drug substance from each source should be provided. The batches should include ones used for the clinical, safety, stability and comparative

bioavailability studies and be identified for their usage accordingly. For quantitative tests, it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". In the cases where a large number of batches have been tested, it is acceptable to summarize the total number of batches tested with a range of analytical results.

A discussion of the results presented should be provided and should focus on the impurity profiles observed in the batches studied with regard to the inclusion or exclusion of impurities and setting of acceptance criteria in the drug substance specifications. The selection of impurities to be included in the specifications and the acceptance criteria should be based on and consistent with the actual levels of impurities reported and conforming to the applicable VICH guidance documents GL10[14.1] and GL18[14.3].

Results on the drug product can also be presented for comparative batches e.g., for a comparative purity study of a subsequent entry drug product against the Canadian reference product (See Section 6.6).

6.3.4.3 Other Considerations

It is recognized by the compendia that drug substances can be obtained from various sources and synthetic processes, and thus can contain impurities not considered during the preparation of the monograph. Furthermore, a change in the production or source may give rise to impurities that are not adequately controlled by the published compendial monograph.

As a result, each drug submission is reviewed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the VICH limits for unspecified impurities (e.g., Not More Than (NMT) 0.2%) are generally recommended, rather than the general limits for unspecified impurities that appear in the compendial monograph that could be potentially higher than the VICH limit.

Depending on the nature of the drug substance, and the extent of the chemical modification steps, the principles on the control of impurities can also be extended to drug substances of semi-synthetic origin. As an illustrative example, a drug substance whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin, and has subsequently undergone several chemical modification reactions generally would fall within this scope, whereas a drug whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. It is understood that there is some latitude for these types of drug substances (e.g., NMT 0.5% for unspecified impurities may be

appropriate, rather than NMT 0.2%).

If there are identified impurities specified in a compendial monograph that are not monitored by the proposed routine analytical method (e.g., House method), a justification should be provided for their exclusion. If acceptable justification cannot be provided, it should be demonstrated that the house method is capable of detecting the impurities specified in the compendial monograph at an acceptable level (e.g., 0.2%).

6.3.5 Control of the Drug Substance

6.3.5.1 Specification

The specification for the drug substance should be provided. The drug substance specifications should as a minimum include tests for appearance, identity, potency, and purity.

A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

The specification should include test, method type, source, and code number/version/date. The acceptance criteria should also be provided. The method type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction, etc.); the source refers to the origin of the analytical procedure (e.g., USP, Ph.Eur., BP, House, etc.); and the code number/version/date should be provided for version control purposes.

A copy of the drug substance specification from the company responsible for release testing should be provided, dated and signed by the person in charge of the Quality Control department. The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a Schedule B compendial standard (e.g., USP, Ph. Eur., BP, etc.), Manufacturer's or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the *Food and Drug Regulations*), or a Professed Standard.

Although a Schedule B compendial monograph may exist, a sponsor can

choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the compendial standard. However, according to section C.01.011 of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the Act. Therefore, if a manufacturer's standard is used, the controls on purity (e.g., limits on specified impurities) and potency should be as tight as the most stringent of those listed in the Schedule B compendial monographs, and any house methods used in testing should demonstrate their equivalence to the compendial methods.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

For drug substance used for parenteral preparation, the limit for bacterial endotoxins should be included.

Further guidance on standards is available in the Health Canada's "*Guide for the Labelling of Drugs for Veterinary Use*"[14.4]

6.3.5.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided.

Copies of the analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures. HPLC is normally considered the method of choice for determining drug-related impurities, and some other chromatographic methods such as GC and TLC may also be used, if appropriate. For impurity methods, reference standards should be prepared for each of the identified impurities, particularly those known to be toxic, and the concentration of the impurities quantitated against their own reference standards. It is considered acceptable to use the drug substance as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the drug substance. In cases where the response factor is not close (e.g., less than 80%), it may still be acceptable to use the drug substance, provided a correction factor is applied or the impurities are, in fact, being

overestimated. Unspecified impurities should be quantitated using a solution of the drug substance as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g., 0.1%).

A system suitability test (SST) is an integral part of any chromatographic analytical procedures. As a minimum HPLC and GC methods should include a SST for repeatability and are expected to include additional SSTs such as tailing factor, resolution, number of theoretical plates, tailing factor, etc., appropriate for the intended purpose of the method. The repeatability test should include at least five replicate injections.

For TLC methods, the SST's should verify the sensitivity and ability of the system to separate (e.g., by applying a spot corresponding to the drug substance spiked at a concentration corresponding to the limit of unspecified impurities).

Further guidance is available in Schedule B publications (e.g., USP General Chapters <621> Chromatography).

6.3.5.3 Validation of Analytical Procedures

Validation of an analytical method is the process that establishes, by laboratory studies, that the test parameters of the method meet the requirements for the intended analytical applications. The test parameters that should be generally considered in the validation include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range and ruggedness. However, the test parameters to be established for a particular method depend on the nature and the intended purpose of the analytical procedure being evaluated.

When a compendial method is adopted, the system suitability of the method may be necessary to be verified for its intended use. However, revalidation should be considered in the case of a compendial method applied to a drug substance obtained from a different source, manufactured through a different synthetic process, containing different impurity profiles, or there are changes in the analytical procedure. If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g., for potency or for specified impurities), equivalency of the House and compendial methods should be demonstrated. This is typically accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study.

Copies of the validation reports for analytical procedures proposed for routine

release and shelf life testing of the drug product should be provided as well as copies of those used to generate supporting test results for clinical and stability lots of the drug product. These reports should include a detailed description of the validation protocol used, analytical data for each of the test parameters examined and a discussion of the results including a justification of the test parameters used.

Further guidance regarding the validation of analytical procedures is available in the VDD's adopted VICH guidance documents GL1[14.5] and GL2[14.6], and USP general Chapters <1225> Validation of Compendial methods.

6.3.5.4 Batch Analyses

Descriptions and results of batch analyses should be provided for batches used to establish the specification(s) and evaluate consistency in manufacturing.

Descriptions should include:

- batch number
- batch size
- date and site of production
- type of study in which it was used (nonclinical, clinical, comparative, stability etc.).

Analytical results generated by the company responsible for release testing should be provided for at least two batches from each proposed manufacturing site of the drug substance. The testing results should include the batch(es) used in the nonclinical, clinical and/or comparative bioavailability studies. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total impurity tests and potency tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

6.3.5.5 Justification of Specification

Justification for the drug substance specification should be provided. This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard, etc.. If the Schedule B compendial methods have been modified or replaced, a discussion should be included. The justification for certain tests, analytical procedures, and acceptance criteria may have been discussed in other sections of the drug submission (e.g., impurities, particle size) and do not need to be repeated here, although a cross-reference to their location should be provided.

6.3.6 Reference Standards

Information on primary and secondary reference standard(s) used in the testing of the drug substance to generate analytical results included in the submission should be provided. However, compendial reference standard should be employed as a primary reference standard, if available, in order to be able to claim a compendial standard. For all reference standards, the following information should be provided:

- Source
- Lot number
- Date of manufacture
- Copies of the certificate of analysis

6.3.6.1 Primary Reference Standards

A primary reference standard is a substance that has been shown by an extensive set of analytical tests (e.g., elemental analysis, IR, UV, NMR, MS, DSC, HPLC etc.) to be authentic material of high purity. It can be obtained from:

(1) an official source such as those recognized in the Schedule B compendia. In this case, it is sufficient to submit the information indicated in section 6.3.6.

(2) an existing lot or batch of drug substance of high purity produced according to the proposed commercial drug substance manufacturing process. In this case, an extensive set of analytical data establishing the drug substance structure and high purity should be provided in addition to the information indicated in (1).

(3) further purification of a portion of a lot, a lot or batch of an existing production material. In this case, a description of additional purification steps performed should be provided in addition to the

information indicated in (2).

(4) independent synthesis. In this case, a description of the process used including all purification steps should be provided in addition to the information indicated in (3).

6.3.6.2 Secondary Reference Standards

A secondary reference standard is a substance used as reference standard for routine laboratory analysis and for which quality and purity is established by comparison against a primary reference standard.

For a secondary reference standard, in addition to the information indicated in section 6.3.6, results of an appropriate validation against a suitable primary reference standard should be provided including legible copies of the IR and UV spectra of the secondary and primary reference standards run concomitantly. If the manufacturing process used to produce a secondary reference standard differs from the proposed commercial manufacturing process for the drug substance, a brief description of the manufacturing process of the secondary reference standard outlining these differences should be provided.

6.3.7 Packaging

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component (i.e., those in direct contact with the drug substance), and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate. For non-functional secondary packaging components (i.e., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including absorption to container and leaching, and/or safety of materials of construction as appropriate.

6.3.8 Stability

The purpose of stability testing is to provide evidence of how the quality of

a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and enables recommended storage conditions, re-test period or shelf life (where appropriate) to be established.

The types of studies conducted (e.g., stress, long term, accelerated, etc.) protocols used, and results from these studies should be provided in the submission.

In addition to the guidance outlined in this section, more detailed guidance regarding stability is available in VDD'S adopted VICH guidance documents GL3[14.7], GL4[14.8], GL5[14.9] and GL8[14.10].

6.3.8.1 Forced Degradation (Stress) Studies

Stress testing helps to determine the intrinsic stability of the molecule by establishing potential degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

The nature of the stress testing will depend on the individual drug substance and the type of dosage form involved. Stress study information can also help in pharmaceutical development and selection of suitable packaging material. Stress testing is expected to be carried out on at least one batch of drug substance and to include the effect of conditions such as:

- High Heat
- High humidity
- UV Light
- Acid/base hydrolysis
- Oxidation

Details of the treatment conditions (e.g., concentrations of solutions prepared, storage temperatures and durations) should be provided along with actual numerical test results in an appropriate format such as tabular, graphical, or narrative.

6.3.8.2 Accelerated and Long Term Studies

Results from stability studies under controlled conditions in accordance with the following table should be provided.

Study	Storage Conditions	Minimum Time Period Covered by Data at the time of Submission
Long term	25˚C ± 2˚C / 60% RH ± 5% RH	12 months
Accelerated	40˚C ± 2˚C / 75% RH ± 5% RH	6 months

When failure to meet specifications occurs at any time during testing at the accelerated storage conditions, additional testing at the intermediate storage condition (30°± 2°C / 60% RH ± 5% RH) for 6 months should be conducted and evaluated against significant change criteria.

Other study conditions may be required for drug substances intended for storage in a refrigerator and those intended for storage in a freezer. Drug substances intended for storage below -20˚C should be treated on a case-by-case basis.

For existing drugs, available information on the stability of the drug substance under accelerated and long term conditions should be provided, including information in the public domain or obtained from DMF Holders. The source of the information should be identified. In certain cases, information available in the public domain may be sufficient to establish an appropriate re-test period (e.g., when a substantial body of evidence exists that establishes that the drug substance is inherently stable). In all instances, sponsors should provide all relevant information available on the stability of the drug substance.

The information on the stability studies should include:

- date of manufacture of the lots studied
- batch or lot number and batch size,
- description of container closure system
- storage conditions
- test intervals completed
- tests performed with acceptance limits
- detailed description of analytical procedures used to generate the data and validation data for these procedures.

Actual results (i.e., raw data) should be presented in an appropriate format such as tabular, graphical, or narrative. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be

ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Also, results from quantitative tests should not be reported as “less than X” unless “X” represents the validated limit of quantitation (LOQ) of the testing method used to generate the results. A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification or frequency).

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This should include ranges of analytical results and any trends that were observed.

6.3.8.3 Proposed Storage Conditions and Re-test Period

The proposed storage conditions and re-test period (or shelf life where appropriate) for the drug substance should be provided and should be consistent with and supported by the long term stability data presented. Based on the results of the stability evaluation, storage precautions should be included if warranted (e.g., "Protect from light", "Protect from moisture").

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the re-test period may be acceptable, if justified.

For drug substances known to be labile (e.g., certain antibiotics), a shelf life can be established rather than a retest date.

6.4. Drug Product

Some of the information to be included in the submission pertaining to packaging materials and certain excipients (e.g., colourants, flavours and other additives) that may be used in the manufacture of the drug product may not be available to the sponsor because such information is of a proprietary nature (e.g., quantitative composition of packaging materials, quantitative formulation of colourants or flavours). In this case, the sponsor can make reference to a Type II (for packaging materials) or Type III (colourants, flavours and other additives) Drug Master File (DMF) which can be filed directly with Health Canada by the holder of the Type II or Type III DMF. This DMF will be held in strict confidence and will be used in support of the drug submission only upon receipt of written authorization from the DMF Holder (i.e., via a letter of access).

Sponsors should note the following with respect to the DMF:

- When a DMF is filed for the first time with Health Canada in support of a Veterinary

Drug submission, then the DMF should be filed with VDD.

- Cross-reference to a DMF previously filed with TPD in support of a human drug product is considered acceptable.

- Reference to the open part of a Type I DMF is not a substitute for providing the information regarding the drug substance as outlined in sections 6.3, of this Guidance Document.

- The non-proprietary information contained in the open part of a Type I DMF should be incorporated into the drug submission. It is the responsibility of the sponsor to obtain all the non-proprietary information from the holder of the DMF for the drug substance.

- Regardless of the information included in a Type I DMF, the sponsor is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the drug substance as well as the results of batch analyses are provided by the drug product manufacturing facilities.

- Reference to a DMF filed with a foreign regulatory authority is not acceptable.

The proprietary information (in the closed part) of the DMF is reviewed in connection with a drug submission. DMF holders will be contacted directly only when deficiencies are determined in the closed part of information of the DMF, and comments regarding such deficiencies are sent directly to the DMF holder. In such a case, the sponsor will be notified in writing that a deficiency letter has been sent to the DMF holder but is not informed of the specific comments contained in the letter. Comments on the deficiencies observed in any other part of drug substance information in the submission are sent to the sponsor of the drug submission.

For further information on the requirements for Drug Master Files, see Health Canada's guidance document: Product Master Files (soon to be renamed Drug Master Files).

6.4.1 Description of the drug product

A detailed description of the drug product should be provided. The information provided should be for the finished drug product intended to be marketed in Canada and should include:

- A detailed physical description, available strengths, release mechanism, as well as any other distinguishable characteristics, e.g., "*The proposed drug product is available as oval, round, immediate-release, aqueous film-coated tablet in three strengths (5 mg, 10 mg, and 20 mg). The two higher strengths include a vertical score line to facilitate the breaking of the tablets.*"

- A description of each type of container/closure system used for the drug product. This description should be brief with further details provided under section 6.4.5. For example: "*The product is available in 100 mL HDPE bottles with polypropylene caps and in PVC/Aluminum foil unit dose blisters.*"

- The proposed storage conditions and expiration period.

Where applicable, the following should also be provided:

(a) Description of accompanying reconstitution diluent(s).

For drug products supplied with reconstitution diluent(s) commercially available in Canada or that have been reviewed and approved in connection with another drug submission , cross reference to the appropriate submission number(s), file number(s) and DIN(s) should be provided.

For drug products supplied with reconstitution diluent(s) that are not commercially available in Canada or have not been reviewed and approved in connection with another drug submission, chemistry and manufacturing information on the diluent(s) should be provided in a separate drug product section of the submission, as appropriate.

(b) Description of each type of container/closure system used for the accompanying reconstitution diluent.

This description should be brief with further details provided under section 6.4.5. For example: "*The product is available in 100 mL HDPE bottles with polypropylene caps and in PVC/Aluminum foil unit dose blisters.*".

(c) Description of accompanying dosing devices.

If the product is to be administered using a device such as dosing spoon, syringe, dropper, etc., a brief description of the device should be provided with further details provided under section 6.4.5.

6.4.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information summarizing the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container/closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the submission.

This summary would typically address issues such as:

- Compatibility of the drug substance with excipients.

- Physicochemical characteristics of the drug substance that can influence the performance of the drug product (e.g., water content, solubility, particle size distribution, polymorphic or solid state form).

- Physicochemical characteristics of the drug product relevant to its performance, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity.

- For combination products, the compatibility of drug substances with each other should be discussed.

6.4.3 Method of Manufacture

6.4.3.1 Manufacturer(s)

The name and address of all sites or facilities (including those contracted) involved in the production of the drug product should be provided. This includes facilities involved in:

(a) fabrication;
(b) packaging;
(c) labeling;
(d) testing;
(e) importing;
(f) storage; and
(g) distribution of the drug product.

If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate), this should be indicated. The list of manufacturers should specify the actual site where the above mentioned activities take place, rather than the administrative offices.

6.4.3.2 Formulae

6.4.3.2.1 Quantitative formula

List all components of the drug product, and their amount on a per-unit basis (e.g., mg per tablet, mg per mL) and percentage basis, including a statement of the total weight or measure of the dosage unit.

The function of each component (e.g.,. active, diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative, etc.), and a reference to their quality standard (compendial or manufacturer) should also be indicated.

The components should be declared by their proper, common or compendial names, and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)"). Alternates for excipients are generally not accepted. Ranges for excipients are normally not accepted, unless supported by appropriate process validation data. Ranges for active ingredients are not accepted.

The qualitative composition should be provided for all proprietary components or blends (e.g., capsule shells, colouring blends, flavours, etc.). This information is used for product labelling purposes. The actual quantitative composition should also be provided either in the submission or via reference to a Type III or IV Drug Master File.

6.4.3.2.2 Batch formula

The batch formula should express the quantity of each component on a per batch basis including a statement of the total weight or measure of the batch. This should include all components used in the manufacturing process, regardless of whether they appear in the final drug product (e.g., solvents, nitrogen, silicon for stoppers, etc.). If the drug product is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride").

Any overage must be justified and supported by analytical data. Overages for the sole purpose of extending the expiration date of the drug product are not allowed. If an overage is used in the formula, it must be clearly indicated (e.g., "Contains 5 kg overage of the drug substance to compensate for manufacturing losses.").

6.4.3.3 Manufacturing Process

6.4.3.3.1 Description

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative summary of the manufacturing process (including packaging/labelling) describing the sequence of steps undertaken should be provided for each proposed strength and intended commercial batch size. This summary should include:

- amounts of ingredients dispensed;
- identification of all equipment by type and working capacity;
- process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, etc.);
- a list of in-process tests with limits;
- precautions necessary to ensure product quality, if applicable (e.g., light, temperature and humidity control, maximum holding times, etc.).

Examples of applicable in-process controls include but are not limited to:

(i) granulations:	moisture, blend uniformity, bulk and tapped densities, particle size distribution;
(ii) solid oral products:	average weight, weight variation, hardness, thickness, friability, disintegration, weight gain during coating;
(iii) semi-solids:	viscosity, homogeneity, pH;
(iv) liquids:	pH, specific gravity, clarity of solutions;
(v) parenterals:	appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter;
(vi) implants:	average weight, weight variation, hardness, thickness, friability, disintegration, weight gain during coating.

6.4.3.3.2 Master Production Documents

Copies of the master production documents should be provided for each proposed strength, commercial batch size, and manufacturing

site.

The details in the master production documents should include, but are not limited to, the following:

- dispensing, processing and packaging sections with relevant material and operational details;

- relevant calculations (e.g., if the amount of drug substance is adjusted based on the potency results or on the anhydrous basis, etc.);

- identification of all equipment by type and working capacity;

- process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, etc.);

- in-process tests (e.g., appearance, pH, potency, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity);

- sampling plan with regard to the:

(i) steps where sampling should be done (e.g., drying, lubrication, compression);

(ii) number of samples that should be tested (e.g., blend drawn using a sampling thief from x number of different parts of the blender);

(iii) frequency of testing (e.g., weight variation every x minutes during compression or capsule filling);

- precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times);

- theoretical and actual yield.

It is recognized that Master Manufacturing Documents may not contain some of the above information per se as reference may be made to SOPs. When this is the case, the pertinent SOPs should be provided with the Master Production Documents.

6.4.3.3.3 Executed Production Documents

Copies of the executed production documents (including certificates of analysis for all raw materials used) should be provided for the batches used in the pivotal, clinical and/or comparative bioavailability studies. Any notations made by operators on the executed production documents should be clearly legible.

A minimum of two batches of each strength should be manufactured (which may include those used for pivotal, clinical and/or comparative bioavailability studies). Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch i.e., at a minimum of 10% of a full production scale.

6.4.3.4 Process Validation

In addition to the guidance outlined in this section, more detailed guidance regarding process validation for sterile and non-sterile drug products is available in the Health Products and Food Branch Inspectorate document entitled "*Validation Guidelines for Pharmaceutical Dosage Forms*." [14.11] For the purpose of the requirements outlined under section 6.4.3.4.1 and 6.4.3.4.2 below, process validation refers to Phase II validation as described in this aforementioned Validation Guideline.

More detailed guidance is also available regarding validation of specific sterilization processes in the HPFB Inspectorate documents website: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/index_e.html), entitled:

- "*Process Validation: Aseptic Processes for Pharmaceuticals*"
- "*Process Validation: Gaseous Sterilization for Pharmaceuticals*"
- "*Process Validation: Irradiation Sterilization for Pharmaceuticals*"
- "*Process Validation: Form - Fill - Seal for Drugs*"
- "*Process Validation: Moist Heat Sterilization for Pharmaceuticals*"

6.4.3.4.1 Sterile Products

The manufacture of sterile drugs needs a well-controlled manufacturing area (e.g., a strictly controlled environment, highly reliable procedures, and numerous in-process controls). A detailed description of these conditions, procedures, and controls should be provided, together with actual copies of the following standard operating procedures:

(a) washing, treatment, sterilizing, and depyrogenating of containers, closures, and equipment;

(b) filtration of solutions;

(c) lyophilization process;

(d) leaker test of filled and sealed ampoules (if applicable);

(e) final inspection of the product; and

(f) sterilization cycle.

A copy of the process validation report specific to this drug product which includes protocol and results should be submitted. This report should identify the critical steps, equipment and process parameters that can affect the quality of the drug product, and should define testing parameters, sampling plans, analytical procedures, and acceptance criteria.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of sterile drugs. The process can make use of moist heat (e.g., steam), dry heat, filtration, gaseous sterilization (e.g., ethylene oxide), or irradiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the drug product. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail, and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the drug product will not be affected. Details such as F_o range, temperature range, and peak dwell time for the drug product and the container/closure should be provided. Although standard autoclaving cycles of 121˚C, 15 minutes or more, would not need a detailed rationale; such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used for sterile filtration should be precisely described and validated with respect to pore size, compatibility with the product,

absence of extractables and lack of adsorption of the drug substance or any of the components.

6.4.3.4.2 Non-sterile products

The following information should be provided:

(a) Confirmation that the drug product will be subjected to process validation in accordance with Health Products and Food Branch Inspectorate *"Validation Guidelines for Pharmaceutical Dosage Forms."*[14.11]

(b) A copy of the process validation protocol, specific to this drug product. The protocol should identify the critical steps, equipment and process parameters that can affect the quality of the drug product, and should define testing parameters, sampling plans, analytical procedures, and acceptance criteria;.

(c) The process validation studies have already been conducted, a copy of process validation report should be submitted in lieu of (a) and (b) above, a summary of these process validation studies should also be provided.

6.4.3.5 Control of Excipients

If reference is made to a Type III DMF (Colourants, flavour and other additives) for certain proprietary information, the DMF number assigned by Health Canada should be provided. It should be ensured that the information included in the DMF is current (i.e., no more than two years old) and that the latest update of the DMF has been received by Health Canada. Copies of the letters of access should be provided in the submission. If an authorized agent is used by the DMF owner, a letter from the DMF owner should be submitted allowing the agent to act on their behalf, rather than the letter coming from the authorized agent.

6.4.3.5.1 Specifications

The specifications for all excipients should be provided, including those that do not appear in the drug product (e.g., solvents, nitrogen, silicon for stoppers, etc.).

If the specification for an excipient is to conform with the requirements of a Schedule B compendial monograph, it is sufficient to provide a commitment that the excipient will be tested according

to the most current compendial requirements, rather than reproducing the specifications found in the Schedule B compendial monograph.

If the specification includes other tests in addition to those prescribed in the compendial monograph, a copy of the excipient specification dated and signed by the person in charge of quality control at the dosage form fabrication site should be provided.

If the specification is for an excipient for which there is no Schedule B compendial monograph, a copy of the excipient specification dated and signed by the person in charge of quality control at the dosage form fabrication site should be provided.

Testing for microbial requirements should be at least as stringent as those specified in the corresponding compendial monograph should one exist (e.g., as for Magnesium Stearate NF). Excipients derived from natural sources should have appropriate microbial tests and limits.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

6.4.3.5.2 Analytical Procedures and Validation

Copies of analytical procedures from Schedule B compendial monographs do not need to be submitted.

Copies of analytical procedures and validation data (where appropriate) should be provided for tests that are supplementary to those appearing in a Schedule B compendial monograph as well as for all tests performed on excipients for which there is no Schedule B compendial monograph.

Further guidance regarding the validation of analytical procedures is available in the VDD's adopted VICH guidance documents GL1[14.5] and GL2[14.6].

6.4.3.5.3 Justification of specifications

Justification should be provided for tests that are supplementary to those appearing in a Schedule B compendial monograph as well as for all tests performed on excipients for which there is no Schedule B compendial monograph.

6.4.3.5.4 Medicinal and Non-Medicinal Ingredients of Animal Origin

Drug Substances of animal origin should be free of BSE and TSE agents. For any material of animal origin used in the manufacture of the drug substance, information should be provided in accordance with the most stringent requirements set out in Schedule B compendial monographs (e.g. USP, Ph.Eur., B.P.) and the requirements of the AIF. This information includes a list of all medicinal ingredients and non-medicinal animal-sourced ingredients (including excipients, auxiliary reagents, medium components used in culture/fermentation, raw and/or starting materials and/or reagents used in synthesis/biosynthesis and processed materials used in the formulation of the drug product), their origin and use in the drug product, specifications, age of animal, country of origin, geographical profile of the animal or herd, BSE status of the country of origin, TSE classification of animal-sourced material(s), measures taken to minimize TSE prions and cross-contamination, testing of the herd where available or required by the agricultural regulations, description of the testing performed and viral safety data. A TSE-Certificate of Suitability and/or a science-based risk assessment and/or other relevant documentation should be provided when appropriate (please refer to the AIF), so that the VDD may confirm that the drug substance of animal origin is free of BSE/TSE agents. This information should be included with the drug submission.

6.4.3.5.5 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, the same information pertaining to non-Schedule B excipients as outlined under sections 6.4.3.5.1, 6.4.3.5.2, 6.4.3.5.3, and 6.4.3.5.4 should be provided. In addition, full details of the manufacture and characterisation of the novel excipient should be provided along with cross references to supporting safety data (non-clinical and/or clinical).

6.4.4 Control of the drug product

6.4.4.1 Specifications

Release and shelf life specifications should be provided for the drug product.

A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a

drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug product , when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

6.4.4.1.1 General requirements

A copy of the drug product release specification from the sponsor as well as from the site responsible for release testing in Canada should be provided, dated and signed by the person in charge of the Quality Control Department. In addition, a copy of the drug product shelf life specifications from the sponsor as well as from the site responsible for shelf life testing should be provided, dated and signed by the person in charge of the Quality Control department.

The specification should include reference number, version, and date for version control purposes.

The specification should include the Tests, Acceptance Criteria, Method Types, Sources, and Code Number /Version/Date. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, etc.); the Source refers to the origin of the analytical procedure (e.g., USP, BP, House, etc.); and the Code Number/Version/Date should be provided for version control purposes.

The specifications should be consistent with the standard declared by the sponsor. The currently recognized standards are:

- Prescribed Standard
- Compendial or pharmacopeial Standard
- Manufacturer's or House Standard
- Professed Standard

For further guidance, regarding labelling requirements in relation to standard declaration and specification, refer to the Health Canada guidance document entitled "Guide for the Labelling of Drugs for Veterinary Use".[14.4]

6.4.4.1.2 Tests applicable to all dosage forms

At release:

- Appearance
- Identity
- Assay
- Degradation products (only if degradation occurs during the manufacturing process)
- Residual solvents (only if used in the manufacturing process)

During shelf life:

- Appearance
- Assay
- Degradation products

The appearance test should consist of a qualitative description of the dosage form. The attributes to be included in this description should be consistent with the type of dosage form tested. e.g., for tablets: size, shape, colour, markings/identifiers; for semi-solids: colour, separation, leakage; for premixes: odour, settling, insects etc.).

The identity test should be specific for the active ingredient.

6.4.4.1.3 Tests typically applicable for specific type of dosage forms

The following should be noted:

-Specifications for modified release versions of any of the following types of dosage form should also include a meaningful drug release test.

-The test for uniformity of dosage units should be included in the specifications of all dosage forms where a variation in uniformity of dose from unit to unit can occur. The requirements for testing the uniformity of dosage units have been developed by the Schedule B compendia, and it is recommended that these be used in order that an appropriate test be established. It is expected that the strictest compendial standard will be adopted.

-Specifications for ophthalmic and intramammary dosage forms should include a test for sterility.

Lists of tests for each of the following categories of dosage form are provided as typical examples of tests that should be considered for inclusion in the specifications in addition to those listed under 6.4.4.1.2. These lists should not be seen as encompassing all possible

situations. Therefore some of these tests could be omitted if proper justification is provided and other tests could be added as required.

(a) Tablets and capsules:
- Dissolution
- Disintegration
- Average weight
- Hardness or friability
- Diameter and thickness
- Content uniformity or weight variation
- Moisture content

(b) Powder and powder for solution
- Weight variation
- Moisture content
- Solution rate
- pH of reconstituted solution
- Assay of reconstituted solution

(c) Semi-solids (Pastes, gels, creams, ointments):

Tests	Oral	Topical
pH	A	A
Specific gravity	T	T
Antimicrobial preservative content	A	A
Antioxidant content	A	A
Microbial testing	T	N
Viscosity	T	T
Sterility	N	A
Particle size	T	T
Content uniformity	T	T
Dose delivery and weight variation	T	T
Syringeability	A	A
Separation	T	T

T: Typically required.
A: May be required if considered appropriate.
N: Not likely to be required.

(d) Solutions:

Tests	Oral	Topical	Parenteral
pH	T	T	T
Specific gravity	T	T	T
Antimicrobial preservative content	A	A	A
Antioxidant content	A	A	A
Microbial testing	T	A	N
Viscosity	A	T	A
Bacterial endotoxins	N	N	T
Sterility	N	A	T
Particulate matter	N	N	T

T: Typically required.
A: May be required if considered appropriate.
N: Not likely to be required.

(e) Liquid suspensions:

	Oral	Topical	Parenteral
pH	T	T	T
Specific gravity	T	T	T
Antimicrobial preservative content	A	A	A
Antioxidant content	A	A	A
Microbial testing	T	A	N
Viscosity	A	T	A

Bacterial endotoxins	N	N	T
Sterility	N	A	T
Particulate matter	N	N	A
Particle size	T	T	T
Resuspendability	T	T	T
Content uniformity	T	T	T

T: Typically required.
A: May be required if considered appropriate.
N: Not likely to be required.

(g) Implants:
- Diameter, length
- Hardness, friability
- Release rate/dissolution
- Microbial testing

(h) Teat dips/udder washes:
- pH
- Specific gravity
- Viscosity

(I) Aerosols/sprays:
- Pressure
- Leakage
- Spray pattern

(j) Premixes:
- Moisture content
- Particle size/sieve analysis

6.4.4.2 Analytical Procedures

Copies of the analytical procedures proposed for routine release and shelf life testing of the drug product should be provided as well as copies of those used to generate supporting test results for clinical and stability lots of the drug product, outlining differences if any. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures.

A system suitability tests (SST) is an integral part of any chromatographic analytical procedure. As a minimum HPLC and GC methods should include

a SST for repeatability and are expected to include additional SSTs such as resolution, number of theoretical plates, tailing factor, etc., appropriate for the intended purpose of the method. The repeatability test should include at least five replicate injections.

For TLC methods, the SST's should verify the sensitivity and ability of the system to separate (e.g., by applying a spot corresponding to the drug substance spiked at a concentration corresponding to the limit of unspecified impurities).

Further guidance is available in Schedule B publications (e.g., USP General Chapters <621> Chromatography).

6.4.4.3 Validation of Analytical Procedures

Copies of the validation reports for analytical procedures proposed for routine release and shelf life testing of the drug product should be provided as well as copies of those used to generate supporting test results for clinical and stability lots of the drug product. These reports should include a detailed description of the validation protocol used, analytical data for each of the validation parameters and a discussion of the results. The choice of validation parameters should be justified and consistent with the type of analytical procedure and its intended purpose.

Validation is still necessary for methods that appear in a Schedule B compendial monograph. This need for validation is recognized by other Regulatory Agencies and the compendia themselves. The compendial methods, as published, are typically validated using a drug substance and drug product originating from specific manufacturers. Different sources of the same drug substance may contain impurities that were not considered during the development of the monograph. Also, different sources of the same dosage form may contain excipients that were not previously examined.

Therefore, compendial methods used for a specific drug product would require partial to full validation depending on the type of method (i.e., identity, potency, purity etc.) and dosage form. If a Schedule B compendial method exists and a house method is used in lieu of that method, the house method should be fully validated and its equivalency to the compendial method should be demonstrated. This is typically accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study.

Further guidance regarding the validation of analytical procedures is available in the VDD's adopted VICH guidance documents GL1[14.5] and GL2[14.6].

6.4.4.4 Batch Analyses

Results of batch analyses should be provided and discussed.

Certificates of analysis should be provided in the submission for:

- Batch(es) used in the non-clinical, pivotal, clinical and/or comparative bioavailability studies.

- At least two batches of each strength manufactured (which may include those used for pivotal, clinical and/or comparative bioavailability studies) by a procedure fully representative of and simulating that to be applied to a full production scale batch (i.e., at least 10% of full production scale). Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. The analytical results for these batches should be generated by the facility responsible for release testing in Canada.

- Production scale batches (if available).

- In the submission, the following information should be provided for each of the batches for which analytical results are reported:

    - Identity of the facility responsible for generating the results.

    - Batch/lot number, size, strength.

    - Date and site of production.

    - When performed, the individual results or the mean, the relative standard deviation (RSD), and the range for the content uniformity and dissolution tests.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "*All tests meet specifications*". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., individual and total degradation product tests, potency tests etc.), it should be ensured that actual numerical results are submitted rather than vague statements such as "*within limits*" or "*conforms*". Also, results from quantitative tests should not be reported as "*less than X*" unless "*X*" represents the validated limit of quantitation (LOQ) of the testing method used to generate the results. A discussion and justification should be provided for any incomplete analyses (e.g., not tested according to the proposed specification).

If the proposed dosage form is a scored tablet, the results of a study should be provided testing the uniformity of dosage units of the manually-split tablets. The data provided in the drug submission should include a description of the test method, individual values, mean, and RSD. Uniformity testing (i.e., content uniformity or weight variation, depending on the dosage form) should be performed on each split portion from a minimum of 10 randomly selected whole tablets.

The splitting of the tablets should be conducted in a manner that would be representative of that typically performed by the user (i.e., split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the drug product specifications. The acceptance criteria (range and variation) should be as described in the USP General Chapter <905> Uniformity of Dosage Units for whole tablets. The tablet description in the drug product specifications, and under the presentation section of the package insert, should reflect the presence of a score.

6.4.4.5 Justification of Specifications

Justification for the proposed drug product release and shelf life specifications should be provided.

This should include a discussion on:

- The selection of tests and their suitability to ensure reproducible drug product quality.

- Evolution of tests, analytical procedures, and acceptance criteria leading to the proposed specifications.

- Modifications to Schedule B methods.

The justification for certain tests, analytical procedures, and acceptance criteria may be discussed in other sections of the drug submission (e.g., stability) and do not need to be repeated here, although a cross-reference to their location should be provided.

The considerations for the justification of drug release methods and acceptance criteria are outlined as follows.

In vitro Dissolution or Drug Release

The results of studies justifying the choice of *in vitro* dissolution or drug

release conditions (apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in the manufacturing process and to any changes in the product that might occur during storage. Use of single point test or a dissolution range should be justified based on the solubility and permeability characteristics of the drug.

Modified-release dosage forms should have a meaningful *in vitro* release rate test that is used for routine quality control. Preferably this test should possess *in vitro-in vivo* correlation. Results demonstrating the effect of pH on the release profile should be submitted if appropriate for the type of dosage form. The testing conditions should be set to cover the entire time period of expected release (e.g., at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g., within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed ± 12.5% of the targeted value. Results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability studies.

6.4.5 Packaging

The sponsor should describe all proposed container/closure systems to be used for the drug product intended for the Canadian market including sample packs for veterinarians.

6.4.5.1 Description and specifications

A description and specifications should be provided in the submission for each of the following:

(a) Primary packaging component i.e., those that come in direct contact with the dosage form (e.g., container, closure, liner, desiccant, cotton, rayon).

(b) Functional secondary packaging component i.e., those not in direct contact with the dosage form but necessary for any of the following purpose:

- as a protective barrier to help ensure stability or sterility

- for drug delivery (e.g., dosing spoon, syringe, etc.)

- to ensure drug product quality during transportation and storage.

(c) Non functional secondary packaging component i.e., those other than primary and functional secondary packaging components.

For each primary (a) and functional secondary (b) packaging component:

-The description should be detailed, including identity of the supplier(s), dimensions, drawings (where appropriate), the identity of materials of construction (e.g., resin type for plastic containers) and indicating whether the packaging component is subjected to additional treatments.

-A copy of the specification dated and signed by the person in charge of the Quality Control at the site where packaging of the dosage form is performed should be included in the submission. These specifications should at least include a visual (name, description), a dimensional (e.g., diameter, thickness, etc.) and a specific (e.g., IR) identity test. Additional tests may be required depending on the suitability/qualification data submitted. Description and validation data for non-compendial methods should be included, where appropriate.

For each non-functional secondary (c) packaging component:

-Only a brief description should be provided.

-Only an outline of the specifications should be provided.

6.4.5.2 Suitability

The suitability of each of the proposed container/closure system of the drug product intended for the Canadian market should be established. This is typically done by submitting results from appropriate tests and studies which demonstrate each packaging system suitability for its intended use. These tests and studies should address considerations such as:

- protection from moisture and light

- compatibility of the materials of construction with the dosage form (e.g., absorption to container and leaching)

- safety of materials of construction

- performance (e.g., reproducibility of delivery from the dosing device when included as part of the drug product).

The information submitted to establish suitability may be generated by the

sponsor or the supplier of the packaging component. If generated by the sponsor, the information should be included in the submission. If generated by the supplier, the information should be available to Health Canada either by inclusion in the drug submission or by cross reference to the supplier's Type II (Packaging materials) DMF.

If reference is made to a Type II DMF for certain proprietary information, the DMF number assigned by Health Canada should be provided. The sponsor should ensure that the information included in the DMF is current (i.e., no more than two years old) and that the latest update of the DMF has been received by Health Canada. Copies of the letters of access should be provided in the submission. If an authorized agent is used by the DMF owner, a letter from the DMF owner should be submitted allowing the agent to act on their behalf, rather than the letter coming from the authorized agent.

Since the suitability of a container/closure system depends on the dosage form and route of administration, the following table outlines typical tests and studies that should be considered for various type of dosage forms.

Suitability of primary packaging components	Type of dosage form		
	Solid Oral products	Oral liquid and Topical products	(Sterile products[3] (including parenteral, ophthalmic and intramammary)
Composition of all components (including cap liners, coatings for metal tubes, elastomers, adhesives, silicon, etc.	T	T	T
Description of the process used for any additional treatments[1]	T	T	T
Meet USP <661> Containers requirements	A	T	T[2]
Meet USP <671> Containers-permeation requirements	A	T	T

Meet USP <381> Elastomeric closures for injections requirements	N	N	T[2]

T: Typically required
A: May be required, when appropriate.
N: Not required.

1 e.g., coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials, sterilization and depyrogenation of the components etc. If any additional processes have already been described under section 6.4.3.3, cross reference to that section is sufficient.

2 Includes USP <87> / <88> tests.

3 For sterile products, USP General Chapter <1207> "*Sterile Product Packaging - Integrity Evaluation*"[14.12] provides further information regarding the integrity of sterile product packaging.

Confirmation of the suitability of the packaging system is further established by full shelf life stability studies. Such stability studies should include an in-use study to establish a storage time for which the integrity of a multiple dose parenteral product is preserved after administration of the first dose (often referred to as a "broached vial study").

6.4.6 Stability

The purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and enables recommended storage conditions and shelf life to be established.

The types of studies conducted (stress, long term, accelerated, others), protocols used, and results from these studies should be provided in the submission. These studies should be designed to include conditions relevant to the particular type of dosage form.

In addition to the guidance outlined in this section, more detailed guidance regarding stability is available in VDD'S adopted VICH guidance documents GL3[14.7], GL4[14.8], GL5[14.9] and GL8[14.10].

6.4.6.1 Accelerated and Long Term Studies

Results from stability studies in accordance with the following table should

be provided for a minimum of three primary batches of each strength in each different container/closure system proposed for marketing. Bracketing and matrixing can be applied, if scientifically justified.

Study	Storage Conditions	Minimum time period covered by data at the time of submission
Long term	25˚C ± 2˚C / 60% RH ± 5% RH	12 months
Accelerated	40˚C ± 2˚C / 75% RH ± 5% RH	6 months

When failure to meet specifications occurs at any time during testing at the accelerated storage conditions, additional testing at the intermediate storage condition (30°± 2°C / 60% RH ± 5% RH) for six months should be conducted and evaluated against significant change criteria.

The studies should include testing carried out at the following intervals:

Long term testing: 0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months

Accelerated testing: 0, 1, 2, 3, 6 months

Intermediate testing: 0, 1, 2, 3, 6 months

A justification should be provided when the frequency of testing departs from the above schedule.

Consideration should be given to the following specific situations:

- For sterile products, testing for sterility should be conducted initially and every year thereafter up to the proposed expiry date. Bacterial endotoxins need only be reported at the initial test interval.

- For drug products intended for storage in a refrigerator and those intended for storage in a freezer, other study conditions may be required.

- For drug products that require reconstitution or dilution according to labelling instructions, stability results should be provided to support the shelf life of the reconstituted or diluted product.

- For each lot studied, the information on the stability studies should include:

- Date of manufacture

- Batch or lot number and size

- Detailed description of container/closure system

- Storage conditions

- Test intervals completed (and proposed)

- Tests performed with acceptance limits

- Detailed description of the analytical procedures used to generate the data and validation data for these procedures.

All studies should include tests for appearance, assay of active ingredient(s) and degradation products. Additional tests relevant to the dosage form studied should be added as appropriate (refer to section 6.4.4.1.3).

Actual results (i.e., raw data) should be presented in an appropriate format such as tabular, graphical, or narrative. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that actual numerical results are provided rather than vague statements such as "*within limits*" or "*conforms*". Also, results from quantitative tests should not be reported as "less than X" unless "*X*" represents the validated LOQ of the testing method used to generate the results. A discussion and justification should be provided for any incomplete analyses (e.g., not tested according to the proposed specification or frequency).

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "*All tests meet specifications*". This should include ranges of analytical results and any trends that were observed.

6.4.6.2 Proposed storage conditions and shelf life

The proposed storage conditions and shelf life for the drug product should be provided. They should be based on and consistent with the results of the stability studies submitted.

Proposed storage conditions should include a temperature range. Storage conditions defined only by vague terms such as "Store at ambient conditions" or "Store at room temperature" are not considered acceptable. However,

storage conditions such as "Store at room temperature (15°C to 30°C)" would be considered acceptable if supported by the stability data.

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Protect from light", "Protect from humidity", "Protect from freezing").

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life may be undertaken at approval time, if justified.

6.4.6.3 Stability Commitment

A commitment to conduct post approval stability studies should be provided. The protocols for these studies should also be provided and should be consistent with the stability information already included in the submission.

6.4.6.3.1 Primary Batch Stability

When available long term stability data on primary batches do not cover the proposed shelf life at the time of submission, a commitment should be made to continue the stability studies post approval.

6.4.6.3.2 Production scale batch stability

A commitment to conduct stability studies on at least the first 3 production scale batches of each strength in each different container/closure system proposed for marketing should be provided. The protocol for these studies should also be provided and should be consistent with the stability information already included in the submission (see section 6.4.6.1). Bracketing and matrixing can be applied, if scientifically justified.

Any differences in the stability protocols used for the primary batches and the one proposed for the production scale batches should be described and scientifically justified. Any changes to or replacement of analytical procedures used for primary batches (see section 6.4.6.1) should be described in detail and justified.

6.4.6.3.3 Continuing batch stability

A commitment to establish and implement a continuing stability programme to ensure compliance with the approved shelf life specifications should be provided. The protocol for this continuing

stability programme should also be provided and should be consistent with the stability information already included in the submission (see section 6.4.6.1).

Any differences in the stability protocols used for the primary batches and the one proposed for the production scale batches should be described and scientifically justified. Any changes to or replacement of analytical procedures used for primary batches (see section 6.4.6.1) should be described in detail and justified.

Further guidance regarding the continuing stability programme is available in the Health Products and Food Branch Inspectorate documents entitled: "*Good Manufacturing Pratices Guidelines ,2002 Edition, Version 2*"[14.13] and " Veterinary Drugs Annex to the current *Good Manufacturing Practices Guidelines.*"[14.14]

6.5. Additional Information for Drug Premixes

Because premixes are not intended to be administered directly to animals, but are formulated for blending into feeds, there are certain special requirements for mixing and stability studies.

6.5.1 Stability of Medicated Feeds

Results from the study of at least two batches of medicated feed for three months at 25°C ± 2°C / 60% ± 5% RH and at 40°C ± 2°C / 75% ± 5% RH should be provided. Assay is the only test typically required. Testing should be carried out initially and then at one-month intervals. If the premix is to be incorporated at various concentrations into feed, stability studies should be carried out at both the lowest and highest levels recommended.

The effects of pelletizing should be demonstrated by performing assays on the feed before and after pelletizing, and, subsequently, at monthly intervals up to three months. If it is expected that pellet-binding agents will be used, then the three-month study should include at least one feed pelletized with and without the binding agents at the recommended use level.

6.5.2 Mixing Studies

Drugs in medicated feeds, although present in only small amounts, must be evenly distributed throughout the feed. To demonstrate homogeneity, samples should be taken for assay from various points in the blender following the usual mixing cycle. Note should also be taken of any demixing tendencies or electrostatic separation so that suitable precautionary statements can be included in the Directions for Use.

6.5.3 Premixes Proposed for Concurrent Use

For premixes that are recommended for concurrent use, demonstrate that the analytical method used for the assay of each drug retains its accuracy and precision in the presence of the other drugs. If the other drugs interfere in the analysis, a new analytical method will be required.

6.5.4 Feed Assay Validation

If a drug is to be administered as a medicated feed, an acceptable method of analysis for the drug, when mixed in typical complete feeds at the recommended level, must be provided. The information listed below should be included:

(a) A clear and concise description of the methodology.

(b) Method performance standards (i.e., recoveries, analytical ranges, limits of quantification and detection, and coefficients of variation for repeatability).

(c) Critical control points.

(d) Experimental designs and statistical plans.

(e) Raw data, chromatograms, tracings, calculated results, statistical results, and quality control for methods.

(f) Interference studies and documentation.

(g) Familiarization procedures for new analysts.

(h) Other related documentation such as ruggedness studies. confirmatory and trace level procedures, collaborative studies, and references.

(I) Stability data for two or more lots of typical complete feeds medicated at the recommended level and stored for three months at room temperature and at 37°C as mash or pellets.

6.5.5 Samples

Provide samples for analysis as described below. When prepared to validate the method of analysis, Agriculture Canada will request the samples.

(a) Active ingredient reference standard with a purity percentage indicated on the label (a sufficient quantity to validate the method).

(b) Technical product (10 g), with a purity percentage indicated on the label.

(c) Drug in finished pharmaceutical form (500 g).

(d) Medicated feed in finished form, that is, mash, pellets, or both. Supply five one-kilogram samples of feed, each obtained from a different nutrient formulation. The level of active ingredient is to be verified through analysis, and the method of analysis is to be indicated.

(e) Unmedicated feed blank (1 kg). Supply unmedicated samples of feed from each of the five feeds requested in (d). The feeds are to be analysed to verify the absence of the active ingredient or of interference.

6.6 Additional Information for Subsequent Market Entry Drug Products

In addition to the information and data provided in sub-sections 6.3 and 6.4, the following information should be provided for all subsequent market entry drug products:

(a) Analytical results from a comparative impurity profile of the subsequent entry drug product against the Canadian reference product (innovator product) should be provided. Results of a concomitant analysis of the lot of the drug substance used in the manufacture of the subsequent entry drug product should also be provided as a control. The analytical results should be generated using the test method proposed by the manufacturer of the subsequent entry drug product.

(b) When known toxic degradation products are formed, analytical results from a comparative stability study under accelerated and/or long term conditions of the subsequent entry drug product against the Canadian reference product should be provided.

(c) Where applicable, analytical results establishing the isomeric composition of the subsequent entry drug product against the Canadian reference product should be provided.

Additional appropriate comparative data versus the Canadian reference product may be needed for specific dosage forms, e.g., comparative dissolution profiles for solid oral immediate release subsequent entry drug products. Such data should be generated for subsequent entry drug product lots used in the comparative bioavailability studies and at least one recent lot using the test method(s) proposed by the manufacturer of the subsequent entry drug product.

7. PART III. REQUIREMENTS FOR ANIMAL SAFETY

7.1 Laboratory Animal Studies

Laboratory animal studies will normally be required for new chemical entities proposed for use as veterinary drugs. The information available in the published scientific literature may be accepted in lieu of studies outlined in this section. For the purpose of these guidelines, these studies are required to determine potential toxic effects for the target animal species.

The basic toxicity data obtained in laboratory animals complement the data required to support the safety of a new drug in the target animal species. Depending on the intended route(s) of administration of the drug for the target animal species, the toxicity studies may be conducted by oral and/or parenteral routes of administration of drugs. The laboratory animal toxicity studies in general may be classified as acute, subchronic or chronic.

Due regard should be given to the welfare of the study animals. The use of animals for research and testing should conform to the rigorous ethical standards that are compatible with the goals of science for benefiting humans or animals. Those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information. For standards for use and care of animals a reference may be made to the Guide to the Care and Use of Experimental Animals[14.15] , by the Canadian Council on Animal Care (CCAC).

7.1.1 Comprehensive Summary

A comprehensive summary of safety studies conducted in laboratory animals should be presented in a factual and descriptive format. The summary must contain separate discussions and evaluations for each area of study.

7.1.2 Sectional Reports

The data should be presented in sections in such a way that studies are grouped separately for each route of administration, each dosage regimen and each laboratory animal species.

7.1.2.1 Acute Toxicity Studies

It should be noted that these guidelines do not require death as an end-point for acute toxicity. For establishing humane end-points appropriate guidelines from CCAC[14.16], Organization for Economic Co-operation (OECD)[14.17, 14.19] or Institute for Laboratory Animal Research (ILAR)[14.18], should be consulted.

Acute toxicity studies in laboratory animals may be conducted to determine toxic effects on body systems and functions[14.20, 14.21, 14.22], dermal toxicity[14.23], skin sensitization[14.24, 14.25], skin irritation[14.26] or eye irritation[14.27]. These studies may be conducted by single administration (or multiple administrations within a period of 24 hours) of the test drug to an animal with an observation period of up to two weeks. The purpose of these studies is to

determine the dosage range and relative toxicity of the test material and to identify its primary site of action. A description of all clinical signs of toxicity should be recorded.

7.1.2.2 Subchronic Toxicity Studies

These studies are conducted by repeated administrations of the test drug for 90 days and are designed to determine the adverse effects of test drugs given in regularly repeated doses to rodent and/or non-rodent species[14.28, 14.29]. These studies may be extended to 12 months. The intent of these studies is to define a level that results in no observable effect. These studies provide guidance for selection of dosage for chronic toxicity studies and indicate any special studies that may need to be conducted.

7.1.2.3 Chronic Toxicity Studies

These studies are conducted by repeated administrations of the test drug for 12 months or more[14.30]. The object of these studies is to determine observable effects of a test substance in rodent and/or non-rodent species following prolonged and repeated oral or parenteral exposure. Under the conditions of these tests, effects that have a long latent period or that are cumulative should become evident. Ideally, the design and conduct of these studies should allow for the detection of general toxicity, including neurological, physiological, biochemical, and exposure-related morphological effects. The studies should be conducted according to an acceptable protocol and must consist of three dosage levels plus a control.

7.1.2.4 Irritation Studies

Irritation studies or acceptable alternatives may be required for topical, parenteral and other drugs.

7.1.2.4.1 Dermal Sensitization Studies

The methods to determine skin sensitization involve topical or intradermal application of the test material in guinea pigs[14.24]. Initial induction application is followed by a challenge application following an interval of two weeks. Local erythema and edema reactions are scored as skin irritation. The test material is considered to produce sensitization if the reaction after challenge application is more severe than the induction application. The sensitization is scored on a numerical score and expressed as Degree of Sensitization Index (DSI). These studies may be required for topical drugs or drugs that may come in contact with animal skin.

The dermal sensitization test in guinea pigs may be replaced by the local lymph node assay (LLNA) test in mice[14.25].

7.1.2.4.2 Primary Skin/Dermal Irritation Studies

These studies are usually conducted in albino rabbits. Skin irritation can vary from slight reddening and hyperemia to severe clinical burns with all stages of edema and vesiculation in between. These studies are conducted on both intact and abraded skin. A 2.5 cm^2 patch is applied to the animal skin under which is placed 0.5 g of the test material. The patch is secured for 24 hours. The observations as to the effects are made at 24 and 72 hours, and at one week. Skin reactions are scored on a numerical scale and expressed as Primary Dermal Irritation Index (PDII). These studies may be required for topical drugs.

The dermal irritation studies may be conducted in accordance with updated OECD Guideline No. 404[14.26]. The skin corrosion studies in animals should be performed before eye irritation studies.

7.1.2.4.3 Primary Ocular Irritation Studies

These studies are usually conducted in rabbits. A small quantity of the test material (0.1 mL) is instilled into one eye. The other eye is left as untreated control. Corneal, iris and conjunctival lesions are observed and recorded immediately and at 24 hours through the first four days and at weekly intervals thereafter as long as there is a reasonable chance of change in the degree of injury. The damage to the cornea and/or iris that has not subsided by the end of seven days is considered a severe injury. The lesions are scored on a numerical score and expressed as Maximum Mean Total Score (MMTS). These studies may be conducted when a new drug is likely to come in contact with the target animal's eyes or is indicated for ophthalmic use.

Alternatively, eye irritation studies should be conducted in accordance with updated OECD Guideline No. 405[14.27]. The skin corrosion studies in animals should be performed before eye irritation studies. The ocular irritation studies may not be necessary if the subject compound is determined to be severely irritating from other available information.

7.1.2.4.4 Tissue Irritation Studies

Studies to determine the safety of a new drug recommended for injection may be conducted in rabbits. The observations may include the extent and duration of erythema and swelling at the injection site, and histopathological observations for migration of blood cells.

7.1.2.5 Reproduction and Teratogenicity Studies [14.37, 14.38, 14.39]

These studies may be required for drugs that are to be used in pregnant, breeding or lactating animals.

7.1.2.5.1 Reproductive Function Studies

Three generation studies are conducted to provide information on the reproductive capacity of the parental generations from weaning through mating and lactation, and on the offspring from conception through weaning, mating and lactation. Maternal and fetal effects and all the usual fertility indices should be recorded.

7.1.2.5.2 Teratogenicity Studies

Studies to provide data on the potential of the drug to produce or to alter the incidence of congenital malformations in laboratory animals. A comprehensive gross, visceral and skeletal examination of fetuses should be conducted.

7.1.2.6 Other Studies

This category of studies includes carcinogenicity studies, mutagenicity studies, and studies to determine the effects of test drugs on specific organ systems. These studies may be required depending on the nature and intent of use for a drug.

7.1.3 Curriculum Vitae of Investigators

A resumé of education, experience and publications should be submitted for each study investigator.

7.2 Target Animal Safety Studies

The objectives of these studies are to document: signs and effects associated with the toxicity of the new drug for the test species and its organs, tissues and functions; minimum toxic dose; maximum no-toxic-effect dose; and margin of safety. The data required for the safety in the intended target animal species may vary according to the nature of the basic toxicological data, the intended use of the proposed drug and the intended use of the target

animal. The basic toxicology data are generally obtained from studies in laboratory animals. The data to establish safety of the proposed drug to the intended target animal species are obtained from the studies conducted in the target animal species. For the design and conduct of these studies a reference may be made to the Target Animal Safety Guidelines for New Animal Drugs[14.31] .

7.2.1 Comprehensive Summary

A comprehensive summary of safety studies of the intended target animal species should be presented in a factual and descriptive format. Because studies vary according to the toxicological data, the intended use of the drug and the intended use of the target animal, the summary must contain separate discussions and evaluations for each area of study.

7.2.2 Sectional Reports

The data should be presented in such a way that studies are grouped in separate sections for each route of administration, each dosage regimen and each target animal species.

7.2.2.1 Margin-of-Safety Studies

Margin of safety (or therapeutic index) is the ratio between the effective dose (optimum dose) and the toxic dose (lowest dose exhibiting toxic signs). Margin-of-safety studies should be conducted using the recommended route of administration in healthy animals of each intended target animal species using multiples of the recommended dose. These studies should be conducted for the recommended duration of treatment, until market term or until the achievement of an appropriate weight or age, considering the special production type or function involved (e.g., breeding or production of milk, eggs or fur). Baseline values should be established before the study begins. For most drugs, data obtained following the administration of 0 (control), 1X, 3X and 5X the maximum recommended dose for maximum recommended duration will be sufficient. For drugs with a narrow margin of safety, administration at 0, 1X, 1.25X, 1.5X and 2X may be required. For drug substances known to have a high safety margin, margin-of-safety data may be replaced by data from studies in which the drug product is administered to the intended species at 10X to 25X the maximum recommended use level and for the maximum duration of use (or 21 days, for drugs intended for long-term administration).

Evaluation of drug response parameters should continue until the study is terminated. Evaluations for signs of toxicity should include: feed and water consumption, clinical observations, physical examinations, clinical

pathologic tests, and gross and histopathological examinations.

Effects of overdoses should be described.

7.2.2.2 Safety Under the Proposed Conditions of Use

Controlled safety studies should be conducted using the subject drug in the formula intended for the market, by the recommended route of administration and under the proposed conditions of use. The test animals should be of the age, weight, sex, species, reproduction status and production type indicated on the labeling. These studies may be combined with efficacy studies. The number of animals tested should be adequate to provide meaningful results. The adverse effects of medication should be monitored and recorded in detail.

The adverse effects observed during safety studies should be reflected in caution, precaution or contraindication statements on the labeling of the subject product(s).

7.2.2.3 Topical Drug Studies

For topical drugs (dermal, ophthalmic, vaginal, or intra-uterine), standard toxicity tests may be used. Consideration should be given to such secondary factors as:

- acceleration or delay of healing when the product is intended for application to wounds;

- local irritation studies for drugs applied to intact skin for extended use; and

- systemic toxicity, if the product is appreciably absorbed after topical application, or if it is likely to be ingested as a result of licking.

For topical drug products such as teat dips, for antisepsis on teat skin, lack of irritation of teat skin and teat-ends should be demonstrated. A reference may be made to VDD's "Guidelines for Evaluation of Safety and Efficacy of Teat Dip Formulations".[14.32]

7.2.2.4 Inhalant Drug Studies

The objective of these studies is to demonstrate that the proposed formulation is non-toxic when administered by nasal or oral respiratory routes for 2X the proposed duration of medication and repeated at least twice in the same subject.

Adverse effects of medication should be monitored by appropriate physical examination, clinical pathology and laboratory tests.

7.2.2.5 Tissue Irritation Studies

Tissue irritation studies should be submitted for drugs administered by injection. Include observations of inflammation, swelling, necrosis and histopathological examination of injection sites, with pre-test and post-test measurements and photographic evidence.

The findings of these studies should be taken into account when establishing the maximum amount of the product recommended for administration at each injection site and the period of time required for the tissues at the injection site to return to an acceptable condition. The observations can also be used to draft carcass trim-out statements for the proposed label.

7.2.2.6 Udder Irritation Studies

Udder irritation studies should be submitted for intramammary drugs administered via the teat canal. The studies should include observations on somatic cell counts in milk, abnormal secretion and signs of inflammation of the mammary glands. These observations can be used for determining the safety of intramammary drugs in cows and for determining appropriate cautionary statements on their labelling. A reference may be made to VDD's "Guidelines for Evaluation of Safety and Efficacy of Anti-mastitis Intramammary Infusion Drugs".[14.33]

7.2.2.7 Reproductive Function Studies

The nature of the drug or its effects on reproduction in laboratory animals may provide an indication of the type and extent of the reproduction studies required in the intended species.

If the drug is recommended for use in replacement stock or animals of breeding age, tests or studies are required to demonstrate the drug's effect on male and female reproductive functions. In the case of drugs proposed for use in pregnant animals, data from teratology studies conducted in the intended species are required.

When data from reproduction or teratology studies are required but are not available, the inclusion of a cautionary statement on the label may be considered. This statement would advise the user that reproduction and teratology studies have not been performed and that the effect of the drug on the reproductive function of treated animals is therefore unknown.

7.2.2.8 Clinical Safety Studies

Clinical safety studies provide evidence for the safety of the drug under actual field use conditions and situations not encountered in toxicity studies. The clinical safety studies are normally combined with the clinical efficacy studies.

All adverse effects encountered during the clinical use of the drug are to be well documented. All adverse effects should be discussed individually in terms of their incidence, severity, dose relationship and other factors related to the occurrence, prevention and management of the particular effect. The adverse effects observed during efficacy studies should be reflected in the caution or contraindication statements on the labelling of the subject drug.

7.2.2.9 Pharmacovigilance Data

The submission should include adverse reactions reported from experience-in-use data gathered in other countries. All side effects and adverse experiences should be tabulated, including drug interactions and abnormal laboratory findings, regardless of whether or not the manufacturer considers the reported effects to be drug-related.

7.2.3 Curriculum Vitae of Investigators

A resumé of education, experience and publications should be submitted for each study investigator.

8. PART IV. REQUIREMENTS FOR EFFICACY

Efficacy studies must demonstrate the efficacy of the subject product by providing substantial evidence obtained from the clinical use of the product in the target animal species as per label recommendations. The efficacy guidelines given in this document are general in nature. For the efficacy of specific categories or classes of veterinary drugs, e.g., animal production drugs, anti-mastitis drugs, antimicrobial drugs, antiparasitic drugs, aquaculture drugs, drugs for concurrent use, drugs in fixed combinations, generic drugs, hormonal drugs, non-steroidal anti-inflammatory drugs and the drugs affecting the central nervous system, guidance from the CED should be obtained on a case-by-case basis.

8.1 Comprehensive Summary

A comprehensive summary of the efficacy studies, providing factual, concise descriptions of test results should be presented. All data must be presented in sufficient detail, with all statistical analyses performed using appropriate procedures.

8.2 Sectional Reports

The data should be presented in sections in such a way that studies are grouped separately for each route of administration, each dosage regimen and each target animal species.

8.2.1 Microbiology Studies

Microbiological studies are required for antimicrobial drugs and should provide the following information on the new drugs:

- Antimicrobial spectrum of each antimicrobial active ingredient of the formulation;
- Minimum inhibitory concentration(s) (MIC) of each antimicrobial active ingredient of the formulation against several clinical isolates and/or standard laboratory strains of the infectious agents indicated on the labeling;
- Minimum bactericidal concentration(s) (MBC) of each antimicrobial active ingredient of the formulation against several clinical isolates and/or standard laboratory strains of the infectious agents indicated on the labeling;
- Physiological studies to elucidate the bacteriostatic or bactericidal actions of the drug(s) on the target microbial cell;
- Studies on the incidence and development of resistance of target microorganisms to antimicrobial active ingredients of the drug;
- Studies to show lack of cross resistance of microorganisms to antimicrobial agents other than those present in the formulation; and
- Interactions of antimicrobial agents in the formulation with other antimicrobial agents.

8.2.2 Laboratory Studies

All laboratory studies demonstrating the activity of the subject drug substance or efficacy of the subject drug formulation for indicated (disease) conditions and performed without the use of live animals should be submitted.

8.2.3 Animal Model Efficacy Studies

All efficacy studies conducted on animals other than the intended target animal species should be submitted.

8.2.4 Clinical Pharmacology Studies

For the purpose of these guidelines, clinical pharmacology studies may be limited to pharmacokinetic and pharmacodynamic studies of the drug substance in the intended target animal species. These studies are to be designed to elucidate:

- Absorption, distribution, metabolism and excretion (ADME) patterns of the test

substance; and
- pharmacologic actions of the test substance relative to the intended use.

8.2.4.1 Pharmacokinetic Studies

The purpose of these studies is to obtain basic information on the absorption, distribution, metabolic and excretion patterns of the test substance in the intended species. In these studies the following concepts should be elucidated:

- Half-Life ($T_{½}$): the time taken for a drug concentration to decline by 50%;
- Apparent Volume of Distribution (Vd): the volume of fluid that the drug would occupy if it were evenly distributed throughout that volume at the concentration measured in plasma.
- The Bioavailability (F or f): the rate and extent of transfer of the drug from dosage form to the site of action.
- The Clearance (CL): the phenomenon of the removal of drug from the body and expressed as the volume of fluid from which the drug substance is completely removed in unit time.

8.2.4.2 Bioavailability Studies

When the absorption of the subject drug is sufficient to measure drug concentration in the blood (or other appropriate biological fluids or in tissues) and systemic absorption is relevant to the drug's action, then a blood (or biological fluid or tissue) level study should be conducted. The results of such a study should be used to assess the rate and extent of availability of the drug substance(s) in the systemic circulation following administration in a particular dosage form. The parameters to be considered for measurement and expressed in appropriate units are: peak or maximum concentration (Cmax), time taken to reach the peak concentration (Tmax) and area under the time-concentration curve (AUC). The results of these studies may be used for determining the dosage of the subject drug or for comparing similar/identical drug products.

8.2.4.3 Pharmacodynamic Studies

These studies are conducted to demonstrate the primary and secondary pharmacologic activities. The primary pharmacologic or therapeutic activity provides the primary basis for clinical trials. The secondary pharmacologic actions may be relevant to the expected use or adverse effects of the new drug. The secondary pharmacologic actions may determine the requirements for the tolerance studies, margin of safety studies and specific monitoring of clinical trials for potential side effects in the target animal species, directions

for use of the product and/or cautionary statements to appear on the labeling of the subject product.

Studies should be conducted to elucidate a quantitative dose-response relationship with respect to the substance under investigation, and if applicable to a control substance. The desired and untoward effects of medication should be assessed in terms of doses that can be tolerated and possibly calculating a therapeutic index for the target animal.

8.2.5 Dose Determination Studies

8.2.5.1 Optimum Dose Studies

The objective of these studies is to determine an optimum dose that will be effective for the prevention, treatment and/or control of the conditions indicated on the proposed label. These studies should include 0, <1X, 1X and >1X levels of the proposed dose of the drug to be used in clinical efficacy studies. If feasible, a drug marketed for similar claims may be included as a positive control. These studies may be conducted under experimentally induced or naturally occurring disease conditions. The number of animals selected should be such as to be amenable for meaningful statistical comparisons.

8.2.5.2 Challenge Studies

The objective of these studies is to determine if the proposed drug is effective for the proposed indications under experimental exposure conditions of infection. These studies should include 0, <1X, 1X and >1X levels of the proposed dose of the drug to be used in clinical efficacy studies. If feasible, a drug marketed for similar claims may be included as a positive control. For treatment claims, the animals should be medicated following the onset of clinical symptoms. For prevention claims, the animals should be medicated either before or at the time of experimental exposure to the challenge organisms.

8.2.6 Dose Confirmation Studies

8.2.6.1 Pivotal Studies

Basic evidence obtained from pivotal studies for determining the efficacy, properties and conditions of use of the drug should be included in the NDS. Pivotal studies must be conducted by qualified investigators in the domestic breeds of the intended species under Canadian or Canada-like conditions of climate and management, at the recommended doses with the proposed

formulation, for the proposed indications.

For example, in a controlled test designed to evaluate the efficacy of an antiparasitic drug, naturally or artificially parasitized animals are randomly allocated to two treatment groups: a treated group and an untreated (or placebo treated) control group. After a predetermined time period, the animals are necropsied, and the parasites recovered, identified and counted. The efficacy of the drug is then determined by comparing the number of parasites remaining in the treated animals with the number of parasites in the control animals by using appropriate statistical procedure(s).

8.2.6.2 Clinical Studies

Substantial evidence from clinical studies should be submitted in support of efficacy for the proposed indications. Each study should include information on the investigators, site of study, description of facilities, number of animals, criteria for inclusion and exclusion of animals, groups or replicates, sex of animals, age of animals, type of animals, diagnosis, diagnostic procedures and tests, drug formulation, dosage, criteria of effectiveness, morbidity and mortality rates, lesion descriptions and scores, duration of study, results, description of adverse effects, statistical procedures used and conclusions and interpretations.

The individual case reports are to be collated by relevant claim and by the investigator. All case reports and other raw data from a study should be included towards the end of a study report.

All data generated from individual experiments should be properly summarized and statistically analysed using appropriate statistical procedures. A pooled statistical analysis of the data generated from studies designed specifically for pooling should be included. A probability level of five percent ($P < 0.05$) should be used in deciding to accept or to reject the null hypothesis. Detailed information on the statistical methodology used, including computer programs, should be provided or referenced.

The method of handling missing observations or animals removed from group-fed experiments, and the method used for adjusting feed intake should be presented. Where data are excluded from a conducted or terminated study, an explanation should be included.

8.2.7 Supplementary Supportive Efficacy Studies

These are studies that use a drug formulation considered to be significantly different from the formulation intended to be marketed in Canada, or that are conducted

elsewhere under climatic or production conditions believed to inadequately represent Canadian conditions.

8.2.8 Pharmacovigilance Data

The submission should include adverse reactions reported from experience-in-use data gathered in other countries. All adverse experiences respecting lack of efficacy should be tabulated regardless of whether or not the manufacturer considers the reported effects to be drug-related.

8.3 Curriculum Vitae of Investigators

A resumé of education, experience and publications should be submitted for each study investigator.

9. PART V. REQUIREMENTS FOR HUMAN SAFETY

This Part of the NDS pertains to the drugs used in food-producing animals. However, basic toxicity data obtained in laboratory animals are used to complement the data required to support the safety of the drug residues in food-producing animals. Under certain circumstances, the microbiological safety assessment may be required for veterinary antimicrobial products intended for use in non-food-producing animals.

Before a new drug intended to be used in food-producing animals can be sold in Canada, manufacturers are required by law to submit scientific evidence demonstrating that the drug has been carefully assessed for the safety of drug residues in meat and other food products intended for human consumption. Microbiological safety assessment is also considered as a key aspect of the requirements for human safety of veterinary antimicrobials.

9.1 Laboratory Animal Toxicity Studies

Toxicity studies are used to determine toxic effects of veterinary drugs and/or their metabolites in laboratory animal species, usually rodents and non-rodents (e.g., dogs), so that adequate extrapolations can be made to estimate the potential risks of the residues of veterinary drugs for consumers ingesting foods of animal origin. All laboratory animal toxicity studies, except for tests of mutagenicity, submitted in support of human safety for use in food-producing animals are conducted using the oral route of administration. Data generated under the toxicity studies are used to establish a no observable effect level (NOEL) in the most sensitive species/strain. The established NOEL is then used to calculate an Acceptable Daily Intake (ADI) for the specific drug and/or its metabolites by using an appropriate safety factor.

It is recommended that all toxicity studies be conducted in accordance with the guidelines

and Good Laboratory Practice (GLP) as approved by the OECD (website: www.oecd.org).

Specific requirements for toxicity studies may vary from one drug to another depending on the class of veterinary drug and the extent of its proposed use.

9.1.1 Comprehensive Summary

A comprehensive summary of all the toxicity studies in a tabular form should be submitted as follows:

a) the species, number, sex, age, weight and strain of animals;
b) information on dosage formulation(s);
c) routes of administration;
d) treatment regimen;
e) duration of treatments;
f) parameters evaluated;
g) significant observations; and
h) conclusions.

The dates of the studies and name(s) of the laboratories conducting these studies should be reported. All data must be presented in sufficient detail and must be cross-referenced to the sectional reports. Data from all toxicity studies conducted using the drug or its metabolites should be included in the submission.

9.1.2 Sectional Reports

Specific requirements may vary on the basis of exposure level of proposed drug and/or formulation usage. However, generally, toxicity studies fall into the following categories:

a) *Subchronic*: using repeated administration for 3 to 12 months;
b) *Chronic*: using repeated administration for at least 12 to 24 months;
c) *Special studies*: include reproductive, teratogenicity, genotoxicity, carcinogenicity, pharmacological, immunotoxicity, neurotoxicity, and hormonal studies in primates, etc.

9.1.2.1 Subchronic Oral Toxicity Studies

Subchronic oral toxicity studies are designed to determine the adverse effects of substances when given in regularly repeated doses (at a minimum of three dosage levels) over periods of three months, but may extend up to 12 months. The intent of these studies is to characterize the toxicity of the substance and to establish the NOEL. These studies are usually conducted in two animal species, one being a non-rodent (dog) by the oral route. At least 20 animals

(10 of each sex) per treatment, and at least three treatment doses are used: a high dose that produces toxicity but does not cause more than 10% mortality, an intermediate dose, and a low dose that produces no apparent toxic effects. **All treated animals should be exposed to the test product seven days per week for at least 90 consecutive days (three months).** Requisite number of animals per sex should be included for the control group.

Animals are observed daily for clinical signs of toxicity. Body weights and food consumption are recorded daily or weekly for all animals. Haematology, clinical chemistry determinations, and urine analysis are performed prior to, in the middle of, and at the end of the testing period. Necropsy and histopathological examinations of organs and tissues are performed on animals that died prematurely and on all remaining animals at the end of the study.

For further details regarding subchronic oral toxicity studies, please refer to the OECD Guidelines No. 408[14.28], and 409[14.29].

9.1.2.2 Chronic Toxicity Studies

Chronic toxicity studies are conducted to assess the cumulative toxicity of a drug. The objective of these studies is to determine the effects of a test substance in a rodent and a non-rodent species following prolonged and repeated oral exposure, for a minimum of one year. Chronic toxicity studies are conducted similarly to the subchronic studies except that the period of exposure is longer. Since there is a potential of lifetime exposure to the residues of veterinary drugs in foods for human consumption, chronic toxicity studies in rodents are usually conducted for the duration of two years, and in non-rodents for one year or longer. Ideally, the design and conduct of the study should allow for the detection of general toxicity including neurological, physiological, biochemical and exposure related to the morphological effects.

Three test dosage groups and a control group per sex are recommended with the highest dosage producing some clinical signs of toxicity in the treated animals. Each of the three test groups and concurrent control group should contain at least 50 animals of each sex. **All treated animals should be exposed to the test product seven days per week for the duration of the study.**

For further details on chronic toxicity studies, please refer to OECD Guideline No. 452[14.30]. Also, see the section 9.1.2.4 of these guidelines for more information.

9.1.2.3 Carcinogenicity Studies

Carcinogenicity studies may be required under the following conditions:
1) a battery of mutagenicity tests are positive;
2) there is a close structural similarity between the test compound and a known carcinogen;
3) histopathological examination of the data from subchronic and chronic toxicity studies have given some indications of carcinogenic potential.

The objectives of a long-term carcinogenicity study are to observe test animals over a major portion of their life span for the development of neoplastic lesions during or after exposure to various doses of a test substance administered by oral route. Such an assay requires careful planning and documentation of the experimental design, a high standard of pathology and unbiased statistical analysis. It is necessary that the duration of a carcinogenicity test comprise the majority of the normal life span of the animals to be used, i.e., 24 months for rats and 18 to 24 months for mice. **All treated animals should be exposed to the test product seven days per week for the duration of the study.**

It is recommended that the study of a test substance be conducted in two rodent species, by the oral route of administration (dietary). It is essential that treatment be started in young animals and continued for the entire duration of the experiment, because of the long latent period required for induction and manifestation of tumours.

For the risk assessment purposes, at least three dose levels should be used, in addition to the concurrent control group. Each of the three dose groups and concurrent control group should contain at least 50 animals of each sex. The highest dose level should be sufficiently high to elicit signs of minimal toxicity without substantially altering the normal life span due to effects other than tumours. The lowest dose should not interfere with the animal's normal growth, development and longevity; and it must not cause any other indications of compound related toxicity. The intermediate dose should be established approximately midway between the high and low doses.

The evaluation of carcinogenicity bioassay results rests on the extent and accuracy with which organs and tissues of both treated and control animals are examined for morphological changes. Although a well conducted pathological examination cannot rescue a poorly designed or conducted bioassay, inadequate pathologic examination can significantly reduce or eliminate the value of an otherwise well conducted experiment. The strength of evidence provided by a bioassay depends on the number of tissues examined. The absence of a carcinogenic effect in a study cannot be assured unless all organ systems have been examined grossly in all animals, and all grossly visible suspect lesions examined microscopically. An attempt should be made to

correlate gross observation with the microscopic findings.

The criteria on which a substance may be defined as carcinogenic in evaluating the results of chronic bioassay are:

1) an increase in incidence of tumours as compared with the untreated control animals;
2) an increase in incidence of tumours as compared with the historical control data;
3) the development of tumours earlier than in the control animal (time to tumour); and
4) the occurrence of types of tumours usually not seen in untreated control animals.

For further details on carcinogenicity studies, please refer to the VICH Guideline GL 28 [14.34], and OECD Guideline No. 451[14.35]. Also see Section 9.1.2.4 of this guideline for more information.

9.1.2.4 Combined Chronic Toxicity and Carcinogenicity Studies

Combined chronic toxicity and carcinogenicity studies are suggested for use with one species, typically the rat. The objective is to obtain data to determine the effects of a test substance which would be provided separately in a carcinogenicity or a chronic toxicity study. **All treated animals should be exposed to the test product seven days per week for the duration of the study.** In addition to three dosage levels and a concurrent control group, each of which contain at least 50 animals per sex, these guidelines recommend three satellite treatment groups of 10 animals per sex. Whereas the high dose for the carcinogenicity phase should not produce toxicity, the highest dose for the satellite treatment group should be chosen so as to produce overt toxicity without causing excessive mortality. These satellite groups should be retained in the study for at least 12 months. These animals should be scheduled for sacrifice for determination of test substance-related pathology, uncomplicated by geriatric changes. The other three treated groups and the control group would be handled as in the carcinogenicity guidelines. In these guidelines, recommendations are included for periodic observations of signs, onset, and progression of toxic effects, hematological and organ function tests, and clinical examinations for neurological and ocular changes.

For further details on combined chronic toxicity and carcinogenicity studies, please refer to OECD Guideline No. 453[14.36].

9.1.2.5 Multigeneration Reproductive Studies

These studies are designed to provide general information concerning the effect of the test substance on gonadal function, estrous cycle, adult sperm parameter, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring. The study may also provide information about the effects of the test substance on neonatal morbidity, mortality, and preliminary data on teratogenesis and serve as a guide for subsequent special tests. Animals must be treated with the test product orally.

For further details on reproductive studies, please refer to VICH Guideline GL22[14.37] and OECD Guideline No.416[14.38].

9.1.2.6 Teratogenicity Testing

The purpose of this test is to yield data to help determine the effects of a test substance administered to the mother during *in utero* development of their young. Treatment by the oral route of administration must be started early enough and be continued long enough to include the period of organogenesis (i.e., rats 6-15 days, rabbits 7-18 days).

Such study may also be performed in conjunction with a multigeneration reproduction study as long as the fetuses are exposed continuously through organogenesis. These guidelines recommend that the test substance be administered in graduated doses, for at least that part of the pregnancy covering the period of organogenesis, to several groups of pregnant experimental animals, one dose being used per group. The fetuses are removed by cesarean section a day prior to the expected time of delivery. Live fetuses are weighed, and one-half of each litter is examined for skeletal abnormality and the remaining one-half for soft-tissue anomalies.

For further details on teratogenicity studies, please refer to OECD Guideline No. 414[14.39].

9.1.2.7 Short-term Tests for Genetic Toxicity Studies

Genetic toxicity tests are used to determine the ability of chemicals to cause molecular changes in the DNA or structural or numerical changes in chromosomes of cells. These tests are performed for two distinct reasons: 1) to test chemicals for potential carcinogenicity; or 2) to assess whether or not a chemical may induce heritable genetic damage.

Tests used to evaluate genetic toxicity are diverse and include *in vitro* tests using microorganisms and cells from multi-cellular animals, as well as *in vivo* tests using insects, plants and mammals. Both *in vitro* and *in vivo* tests can be further characterized and grouped on the basis of the end-point detected.

Presently, genetic toxicity assays can be divided into three major groups: 1) forward and reverse mutations [*e.g.*, point mutations, deletion mutations, etc.]; 2) clastogenicity assays detecting structural and numerical changes in chromosomes [*e.g.*, chromosome aberration, micronuclei, etc.]; and 3) assays that identify DNA damage [*e.g.*, DNA strand breaks, unscheduled DNA synthesis, etc].

For further details on genetic toxicity studies, please refer to VICH Guideline GL 23[14.40], and OECD Guidelines No. 471, 473, 474, 476, 479, 482 and 486[14.41-14.47].

9.1.2.8 Pharmacological Studies

In case the active principle of the test product has a pronounced pharmacological effect, and the NOEL based on this pharmacological effect is much lower than the most sensitive toxicological NOEL; then special pharmacological studies in laboratory animals may be required.

9.1.2.9 Immunotoxicity Studies

The toxicological manifestations in experimental animals during the repeated dose toxicity studies should include effects on the immune system and those effects should be addressed adequately by specific testing.

9.1.2.10 Neurotoxicity Studies

The neurotoxic effects of substances with potential adverse effects on the nervous systems should be studied adequately. Such substances include, avermectins, pyrethroids, organophosphates and carbamates. In order to evaluate the neurotoxic effects of organophosphates and carbamates, studies should be conducted to monitor cholinesterase levels in blood/plasma and brain in laboratory animals. Delayed neurotoxic effects for organophosphates should be conducted in hens.

For further details, please refer to OECD Guidelines No. 424[14.48], and 426[14.49].

9.1.2.11 Hormonal Studies in Primates

For some hormonal products, a 180-day study in rhesus monkeys or other suitable sub-human primates may be required (at least six females per treatment). Monkeys should not have been exposed previously to any hormonal product. The study should establish a dose that gives no observed hormonal response. The study should assess the effect of test substance on ovulation, the duration of menstruous cycle and changes in the concentration

in the blood of gonadotropins (luteinizing hormone, follicle stimulating hormone) and of the endogenous sex-steroids (estradiol, estrone and progesterone).

9.1.2.12 Observations in Humans

Safety evaluation of the active ingredient in any epidemiological, pharmacological, toxicological and clinical human data should be submitted for review.

9.1.2.13 Other Studies

In addition to the above-described animal toxicity studies, other special studies may be required to provide information on any specific effect of the drug on specific organ systems such as cardiovascular, renal, hepatic, endocrine, central nervous and immune systems.

9.2 Microbiological Safety Studies

In this section of the Human Safety Requirements, information is provided regarding the data requirements expected for demonstrating the microbiological safety of a drug product. This section pertains to antimicrobial drug products as well as products containing bacteria, for example, direct-fed microbial products.

9.2.1 Veterinary Antimicrobial Products

This section pertains to antimicrobial drug products (including antibacterials, antiparasitics and antivirals). However, information in this guidance is often targeted to antibacterial products. Sponsors submitting applications for other antimicrobial products may wish to consult with the Directorate for the specific requirements for their submission.

The impact of the use of antimicrobial products in food-producing animals on the development and the potential for enrichment and dissemination of antimicrobial resistant human bacterial pathogens is considered one of the principal aspects of the human safety review.

The objective of this guidance is for the sponsor to provide information necessary for assessing the potential impact of the use of veterinary antimicrobial products on the development of antimicrobial resistance in bacteria of animal origin, which may affect antimicrobial therapy in veterinary and human medicine. One of the recommendations of the *Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health*[14.50] is to conduct risk-based evaluation of the potential human health effects of all uses of antimicrobials in food-producing animals.

This guidance document emphasizes a preliminary risk analysis approach and outlines the data requirements to evaluate the potential for the development of bacterial resistance or cross-resistance to veterinary antimicrobial products as it might occur in the intended species, under the proposed conditions of use of the product as well as the potential for transfer of resistant bacteria or resistance determinants to humans.

9.2.2 Sectional Reports

In general, the microbiological safety studies required for assessing human safety of a veterinary antimicrobial product should include the following sectional reports. However, specific requirements may vary on the basis of importance of the proposed antimicrobial to human medicine or on its formulation usage. It is understood that some of the studies described in this section may be the same as those provided for the evaluation of target animal species safety and efficacy. If this is the case, cross-reference should be provided to those studies.

9.2.2.1 Information about the Antimicrobial

The following information should be included in this section:

- The drug's generic name, chemical name and chemical structure;
- Manufacturer's name, contact information and Canadian distributor;
- Class of antimicrobial;
- Information on the mechanism(s) of action (literature reports and/or specific studies undertaken by the sponsor);
- Characterization of the product (i.e., bacteriostatic vs. bactericidal).

9.2.2.2 Activity Spectrum of the Antimicrobial

Antimicrobial susceptibility testing should be performed according to standardized methods using appropriate quality control, and be reported quantitatively to allow comparison of results. Data from minimum inhibitory concentration (MIC) tests against a wide variety of microorganisms, or from literature reports, should be provided in order to determine the overall spectrum of activity.

- Data should be presented to show MICs for food-borne pathogens and commensal bacteria. This information can be based on literature data or on studies done by the sponsor. Based on consideration of the spectrum of activity, appropriate organisms may include:
  - Food-borne pathogens: *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli* O157:H7;
  - Other food-borne bacteria: *E. coli* and *Enterococcus* spp.
- The strains or isolates that are used should be of normal susceptibility

that are not already selected by selection pressure.

- Information on MICs for target animal pathogens (as per the claim on the label) may be obtained within the clinical efficacy section of the submission.
- Relevant bacterial species/serotypes should be isolated from the proposed intended species.

9.2.2.3 Administration of the Antimicrobial

Information on administration of the antimicrobial product, whether to be given on an individual or herd/flock basis, the duration as well as the route used, should be provided to help ascertain the product's potential for the development of resistance in pathogenic organisms or normal bacterial flora of treated animals and the potential for spread of resistance to other animals.

9.2.2.4 Antimicrobial Resistance Studies

9.2.2.4.1 Resistance Mechanism

Resistance to a given antimicrobial can be inherent to a bacterial species or genus (intrinsic or natural resistance) or resistance may be acquired by some strains within a species usually susceptible to the antimicrobial under consideration (acquired resistance). Information on the resistance mechanism(s) and information on the molecular genetic basis of resistance to the subject antimicrobial should be provided from literature or from studies performed by the sponsor. Information from related analogues within the same drug class may be provided in the absence of data on the drug substance.

Where applicable, details of microbial resistance patterns in relevant microorganisms which have emerged with the use of the proposed product elsewhere in the world and/or Canadian data should be supplied in this section. This would include changes that have been identified in MICs of the antimicrobial against isolates of relevant microorganisms collected from clinical cases, field trials or other uses of the antimicrobial product.

9.2.2.4.2 Transfer of Antimicrobial Resistance Genes

Estimated rate of development of resistance or information on the occurrence, or absence, of transfer and rate of transfer of resistance gene(s) can be provided by literature information or from studies performed by the sponsor. Specific studies to evaluate the occurrence of genetic transfer may follow an internationally recognized protocol.

The sponsor should consider including target animal pathogens, relevant food-borne pathogens, and relevant commensal organisms.

9.2.2.4.3 Cross-resistance

Information on cross-resistance in relevant microorganisms to the antimicrobial in question and other antimicrobials in the same class or other antimicrobial class should be provided in this section. This should include a phenotypic as well as genotypic description and this information can be derived from literature or from studies performed by the sponsor. If this information is not available, relevant scientific explanation must be supplied.

9.2.2.4.4 Co-resistance

If applicable, information on co-resistance of the antimicrobial in question with other antimicrobials can be provided by literature information or studies performed by the sponsor. This should include a phenotypic as well as genotypic description.

9.2.2.4.5 Resistance Development

Where applicable, properly conducted studies to demonstrate *in vitro* or *in vivo* rate and extent of resistance development may be included under this section. The *in vivo* studies could include laboratory animal studies and/or field trials with target animals under the proposed conditions of use of the antimicrobial product. This section could also include *in vitro* mutation frequency studies.

9.2.2.5 Effect on the Animal Gut Microflora

The sponsor should discuss in detail the information provided in the other sections of the submission in terms of the exposure of food-borne pathogens and commensal organisms to microbiologically active substance in the target animal after administration of the veterinary antimicrobial product under the proposed conditions of use, and the potential for resistance selection in such bacteria. Where available, details should be provided on the concentrations of microbiologically active compounds which might be expected to occur within the large intestine or the faeces of the intended species. Where such data are not available, details may be provided by metabolism studies relevant to the gastrointestinal tract. Information should be provided on the expected effects of the antimicrobial on colonic microorganism content (including anaerobes) and resistance patterns in relevant microorganisms in target animals or animal products. Bacteria of interest in this section would be the

zoonotic enteropathogens such as *Salmonella* spp., *Campylobacter* spp. and commensal bacteria such as *E. coli* and enterococci. The main objective for these data is to determine the effect of the drug on the faecal shedding of pathogens, the duration of their shedding and changes in their antimicrobial susceptibility pattern. Relevant scientific arguments should be provided if this information is not available.

9.2.2.6 Effect on Human Gut Microflora

The *in vitro* and *in vivo* microbiological effects of the drug and its microbiologically active metabolites on the human gut flora will be reviewed as part of the human safety consideration. This information will also be used to calculate the microbiological Acceptable Daily Intake (mADI) and detailed guidance on the calculation of mADI is available in the VDD adopted VICH GL36 guideline[14.51]. The mADI, where applicable, could be used to determine the MRLs as described in the section on Residue Studies (sub-section 9.3.2.2) of this document.

Representative microorganisms that are considered relevant for the human gut flora include species of *Bacteroides, Bifidobacterium*, *Clostridium*, *Enterococcus*, *Eubacterium*, *Fusobacterium, Lactobacillus*, and *Peptococcus*/*Peptostreptococcus* and *E. coli* among others. It is recommended that a minimum of 10 strains per species should be tested for MIC determination. MIC determinations should be performed in accordance with recognized standardized tests in order to potentially determine mADI using VICH GL36[14.51].

9.2.2.7 Impact on Human Medicine

The impact of the new veterinary antimicrobial product used in animals on the effectiveness of existing antimicrobials used in human medicine will be considered as part of the review process. The importance of the subject antimicrobial in human medicine and its potential to cause resistance or cross-resistance to antimicrobials used in human medicine need to be evaluated. The criteria of significance include:

- Indication for the antimicrobial product and availability of alternative antimicrobial therapy in case of emergence of resistance to the particular antimicrobial;
- Antimicrobial activity and mode of action; and
- The mechanism of resistance, the potential for resistance development, cross-resistance and/or co-resistance and the potential for transfer of resistance genes from resistant bacteria.

The sponsors are encouraged to provide a risk assessment on the proposed use of their specific veterinary antimicrobial product with respect to human health consequences. The risk assessment methodology used could be qualitative, semi-quantitative or quantitative.

9.2.2.8 Pharmacokinetics

Pharmacokinetic data may be obtained from other sections of the submission. Data relevant to microbiological safety should include the following:

- Serum/plasma concentrations versus time data;
- Half life in the intended species;
- Bioavailability;
- Protein binding;
- Pharmacokinetic/pharmacodynamic data with a particular view to anticipated drug substance concentrations in the intestinal tract.

9.2.2.9 Historical Information

Historical information from literature or studies on previously approved uses of the antimicrobial product or related products should be provided if applicable.

9.2.2.10 Combination Antimicrobial Products

A mixture of more than two antimicrobials should be considered when no other feasible alternative is available. Sound scientific rationale should be provided to support combination of antimicrobials.

9.2.2.11 Post-approval Monitoring

A post-approval monitoring program for the emergence of antimicrobial resistance should be considered by the manufacturer as an important aspect of the review process. In addition, issues of prudent use and the extra-label use vis-à-vis antimicrobial resistance surveillance should be given due consideration. Post-approval surveillance is indispensable and surveillance of resistance to antimicrobials belonging to classes considered important in human medicine should be closely monitored so as to be able to detect emergence of antimicrobial resistance in time to allow corrective strategies to be implemented as part of an efficient post-approval review.

9.2.2.12 Global Harmonization

International approaches for the regulation of veterinary antimicrobial

products will be taken into consideration in the review process (for example, VICH GL27[14.52] and GL36, and OIE[14.53] guidelines).

9.2.3 Direct-Fed Microbial and Competitive Exclusion Products

Direct-fed microbial products (also known as probiotics) contain known microorganisms with known quantities that claim certain health benefits. Competitive exclusion products are used to protect colonization of the intestinal tract by pathogenic bacteria such as *Salmonella* spp. by creating a physical barrier. These products generally contain unidentified live microorganisms that are isolated from the gastrointestinal tract of healthy animals. The use of both product types in food-producing animals are subject to approval by the Human Safety Division of the VDD.

9.2.3.1 Sectional Reports

The data submitted for competitive exclusion and direct-fed microbial products should include:

9.2.3.1.1 Information about the Product

The following information should be included in this section:

- The product name;
- The Manufacturer's name, contact information and Canadian distributor;
- The product composition: list the active ingredients including genus, species and strain. Include the source, growth and method of identification;
- The administration of the product: intended species, dosage, frequency, route of administration, and herd/flock or individual;
- Proposed storage conditions;
- The information on the pathogenicity of the individual organisms in the probiotic product to humans (including opportunistic nature of the organisms).

9.2.3.1.2 Antimicrobial Resistance Profile

Information on the antimicrobial resistance profile of microbial components should be provided. The values should be determined according to internationally accepted method(s).

- Information on resistance mechanism(s) of microbial components which show resistance to antimicrobials of

importance to human medicine should be provided by literature review or investigations conducted by the sponsor.

- If the antimicrobial resistance exists, it should be shown whether or not the resistance factor is mobile and transferable to other bacteria in the same or other genera. The information may be provided based on literature review or investigations conducted by the sponsor.

9.2.3.1.3 Effect on Animal and Human Gut Microflora

Information on the safety and adverse effects of the microbial components of the product in animal and human gastrointestinal tract should be provided by literature review or by studies conducted by the sponsor to assess the microbiological safety of the proposed product.

9.3 Residue (Chemistry) Studies

This portion of Part V of the NDS describes the absorption of the test substance after administration to animals as well as the ADME patterns of the test substance. The extent and duration of persistence of residues of a veterinary drug or its metabolites in edible tissues of treated animals or food products obtained from them determines the withdrawal period (withholding time for milk) needed for the residues to fall below the Maximum Residue Limit (MRL). Practical regulatory analytical methods for the detection and confirmation of residues in food are used by the CFIA in their residue monitoring programs.

Part V includes both a comprehensive summary and sectional reports.

9.3.1 Comprehensive Summary

This should include a comprehensive summary of the residue-related studies, providing factual, concise descriptions of the test results. All data must be presented in sufficient detail and must be cross-referenced to the sectional reports.

9.3.2 Sectional Reports

9.3.2.1 Pharmacokinetics

9.3.2.1.1 Pharmacokinetic Studies in the Intended Species

The purpose of these studies is to obtain basic information on the absorption, distribution, metabolism and excretion of the test substance.

9.3.2.1.2 Metabolism Studies in the Intended Species

Studies should be conducted on metabolism of the drug and on the total residue depletion in the principal edible tissues or products (milk, eggs, honey) of the intended species, at intervals after the last administration of the drug at the maximum recommended dosage regimen. Generally, radiotracer methodology using preferably ^{14}C labelled parent compound is the most useful technique. The principal edible tissues for large animals are muscle, liver, kidney and fat and, where applicable, milk. For poultry, the edible tissues include muscle, liver, kidney, skin with adhering fat and, where applicable, eggs. For fish, the edible tissues include muscle and skin. For bees, the edible product is honey.

For the parenteral preparations, total residue depletion from the injection site(s) should be included. Sampling of the injection sites muscle tissue should result in 500 g amounts (for I.M. this is 10 cm circle 6 cm deep, while for the S.C. it is 15 cm circle 2.5 cm deep).

If the drug is intended to be used with a 0-day withdrawal period, data are required from studies in which the drug is used preferably at 1.5 to 2.0 times the maximum recommended dosage showing total residues at 0-day withdrawal interval. For practical purposes, this interval is 8 to 12 hours after the last administration of the drug to large animals and six hours for poultry and fish.

In the cases other than 0-day withdrawal period, in order to demonstrate the depletion of the total residue after the cessation of treatment, a 0-day withdrawal interval followed by at least three additional slaughter intervals, would be required.

All metabolites of the drug in concentrations exceeding 5% of the total residue concentration should be identified and their persistence and depletion profile in edible tissues or products should be determined.

9.3.2.1.3 Comparative Metabolism Studies in Laboratory Animals

The purpose of these studies is to compare the metabolic profiles of the laboratory test animals and the intended species. The studies determine whether the metabolites generated in the intended species are also produced in the laboratory animals used in the toxicity studies. If major differences in the metabolic profiles are identified, additional toxicity testing for metabolites may be required.

9.3.2.2 Residue Studies

9.3.2.2.1 Analytical Methodology

The manufacturer is responsible for submitting acceptable analytical method(s) for the detection and confirmation of the marker residue in the target tissue and muscle and where applicable, in milk, eggs and honey. The method(s) should be capable of reliably determining and confirming concentrations of marker residue below the proposed MRLs for the respective tissues or products.

9.3.2.2.2 Validation of the Regulatory Method(s) for the Detection and Confirmation of Residues of Veterinary Drug in Food

If a new veterinary drug is to be administered to food-producing animals, the analytical method(s) for the detection and confirmation of drug residues in food must be validated by the Laboratories Directorate of the Canadian Food Inspection Agency for their eventual inclusion and use in residue monitoring programs. The limit of quantitation (LOQ) for such method(s) must be lower than the MRL to enable detection of residue violations as stipulated under the *Food and Drugs Act and Regulations*. The methodology package should include the information listed below:

The following characteristics of the method(s) should be described:

- specificity,
- accuracy,
- precision,
- limit of detection (LOD),
- limit of quantitation (LOQ),
- practicability,
- ruggedness and susceptibility to interference,
- stability of residues under the conditions of procedures employed or prolonged storage of samples,
- stability of standards, including storage conditions for standards and standard solutions, and
- the source of the material for internal standard (if applicable).

The regulatory analytical method(s) must be described in detail, be practical and reasonably expected to be suitable for routine monitoring for veterinary drug residues in food.

The manufacturer shall appoint a contact person responsible for

providing standards, assistance to analysts, if required, and samples of incurred residue and controls.

Standards and samples of incurred residue and controls should be submitted when required to:

Director, Laboratories Directorate
Canadian Food Inspection Agency
59 Camelot Drive
Ottawa, Ontario
K1A 0Y9

9.3.2.2.3 Drug Residue Depletion Studies

Residue depletion studies in the intended species, under simulated field conditions and following the maximum recommended dosage regimen, should demonstrate the depletion of the marker residue upon cessation of drug treatment and at appropriate time intervals thereafter. An appropriate withdrawal period for the drug is to be established from this information.

For the parenteral preparations, residue depletion from the injection site(s) should be included. Sampling of the injection site muscle tissue should result in 500 g amounts (for I.M. this is 10 cm circle 6 cm deep, while for the S.C. it is 15 cm circle 2.5 cm deep).

For the 0-day withdrawal drugs, residue studies preferably using 1.5 to 2.0 times the maximum recommended dosage should confirm the withdrawal period.

9.3.2.2.4 Procedure for Establishing Maximum Residue Limits

Maximum Residue Limit (MRL) is the concentration of the marker residue in edible tissue or product that corresponds to the concentration of total residue considered safe for human consumption (TRL). A six step procedure is currently used to establish MRLs:

1) Metabolism studies in the target species:

The most common way to study the metabolic fate of the drug is to determine the amount and nature of drug-related substances. Usually, the radiotracer techniques are used. The radiolabelled drug is administered to the target species, then the principal edible tissues are harvested and their level of radioactivity is determined at appropriate

time intervals after the administration of the drug.

Provided the specific activity of the radiolabelled drug is known, the concentration of total residues in various tissues expressed in terms of parent compound equivalents, can be calculated. The total residue depletion information can be used to estimate a tentative withdrawal period for investigational studies. Additional information is obtained on the identity, amounts, and persistence of the parent drug and its metabolites in the tissues, body fluids, excreta or products (milk, eggs, honey).

2) Comparative metabolism study in the laboratory test species:

In the comparative metabolism study, qualitative metabolic profiles of the drug obtained from the laboratory test animals are compared to the profiles from the target species. Additional metabolites not present in the laboratory test animals, but present in the edible tissues of food animals, are of concern and must be identified. Moreover, quantification of the identified metabolites may assist in judging the need to test additional metabolites in the toxicity studies.

3)A. Toxicity/carcinogenicity testing to determine a safe level or acceptable level of risk for residues:

A comprehensive assessment of toxicity is required on all aspects of laboratory animals and *in vitro* studies (i.e., acute, subacute, subchronic, chronic, reproductive, teratogenicity, mutagenicity, and, where applicable, special effect studies).

The NOEL, employed in calculation of toxicological ADI by being divided with an appropriate safety factor, is determined from these studies. Depending on the use of the drug in question and the amount and degree of toxicity information presented, a safety factor of between 100 and 1,000 will be assigned for the calculation of the ADI.

3)B Microbiological data to determine a safe level or acceptable level of risk for veterinary antimicrobial drug residues:

If an antimicrobial drug is intended for use in food producing animals, the safety of its residues has to be evaluated with respect to the effect on the human intestinal flora. Microbiological data from *in vitro* tests and/or *in vivo* tests are required to establish a microbiological ADI (mADI, please refer to sub-section 9.2, of this guidance on Microbiological Safety Studies).

An appropriate ADI based on the ADI determined from A and B, where applicable, is used for the establishment of MRLs for a veterinary antimicrobial drug.

4) Determination of maximum acceptable total residue level (TRL), target tissue, marker residue and maximum residue limit (MRL):

In this step, the marker residue and the target tissue are selected. The marker residue is the drug-related substance (parent compound, metabolite, etc.) that is best suited to monitor the level of total residue of toxicological concern. A safe total residue level (TRL) for muscle is first calculated from the ADI, based on the consumption by a human of 60 kg body weight of 500 g of muscle tissue per day. The TRLs for other edible tissues or products are calculated by adjusting for lower consumption of those tissues as compared to muscle consumption (see Figure 1 below).

Figure 1:
Determining TRL Values for Muscle and for Other Animal Tissues or Products

For muscle:

$$TRL = ADI \times 60 \times 2$$

For other products:

$$TRL = ADI \times 60 \times 2 \times CF$$

where:

ADI = Acceptable daily intake, in mg/kg b.w./day
60 = 60 kg human body weight
2 = 0.5 kg muscle consumption
CF = Consumption factor for offal or other edible tissues such as milk, eggs and honey
(the consumption factors for various species are listed in the following table)

Table 3. Consumption Factors (Relative to Muscle)

Tissue	Beef	Pork	Sheep	Horses	Poultry	Fish	Bees
Muscle	1	1	1	1	1	1	N/A
Liver	2	3	5	5	3	-*	N/A

Kidney	3	4	5	5	5	-*	N/A
Skin	-*	4	-*	-*	2	10	N/A
Fat	4	4	5	5	2	-*	N/A
Milk	0.3	N/A	0.333	N/A	N/A	N/A	N/A
Eggs	N/A	N/A	N/A	N/A	1	N/A	N/A
Honey	N/A	N/A	N/A	N/A	N/A	N/A	3
* Not used for human consumption							

The depletion of residues from each of the edible tissues is then examined. Generally, the tissue from which the total residues take the longest time to deplete to the applicable safe level is selected as the target tissue.

Next, the metabolic depletion profile of the target tissue is examined to determine which substance (parent compound or metabolite or combination of both) can best be used to monitor the total residue in the target tissue. This substance is designated as the marker residue. The maximum residue limit (MRL) is the proportion of the marker residue that corresponds to the TRL.

When the drug is proposed for use in lactating cows, milk is also the "target tissue". Similarly, for layers and bees, eggs and honey, respectively, are also "target tissues". It is also desirable to establish a MRL for muscle tissue which may be the only commodity available to be tested for residues.

5) Development of a regulatory analytical assay for the marker residue:
This step requires that a practical method of analysis for detection and confirmation of the marker residue at the required level of measurement be developed. The limit of quantitation (LOQ) of this method should be approximately ½ of the MRL.

6) Establishment of a withdrawal period:
The final step of the human safety evaluation process is the establishment of practical withdrawal periods for tissues and withholding time for milk. Trials are conducted in the intended species under simulated field-use conditions according to label directions. The conditions of use must ensure that residues deplete to a safe level. The proposed regulatory assay method is used to determine concentrations of marker residue. The resulting required withdrawal

period must also be compatible with the normally expected good animal husbandry practices. Withdrawal periods pertaining to slaughter are specified in days. Withholding times for milk are specified in 12-hour milking intervals, up to maximum of eight intervals (96 hours).

9.3.2.3 Drugs for Concurrent Use or in Combination

The following human safety data are required when two or more drugs (for which Notices of Compliance have been issued at Health Canada) are to be used concurrently or in combination:

1. A residue depletion study for each component when administered concurrently or in combination.
2. Demonstration of non-interference of the residue assay methods for the individual components.
3. Tolerance studies in the intended species at the proposed maximum treatment level. This requirement may be modified in certain cases (e.g., to three times or five times the maximum treatment level).

If any of the above or related studies indicate a change in the toxicity or residue pattern of drugs administered concurrently or in combination, additional information may be required.

10. PART VI: ENVIRONMENTAL IMPACT

In September 2001, the *New Substances Notification Regulations* (NSNR) of the *Canadian Environmental Protection Act* (CEPA) came into effect for substances in products regulated under the *Food and Drugs Act*. Under the NSNR, notification is required prior to importing or manufacturing a new substance in Canada.

For information regarding the NSNR, please visit the following websites:

1. Health Canada's Environmental Impact Initiative

http://www.hc-sc.gc.ca/ewh-semt/contaminants/person/impact/guides/notification-declaration/index_e.html

2. Environment Canada's New Substances Branch

http://www.ec.gc.ca/substances/nsb/eng/index_e.htm

For questions regarding the NSNR, please contact the Environmental Assessment Unit:

Phone: (613) 948-3591 or 1-866-996-9913

Fax: (613) 946-6474

Email: eau-uee@hc-sc.gc.ca

Mail: Environmental Assessment Unit
Health Canada
123 Slater Street, 5th Floor
Ottawa, ON K1A 0K9
Postal Locator: 3505A

11. APPENDIX I. INFORMATION SUMMARY OF DRUG PRODUCT AND DRUG SUBSTANCE BATCHES USED FOR GENERATING DATA IN SUPPORT OF A SUBMISSION

Table A-1: Drug Product Batches Used in Studies to Demonstrate Quality, Efficacy, Animal Safety or Human Safety and for Which Data Are Provided in the Submission Including Commercial Batch Size If Available.

DP[(1)] Batch No.	DS[(2)] Batch No.	DP Strength	DP Batch Size [(3)]	DP Formulation No. or Code	DP Date & Site of Manufacture & Packaging	DP Date & Site of Release Analysis	Studies Used in to Generate Data to Demonstrate
AAA-0001	DS-0001	20 mg/mL	200 Kg (10%)	WD-0001	2003-08-08, Company A, City, Country.	2003-08-10 Company B, City, Country.	Quality Efficacy Animal Safety Human Safety
AAA-0002	DS-0001	20 mg/mL	200 Kg (10%)	WD-0001	2003-08-08, Company A, City, Country.	2003-08-10 Company B, City, Country.	Quality Efficacy Animal Safety Human Safety
AAA-0003	DS-0001	20 mg/mL	400 Kg (10%)	WD-0002	2003-08-08, Company A, City, Country.	2003-08-08, Company B, City, Country.	Quality Efficacy Animal Safety Human Safety
AAA-0004	DS-0002	20 mg/mL	200 Kg (10%)	WD-0001	2003-08-08, Company A, City, Country.	2003-08-08, Company A, City, Country.	Quality

(1) DP: Drug Product

(2) DS: Drug Substance used in the fabrication of the corresponding drug product batch.

(3) The batch size should be expressed in Kg or L followed by the percentage relative to the proposed largest commercial batch size in parentheses, e.g., 200 Kg (10%) if the proposed commercial batch size is 2000 Kg.

Table A-2: Information on Each Drug Substance Batch Identified in Table A-1.

Batch No.	Supplier Batch No.	Supplier (DMF No.)[(1)]	Batch Size	Date & Site of Manufacture	Date & Site of Release Analysis
DS-0001	SUP-0001	Company A (N/A)	2000 Kg (100%)	2003-04-08, Company A, City, Country.	2003-04-20, Company A, City, Country.

DS-0002	SUP-0002	Company X (V-1234-01)	1500 Kg (100%)	2003-06-08, Company A, City, Country.	2003-06-20, Company A, City, Country.

(1) If cross-referencing is made to a supplier DMF filed with Health Canada, include the DMF Number in parenthesis beside the supplier name.

(2) The batch size should be expressed in Kg or L followed by the percentage relative to the proposed largest commercial batch size in parentheses, e.g., 200 Kg (10%) if the proposed commercial batch size is 2000 Kg.

Table A-3: Information on Each Drug Substance Batch Used as Is in Studies to Demonstrate Quality, Efficacy, Animal Safety or Human Safety and for Which Data Are Included in the Submission.

Batch No.	Supplier's Batch No.	Supplier (DMF No.)(1)	Batch Size(2)	Date & Site of Manufacture	Date & Site of Release Analysis	Used in Studies to Generate data to Demonstrate:
DS-0001	SUP-0001	Company A (N/A)	2000 Kg (100%)	2003-04-08, Company A, City, Country.	2003-04-20, Company A, City,	Country.Quality Animal Safety
DS-0003	SUP-0003	Company X (V-1234-01)	1500 Kg (100%)	2003-06-08, Company A, City, Country.	2003-06-20, Company A, City, Country.	Quality

(1) If cross-referencing is made to a supplier DMF filed with Health Canada, include the DMF Number in parenthesis beside the supplier name.

(2) The batch size should be expressed in Kg or L followed by the percentage relative to the proposed largest commercial batch size in parentheses, e.g., 200 Kg (10%) if the proposed commercial batch size is 2000 Kg.

12. APPENDIX II LIST OF ABBREVIATIONS AND ACRONYMS

ABNDS	Abbreviated New Drug Submission
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
AIF	Animal Ingredient Form
AUC	The Area Under the Time-Concentration Curve
BAN	British Approved Name
BP	British Pharmacopoeia
BSE	Bovine spongiform encephalopathy
CAS	Chemical Abstracts Service
CCAC	Canadian Council on Animal Care
CED	Clinical Evaluation Division, VDD
CEPA	Canadian Environmental Protection Act
CF	Consumption Factor for organ meats, milk, eggs and honey
CFIA	Canadian Food Inspection Agency
CL	Clearance
C_{max}	Maximum or Peak Concentration
CPID-CE	Certified Product Information Document
CVM	Center for Veterinary Medicine of US FDA
CVMP	Committee for Veterinary Medicinal Products of the EMEA
CRP	Canadian Reference Product
DIN	Drug Identification Number
DMF	Drug Master File
DP	Drug Product
DS	Drug Substance
DSC	Differentia Scanning Calorimetry
EMEA	The European Agency for the Evaluation of Medicinal Products
EP	European Pharmacopeia (see Ph.Eur.)
ESC	Experimental Studies Certificate
EU	European Union
F	Bioavailability
f	See F
FDA	Food and Drugs Administration of US
F&DA	Food and Drugs Act
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GL	Guideline
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice(s)
HC	Health Canada
HDPE	High Density Polyethylene
HECSB	Healthy Environment and Consumer Safety Branch

HPB	Health Protection Branch
HPFB	Health Products and Food Branch
HPLC	High Pressure Liquid Chromatography
HSD	Human Safety Division, VDD
ICCVM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILAR	Institute for Laboratory Animal Research
I.M.	Intramuscular
IND	Preclinical Investigational New Drug Submission
IR	Infrared
LOD	Limit of Detection
LOQ	Limit of Quantitation
mADI	Microbiological ADI
MBC	Minimum Bactericidal Concentration
MCED	Manufacturing and Chemical Evaluation Division, VDD
MIC	Minimum Inhibitory Concentration
MMTS	Maximum Mean Total Score
MRL	Maximum Residue Limit
MS	Mass Spectra
MSDS	Materia Safety Data Sheets
N/A	Not Applicable
NC	Notifiable Change
NDS	New Drug Submission
NF	National Formulary
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
NOC	Notice of Compliance
NOEL	No Observed Effect Level
NRA	National Registration Authority for Agriculture and Veterinary Chemicals, Australia
NSNR	New Substances Notification Regulations
OECD	Organization for Economic Cooperation and Development
OIE	Office International des Epizooties
Ph.Eur	Pharmacopoeia EU (see EP)
PMRA	Pest Management Regulatory Agency
PNDS	Preclinical New Drug Submission (See IND)
PVC	Polyvinyl Chloride
QOS-CE	Quality Overall Summary of Chemical Entities
RH	Relative Humidity
RSD	Relative Standard Deviation
SABNDS	Supplemental Abbreviated New Drug Submission
SC	Santé Canada
S.C.	Sub-cutaneous

SKMD	Submission and Knowledge Management Division, VDD
SNDS	Supplemental New Drug Submission
SOP	Standard Operating Procedure
SRF	Site Reference File
SST	System Suitability Test
$T_{½}$	The Half Life
T_{max}	The time taken to reach the peak concentration
TLC	Thin Layer Chromatography
TPD	Therapeutic Products Directorate
TRL	Total Residue Level
TSE	Transmissible spongiform encephalopathy
UK	United Kingdom
US	See USA
USA	United States of America
USAN	United States Adopted Name
USP	United States Pharmacopoeia
UV	Ultraviolet
V_d	Apparent Volume of Distribution
VABNDS	Veterinary ABNDS
VDD	Veterinary Drugs Directorate
VICH	International Co-operation on Harmonization of Technical Requirements for registration of Veterinary Medicinal Products
VNDS	Veterinary NDS
WHMIS	Workplace Hazardous Materials Information System
XRD	X-ray Diffraction

13. APPENGIX III GLOSSARY OF TERMS

ABBREVIATED NEW DRUG SUBMISSION (ABNDS) - (Section C.08.002.1 of the *Food and Drug Regulations*). An ABNDS is a submission that contains sufficient information and material to demonstrate that the generic product is pharmaceutically equivalent as well as bio-equivalent with the Canadian reference product. In the case of food-producing animals, the ABNDS must confirm that the withdrawal period is identical to that of the Canadian reference product.

APPARENT VOLUME OF DISTRIBUTION (Vd) - the volume of fluid that the drug would occupy if it were evenly distributed throughout that volume at the concentration measured in plasma.

BIOAVAILABILITY (F or f) - The rate and extent of transfer of the drug from dosage form to the site of action.

BIOEQUIVALENCE (see BIOEQUIVALENT) - 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 - Two products are considered to be bioequivalent when their active ingredient(s) (is)are equal in their rate and extent of absorption, and availability at the site(s) of action.

CLEARANCE (Cl) - The phenomenon of the removal of drug from the body and expressed as the volume of fluid from which the drug substance is completely removed in unit time.

CANADIAN REFERENCE PRODUCT (CRP) - (Section C.08.001.1 of the *Food and Drug Regulations).* “Canadian reference product” means

(a) a drug in respect of which a Notice of Compliance has been 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).

DRUG - (Section 2 of the *Food and Drugs Act).* " 'Drug' includes any substance or mixture of substances manufactured, sold or represented for use in:

a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof, in man or animal;

b) restoring, correcting or modifying organic functions in man or animal; or

c) disinfection in premises in which food is manufactured, prepared or kept."

Vitamins, minerals, and other nutrients in injectable and bolus dosage forms for use in animals are also considered to be drugs.

GENERIC DRUG - For the purpose of this document a generic drug is defined as a drug formulation that contains same active ingredient(s) at the same concentration and that has the same pharmaceutical form, route of administration and labeled indications as the Canadian reference product.

HALF-LIFE (T½) - The time taken for a drug concentration to decline by 50%.

INHALANT - A gas, a volatile liquid, a finely aerosolized liquid or a powder for administration by nasal or oral respiratory routes for local or systemic effects.

LABEL - (Section 2 of the *Food and Drugs Act).* "Label" includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package. The labels for a drug must specify adequate directions for use, including withdrawal periods for drugs intended for use in food-producing animals.

MANUFACTURER - (Section A.01.010 of the *Food and Drug Regulations).* "'Manufacturer' means 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 food or drug and includes a firm, partnership, or corporation."

MEDICATED PREMIX (FEED ADDITIVE DRUG) - A drug specifically formulated for blending into animal feed.

NEW DRUG - (Section C.08.001 of the *Food and Drugs Regulations).* "A 'New Drug' is a drug that contains or consists of a new substance, or is a new combination of two or more drugs or has a recommendation for a new condition of use, and that has not been sold as a drug in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of its use a drug.

NEW DRUG SUBMISSION (NDS) - (Section C.08.002, and labeling as per Division 1 of Part C of the Food and Drug Regulations) - An NDS contains sufficient information and material to assess the safety and effectiveness of the subject new drug. It includes details of manufacturing and quality control as well as results of toxicity, pharmacology, residue and clinical studies, and proposed labels for the new drug.

NOTICE OF COMPLIANCE (NOC) - A Notice of Compliance is the document that is issued pursuant to section C.08.004 to the manufacturer of a drug when an NDS, ABNDS or SNDS complies with *the Food and Drug Regulations*. It includes the name, the medicinal ingredient(s), therapeutic classification(s) of the medicinal ingredient(s) and the Drug Identification Number (DIN) of the product. In the case of an ABNDS, the NOC states the name of the Canadian reference product referred in the submission.

PHARMACEUTICAL EQUIVALENCE - When a new drug, in comparison with another drug contains

identical amounts of the identical ingredients, in comparable dosage forms, but does not necessarily contain the same non-medicinal ingredients.

PHARMACODYNAMICS (PD) - The study of biochemical and physiological effects of drugs, their mechanism(s) of action, their structure activity relationships and their interaction with other drugs.

PHARMACOKINETICS (PK) - The study of the time course of drugs: absorption, distribution, metabolism and excretion.

PHARMACOVIGILANCE - For the purpose of these guidelines, pharmacovigilance means adverse drug reaction reporting and post-market surveillance to monitor the safety and efficacy of veterinary drugs.

PIVOTAL STUDIES - Studies from which unequivocal results (positive or negative) are generated with regards to the safety , the efficacy and the conditions of use of a new drug. These are controlled tests conducted by qualified investigators with domestic breeds of the intended species under Canadian or Canada-like (North American) conditions of management and husbandry. These trials must be conducted in accordance with the guidelines published by the VDD or worldwide recognized authorities, e.g., the World Association for the Advancement of Veterinary Parasitology.

PROTOCOL - A protocol is a written procedure describing a study. It includes methods and circumstances under which the study is to be conducted. A protocol is written to ensure that there is agreement between all parties and individuals involved in the study and that the study will be conducted in a satisfactory manner.

RAW DATA - Raw data includes worksheets, records, memoranda, notes, photographs, microfilm, microfiche, computer printouts, magnetic media records (including dictated observation) and recorded data from automated instruments, or exact copies, all of which are the result of the original observations and activities of a study. Raw data are necessary for the reconstruction and evaluation of the report for a study.

SELL - (Section 2 of the *Food and Drugs Act).* "'Sell' includes offer for sale, expose for sale, have in possession for sale, and distribute, whether the distribution is made for consideration or not."

The *Food and Drug Regulations* prohibit the sale of a drug unless certain conditions have been met. "Sell," as defined in the Act, does not necessarily require the exchange of money for commodity. For example, the distribution of free samples to health professionals is considered to be a sale.

SPONSOR - see MANUFACTURER.

SUBMISSION - A submission is documentation consisting of data related to a drug product submitted by a named party and provided in response to a regulatory requirement.

SUPPLEMENTAL ABBREVIATED NEW DRUG SUBMISSION (SABNDS) - (Section C.08.003 of

the *Food and Drug Regulations*) - A supplement to an ABNDS with respect to matters that are significantly different to those contained in the ABNDS, shall contain sufficient and material to enable the Minister (of Health Canada) to assess the safety and efficacy of the new drug in relation to those matters.

SUPPLEMENTAL NEW DRUG SUBMISSION (SNDS) - (Section C.08.003 of the *Food and Drug Regulations*) - A supplement to an NDS with respect to matters that are significantly different to those contained in the NDS, shall contain sufficient and material to enable the Minister (of Health Canada) to assess the safety and efficacy of the new drug in relation to those matters.

THERAPEUTIC INDEX - The ratio between the effective dose (optimum dose) and the toxic dose (lowest dose exhibiting toxic signs).

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