Guidance for Industry

Preparation of Veterinary Abbreviated New Drug Submissions – Generic Drugs

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Veterinary Drugs Directorate
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Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by: • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre :

Foreword

Guidance documents are meant to provide assistance to industry, health care and food safety professionals on **how** to comply with Health Canada policies, 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 officers of Health Canada 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 adequately assess the safety, efficacy, tissue residue (where applicable) and quality of a veterinary final 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.

Revision History

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1. Purpose

This guidance document is intended to provide sponsors with an outline of the chemistry and manufacturing, clinical, and human safety requirements for the filing of the following submission types with the Veterinary Drugs Directorate (VDD):

- Abbreviated New Drug Submission (ANDS);
- Changes to ANDS – Supplemental Abbreviated New Drug Submission (SANDS) and Notifiable Change (NC).

Sponsors intending to make changes to drugs that have received a Notice of Compliance (NOC) pursuant to section C.08.004 of the Food and Drug Regulations should consult the Health Canada Post-NOC Changes Guidance Documents: *Post-Notice of Compliance (NOC) Changes: Framework Document*, *Post-Notice of Compliance (NOC) Changes: Quality Document* and *Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document*.

2. Scope and Application

This guidance document applies to veterinary pharmaceutical products and certain veterinary drugs of biological origin (biologics). Any veterinary biologic whose mechanism of action is by an immunological response, other than that associated with an infectious disease, is regulated by the VDD as a drug under the *Food and Drugs Act*. All other veterinary biologics are regulated by the Canadian Food Inspection Agency (CFIA) under the *Health of Animals Act*.

This guidance document should be read in conjunction with the applicable regulations and with the associated Health Canada guidance documents entitled

- *Guidance for Industry: Management of Regulatory Submissions*
  www.hc-sc.gc.ca/dhp-mps/vet/legislation/guide-ld/mors-gspr_pol-eng.php
- *Guidance for Industry: Preparation of Veterinary New Drug Submissions, Version 1.1, March 2007.*
  www.hc-sc.gc.ca/dhp-mps/vet/legislation/guide-ld/vdd_nds_guide-eng.php

Please note that this guidance document does **not** supersede the above guidance documents.

The following policies may be of use in preparing an ANDS submission:

- *Canadian Reference Product, October 12, 1995.*
  www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/crp_prc_pol-eng.pdf
- *Interpretation of "Identical Medicinal Ingredient", July 9, 2003.*
  www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/medingred_pol-eng.php

The requirements outlined in this guidance document are dynamic in nature, and are offered without prejudice to future measures that Health Canada might take in this area.

Drug manufacturers are encouraged to start using the *Guidance for Industry: Guidelines for the Preparation of Veterinary Abbreviated New Drug Submissions – Generic Drugs* as soon as it becomes available on Health Canada's website.

3. Structure and Content

This guidance document contains three main sections that describe the various requirements that an ANDS must meet.

Section 5, Part I, Chemistry and Manufacturing Requirements

Section 5 provides an outline of the data required by the Manufacturing and Chemistry Evaluation Division (MCED) for the confirmation of pharmaceutical equivalence between the proposed generic formulation and the Canadian Reference Product (CRP).

Section 6, Part II, Clinical Requirements – Bioequivalence Studies

Section 6 provides an outline of the data required by the Clinical Evaluation Division (CED) for the confirmation of bioequivalence between the proposed generic formulation and the CRP.

Sponsors wishing to make a request for a waiver of *in vivo* bioequivalence studies should consult this part to determine the suitability of such a request.

Section 7, Part III, Human Safety Requirements

Section 7 provides an outline of the data required by the Human Safety Division (HSD) for the confirmation of withdrawal period/withholding time between the proposed generic formulation and the CRP. The requirements pertain only to the drugs used in food-producing animals. However, these requirements may pertain to other animal species if the proposed use of a generic formulation is considered to have potential human health concerns.

Sponsors wishing to make a request for a waiver of human safety studies should consult this part to determine the suitability of such a request.

4. Clarifications

Confirming pharmaceutical equivalence between a generic product and the CRP does **not** guarantee a waiver for *in vivo* bioequivalence studies.

According to the *Food and Drug Regulations*, the confirmation of pharmaceutical equivalence of the new drug to the CRP is required for filing an ANDS (C.08.002.1 (1) (a)).

However, the confirmation of bioequivalence is also required (C.08.002.(1) (b)) and pharmaceutical equivalence does not guarantee a waiver for *in vivo* bioequivalence studies. In fact, waivers are granted for specific situations and dosage forms, such as for aqueous solutions of uncomplicated medicinal ingredients of immediate release. For more details on eligibility for a waiver, refer to Section 6, "Clinical Requirements", Subsection 6.2, "Criteria for waivers for Immediate-Release Formulations."

A generic product **cannot** have a different strength or concentration, dosage form, route of administration, or condition of use of the active ingredient from that of the CRP.

According to the *Food and Drug Regulations* (C.08.002.1 (1)), these differences would not fall within the eligibility criteria defined for filing an ANDS. For more details, refer to Section 6, "Clinical Requirements," Subsection 6.1, "Bioequivalence."

However, if a sponsor proposes such changes to their own innovator product, a Supplemental New Drug Submission (SNDS) can be filed. Comparative bioavailability studies are generally requested to confirm that the change does not affect the rate and extent of absorption of the product. For more details, refer to Section 6, "Clinical Requirements", Subsection 6.5.3, "Changes in Dosage Form, Strength, Route of Administration, API Source or Manufacturing Process."

5. Part I, Chemistry and Manufacturing Requirements

5.1 Abbreviated New Drug Submission

When preparing Part I of an ANDS, all section headings and numbering as described in Subsection 5.3, Drug Substance, and Subsection 5.4, Drug Product, should be retained. Where a particular section or subsection is not applicable or 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 I 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.

5.2 Supplemental Abbreviated New Drug Submission and Notifiable Change

For Supplemental Abbreviated New Drug Submission (SANDS) and Notifiable Change (NC) submissions, the required manufacturing and quality control information may vary substantially depending on the type of change as outlined in the *Guidance Document – Post-Notice of Compliance Changes: Quality Document*.

5.3 Drug Substance

Some of the detailed information to be included under the drug substance section of the ANDS may not be available to the sponsor of a generic drug 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) that can be filed directly with Health Canada by the holder of the DMF. The DMF will be held in strict confidence and will be used in support of an ANDS only upon receipt of written authorization from the DMF holder.

If a DMF is used to supply information on the drug substance, the following procedures must be followed:

- The DMF must be filed with Health Canada prior to or at the same time as the sponsor files the ANDS and an appropriate letter of authorization for cross reference be included.
- If a DMF is filed for the first time with Health Canada in support of a veterinary ANDS, the DMF can be filed with VDD or with the Therapeutic Products Directorate (TPD), Health Canada.
- Cross reference to a DMF previously filed with TPD in support of a human drug product is considered acceptable.
- The DMF must be filed in accordance with Health Canada's *Draft Guidance Document: Drug Master Files* and the information in the open part of the Type I DMF must be included in the sponsor's ANDS.

The following authorizations and attestations can also be submitted to VDD:

- Written authorization for VDD to examine the European Directorate for the Quality of Medicines and HealthCare (EDQM) confidential review report for the drug substance, should the need arise.
- Written assurance that there have been no changes in the manufacturing method following the granting of the Certificate of Suitability (CEP) or its current revision by EDQM.
- Written assurance that the manufacturing process described in the Canadian DMF is identical to the one evaluated by EDQM.

It is the responsibility of the sponsor of the ANDS to ensure that the DMF holder is aware of the current Health Canada requirements for the DMF filing and that it is up-to-date in accordance with Health Canada's *Draft Guidance Document: Drug Master Files*. The DMF holder must provide separately written assurances that the DMF and the CEP are current and authorization that allows access to the EDQM reports.

The proprietary information in the closed part of the DMF is reviewed in connection with the review of the ANDS. The DMF holder will be contacted directly only if deficiencies are determined in the closed part of the DMF and comments regarding such deficiencies will be 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. Comments on deficiencies observed in any other part of the drug substance information in the ANDS are sent to the sponsor of the submission.

5.3.1 General Information

5.3.1.1 Pharmaceutical Equivalence

In the context of filing an ANDS where the assumption is made that the active pharmaceutical ingredient of the proposed drug product is identical to the active pharmaceutical ingredient of the CRP, the sponsor must demonstrate that the proposed active pharmaceutical ingredient complies with the definitions as outlined under Division C.08 of the *Food and Drug Regulations* and as a result is considered to be pharmaceutically equivalent.

The *Food and Drug Regulations* provide the following definition:

"pharmaceutical equivalent" means a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage form, but that does not necessarily contain the same non-medicinal ingredients provided they are not known to influence the absorption characteristics of the active ingredients. (Section C.08.001.1)

The term identical medicinal ingredient could be interpreted to imply medicinal ingredients that are both physically and chemically identical. However, in the context of the *Regulations*, only the "chemical identicality" of the medicinal ingredients is taken into account while determining pharmaceutical equivalence. Pharmaceutically equivalent drug products should contain chemically identical, but not necessarily physically identical, medicinal ingredients. Differences in physical properties (e.g., particle size, polymorphism) of the medicinal

ingredients could cause differences in the safety and efficacy profiles of the drug products. To address concerns arising from differences in physical properties, appropriate *in vivo* or *in vitro* studies should be conducted and the results included in the ANDS. The term identical is to be understood in this context.

Based on these considerations, medicinal ingredients containing the same active moiety are classified into *identical* or *non-identical* medicinal ingredients according to the following guiding principles:

1. Anhydrous and anhydrate, and the various hydrated forms of the same active moiety are generally considered identical.
2. Unsolvated and the various solvated forms of the same active moiety are generally considered identical, provided the solvate content is within acceptable levels. Levels within the limits recommended in the Veterinary International Cooperation on Harmonization (VICH) guideline, "Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients" (VICH GL 18), would be considered acceptable without further justification. Solvate levels exceeding the VICH GL 18 limits should be justified, on a case by case basis, and supporting data provided.
3. Different complexes, esters, or salts of the same active moiety are considered to be non-identical.
4. Different isomers or mixtures with different proportions of isomers are considered to be non-identical.

ANDS sponsors are advised to discuss the issue with VDD in advance when the "identicality" of two medicinal ingredients is in doubt for the purposes of establishing pharmaceutical equivalence. For further details on this topic, consult the Health Canada policy on *Interpretation of "Identical Medicinal Ingredient."*

5.3.1.2 Nomenclature

The sponsor should provide information on the nomenclature of the drug substance, including, if available

- Recommended International Non-proprietary Name (INN);
- Compendial name, if relevant;
- Chemical name or names;
- Company or laboratory code;
- Other non-proprietary names, such as the United States Adopted Name (USAN) and the British Approved Name (BAN); and
- Chemical Abstracts Service (CAS) registry number.

5.3.1.3 Chemical Structure

The sponsor should provide the structural formula, including relative and absolute stereochemistry including geometric isomerism or a mixture of isomers, the molecular formula, and the relative molecular mass.

For drug substances existing as salts or hydrates, the sponsor should submit data to demonstrate compliance to the policy on Interpretation of "Identical Medicinal Ingredient."

5.3.1.4 Physicochemical Properties

The sponsor should provide data on the physicochemical and other relevant properties of the drug substance, such as physical description, solubility in common solvents (e.g., water, alcohols, chloroform, acetone,), quantitative aqueous pH solubility profile (e.g., pH 1 to 8, dose/solubility volume), polymorphism, particle size distribution, pH and pKa values, ultraviolet (UV) absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, and partition coefficient.

The following paragraphs discuss in greater detail some of the more important properties to be considered for all drug substances.

5.3.1.4.1 Physical Description

The description should include appearance, colour, and physical state. Solid forms should be identified as being crystalline or amorphous.

5.3.1.4.2 Solubility/Quantitative Aqueous pH Solubility Profile

Sponsors should consider generating data that is specific to the target species. The physiological pH range may differ from species to species. Data should be relevant to demonstrating an understanding of the *in-vivo* performance of the drug product as it relates only to the quality attributes.

The submission should provide solubility for a number of common solvents (e.g., water, alcohols, chloroform, acetone). The solubility over the physiological pH range (pH 1 to 8) in several buffered media should also be provided expressing the results in mg/mL. If this information is not readily available from the literature or from the open part of the DMF, it should be generated in-house.

With respect to the target species, the submissions should provide the dose/solubility volume if the drug product is in solid oral dosage form. The dose/solubility volume is calculated based on the lowest aqueous media solubility of the drug in mg/mL, determined over the physiological pH range at a temperature of 37±1°C for the highest dosage strength of the product.

5.3.1.4.3 Polymorphs

Generally, polymorphism is not a concern for drug substances that are considered to be highly soluble under aqueous conditions or that are present in solution in the drug product.

Information on the potential for polymorphism can often be obtained from the literature. If the polymorphic form has the potential to affect product performance in the targeted species, the submission should include data from a test in the drug substance specifications that were established from the characterization of the lot of drug substance used in the manufacturing of the drug product intended for the bioequivalence studies.

5.3.1.4.4 Particle Size Distribution

Generally, particle size distribution is not a concern if the drug product is a solution or if the drug substance is dissolved during the drug product manufacturing process such as wet granulation or is considered to be highly soluble in water. Furthermore, if the manufacturing process of the drug product includes a compaction step that alters the dimensions of the particle size, then analysis for the drug substance is not required provided a justification is presented in developmental pharmaceutics.

Particle size distribution of poorly soluble drugs may affect *in vitro* and *in vivo* performance of the drug product. Although particle size distribution may be important for other reasons related to drug product manufacture and performance such as content uniformity, the most important regulatory concern relates to its possible impact on dissolution and bioavailability. For poorly soluble drugs, the submission should appropriately characterize the particle size distribution of batches used in comparative clinical or bioavailability studies and include a test in the drug substance specification that ensures that commercial batches match the batch or batches used in the comparative studies.

If a particle size distribution test is included in the drug substance specification, it is recommended that limits be set for d_{10}, d_{50}, and d_{90}. The following formulae are provided for illustrative purposes as possible acceptance criteria for particle size limits:

- d10: NMT 10% of total volume less than X μm
- d50: XX μm - XXX μm
- d90: NLT 90% of total volume less than XXXX μm

5.3.2 Manufacture

5.3.2.1 Manufacturers

The submission should provide the name, address, and responsibility of each manufacturer, including contract manufacturers or testing sites, involved in the manufacturing, packaging, labelling, and testing of the drug substance. The addresses provided should be for the site where the activity takes place, rather than for the administrative offices.

5.3.2.2 Description of Manufacturing Process and Process Controls

The submission should provide a flow diagram or diagrams of the synthetic process or processes. The diagrams should include the chemical structures of starting materials, intermediates, and drug substance reflecting stereochemistry and also include reagents, solvents, and operating conditions.

The submission should provide a narrative description of the manufacturing process. The narrative should include quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, and all process controls, equipment, and operating conditions (e.g., temperature, pressure, pH, time). If a cross-referenced DMF includes a detailed description of the manufacturing process, the sponsor need only include a brief summary of the manufacturing process including a flow diagram representing the route of synthesis in the ANDS. Alternate processes and reprocessing steps, if any, should be justified and described in either the cross-referenced DMF or the ANDS using the same level of detail as is used for the primary process. Reprocessing steps should be identified and justified in either the cross-referenced DMF or the ANDS. The manufacturing process should start from commercially available or well-characterized starting materials.

For sterile drug substances, the submission should include a complete description of the method of sterilization and the controls used to maintain sterility during storage and shipping.

For drug substances produced by fermentation, the submission should contain additional information, including source and type of micro-organisms used, precursors, composition of media, details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration), and name and composition of preservatives.

For drug substances of plant origin, the submission should include a description of the botanical species and the part of plant used, the geographical origin, and the time of year of harvest, when relevant. The submissions should record the nature of chemical fertilizers, pesticides, fungicides, and so on, if these have been employed during cultivation. It may be necessary to include in the drug substance specification limits for residues resulting from such treatments. The submission may also have to confirm the absence of toxic metals and radioactivity.

5.3.2.3 Control of Materials

The submissions should list materials such as starting materials, solvents, reagents, and catalysts used in the manufacture of the drug substance, including the synthesis, fermentation, extraction, isolation, and purification steps, and identify where each material is used in the process. The submission should provide copies of the specifications for each of these materials and the specifications should meet the standards appropriate for their intended use.

The submission should evaluate drug substances of animal origin as to the likelihood of the presence of Bovine Spongiform Encephalopathy (BSE) and

Transmissible Spongiform Encephalopathy (TSE) agents. Additionally, for any material of animal origin used in the manufacture of the drug substance, the submission should provide information in accordance with the most stringent requirements set out in compendial monographs listed in Schedule B of the *Food and Drugs Act* (e.g., United States Pharmacopoeia [USP], European Pharmacopoeia [PhEur], The British Pharmacopoeia [BP], etc.) and the requirements of the Animal Ingredient Form (AIF) or the Drug Product Information Form (DPIF).

Note: If information on the control of materials is included in a cross-referenced DMF, it is appropriate for the submission to refer to the DMF rather than provide the information in the submission.

5.3.2.4 Controls of Critical Steps and Isolated Intermediates

The submission should provide information on the tests, including acceptance criteria and justification, performed at critical steps of the manufacturing process to ensure that the process is properly controlled. The submission should also include specifications for isolated intermediates, including tests and acceptance criteria for identity, purity, and potency, where applicable.

Note: Information on the control of critical steps and intermediates can be cross-referenced to the DMF, if a DMF is being used to support the ANDS.

5.3.2.5 Process Validation and Evaluation

The submission should include process validation or evaluation studies or both for drug substances produced using aseptic processing or sterilization.

Note: Cross references to a DMF are acceptable for this information.

5.3.3 Structure Elucidation and Confirmation

For generic drugs, it is generally sufficient for the ANDS to provide copies of the infrared (IR) and UV spectra of the drug substance from the proposed supplier's run in coordination with a suitable reference standard. A suitable primary reference standard could be obtained from the compendia listed in Schedule B of the *Food and Drugs Act* (e.g., USP, Ph.Eur, BP, etc.). In the case where a Schedule B compendia monograph does not exist, a batch of the drug substance should be fully characterized (e.g., IR, UV, nuclear magnetic resonance [NMR], mass spectra [MS], etc.).

When a drug substance is chiral, the submission should specify whether specific stereoisomers or a mixture of stereoisomers have been used in the bioequivalence studies, and the submission should include information as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

5.3.4 Impurities

The submission should include a discussion of potential impurities arising from the method of manufacture. The discussion should place particular emphasis on

possible impurities arising from a method of manufacture that differs from that used to produce the compendial material. Sponsors should consider drug-related impurities, such as starting materials, intermediates, by-products, and degradation products, and process-related impurities, such as solvents, catalysts, and reagents. The submission should include a table that for each potential impurity lists the name, chemical structure, and origin (e.g., synthetic intermediate, by-product, residual solvent from crystallization step).

The submission should provide actual impurities found in batches tested and include quantitative results, or indicate that the impurities are below the limit of quantitation (LOQ) or not detected. The impurity profile of the drug substance batches should be compared with the impurity profile of the CRP. If the generic drug substance contains impurities not present in the CRP or in a Schedule B compendium, or contains impurities at higher levels than specified in a Schedule B compendium or found in the CRP, it may be necessary to qualify the limits for these impurities.

Unidentified impurities that are specified by relative retention time (RRT) at a limit greater than 0.2% require qualification, as do identified impurities at a limit greater than 0.5%. Limits for specified impurities in a Schedule B publication are generally considered acceptable. VICH limits of no more than (NMT) 0.2% for unspecified impurities apply, rather than the general limits for unspecified impurities that appear in the compendial monograph, unless the compendial limits are more stringent. It is possible that there are specified impurities in the compendial monograph that are not likely to be present in the generic product due to a different method of synthesis. Appropriate justification should be provided for their exclusion from the submission.

Some latitude may be appropriate for drug substances of semi-synthetic origin such as those obtained from chemical modification of a precursor molecule of plant or animal origin, or derived from a fermentation process. A limit of NMT 0.5% for unspecified impurities would generally be considered appropriate.

If there is a need to qualify a limit for a specified impurity, there are two possible approaches. The first approach is to use the CRP for comparative purposes, while the second approach is to use the VICH guideline, “Impurities in New Drug Substances” (VICH GL 10), Attachment II, “Decision Tree for Safety Studies.” The CRP approach is possible only if the impurity appears in the CRP at levels that exceed the VICH qualification threshold.

It is recommended that a minimum of three batches of the CRP be selected for analysis using the same validated analytical procedure used to test the generic product. It is also recommended that the batches selected for analysis be close to but not past the expiry date for the CRP. It is not acceptable to expose these batches to accelerated or stressed storage conditions before testing. The proposed limit for the impurity in the generic product is considered qualified if supported by the levels of the same impurity found in the batches of the CRP. Impurities that are also significant metabolites present in animal or human studies are generally considered qualified.

Impurities classified as residual solvents must conform to the levels specified in the VICH guideline, "Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients" (VICH GL 18).

Note: Solvents such as benzene and chloroform will not be tolerated. In the absence of limits under VICH GL 18, limits recommended in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline, "Impurities: Guideline for Residual Solvents" (ICH Q3C), would be considered acceptable without further justification. The submission should justify solvent levels exceeding the VICH GL 18 or ICH Q3C limits, on a case-by-case basis, and provide supporting data. Supporting data could be based upon concepts of qualification outlined in the VICH and ICH impurity guidelines.

5.3.5 Control of the Drug Substance

5.3.5.1 Specification

The submission should contain a copy of the drug substance specification from the company responsible for release testing. The person in charge of quality control at the responsible company should date and sign the specification in accordance with the Good Manufacturing Practice (GMP) guidelines published by Health Canada's Health Products and Food Branch (HPFB) Inspectorate. The submission should provide the specification reference number, version, and date for version control purposes.

Although the drug substance specification will normally include tests for appearance, identity, potency, and purity, additional tests (e.g., for particle size distribution, crystal form determination [polymorphism], chirality, bacterial endotoxins, etc.) will be required depending on the characteristics of the drug substance and its end use (e.g., oral, parenteral).

5.3.5.2 Analytical Procedures

The submission should contain copies of the analytical procedures used for testing the drug substance. It is not necessary to provide copies of Schedule B compendial analytical procedures unless the procedures are modified. High performance liquid chromatography (HPLC) is normally considered the method of choice for determining drug-related impurities, and some other chromatographic methods such as gas chromatography (GC) or thin layer chromatography (TLC) may also be used, if appropriate.

For impurity methods, it is recommended that the sponsor prepare reference standards for each of the identified impurities, particularly those known to be toxic, and the concentration of the impurities quantified against their own reference standards. It is considered acceptable, however, to use the drug substance as an external standard or to use area normalization to estimate the levels of impurities, provided the response factors of those impurities are

sufficiently close to that of the drug substance (e.g., 80% or more). In cases where the response factor is not close, a correction factor should be applied.

Chromatographic analytical procedures should include system suitability testing (SST) and depending on the method should include tests such as resolution, precision, tailing factor, and sensitivity. For greater understanding of the details, definitions, and design of system suitability testing, sponsors should refer to the USP, General Chapter <621> Chromatography, which is found in the annual publication of the USP monographs.

5.3.5.3 Validation of Analytical Procedures

The submission should contain copies of validation reports for the analytical procedures proposed for release and shelf-life testing of the drug substance. The reports should include the interpretations of the test results. Depending on the method, the parameters to be examined might include accuracy, precision, specificity, linearity, detection limit, quantitation limit, and ruggedness. Further guidance regarding the validation of analytical procedures is available in VDD's adopted VICH guidelines, "Validation of Analytical Procedures: Definition and Terminology" (VICH GL 1) and "Validation of Analytical Procedures: Methodology" (VICH GL 2).

If a compendial method is used for the determination of impurities in a drug substance and the drug substance is manufactured by a method that differs from the method used to obtain the compendial material (i.e., different specified impurities), validation of the method with respect to impurities not present in compendial material is required. If a house method is developed for potency or impurity determination to replace a compendial method, validation data are required, as well as comparative data obtained using the two methods.

5.3.5.4 Batch Analyses

The submission should contain descriptions, including batch number, batch size, date and site of manufacture, type of study (bioequivalence and stability), and analytical results, for at least two batches from each site of manufacture. The data should be generated by the company responsible for release testing and should include certificates of analysis. The submission should provide quantitative results for all quantitative tests (e.g., potency, impurities, and loss on drying). A statement such as "within limits" or "complies" is not considered acceptable for a quantitative test.

5.3.5.5 Justification of Specification

The justification of the specification should include the rationale for the inclusion or the exclusion of tests, discussion of the development of methods and acceptance criteria, and the rationale for differences from compendial tests, methods, or acceptance criteria. Certain specific tests on the drug substance may be justified by the manufacturing process of the drug product that was realized during developmental pharmaceutics such as particle size determination or other unique physicochemical property.

The justification for certain tests, analytical procedures, or acceptance criteria may have been discussed in other sections of the ANDS and cross-references to those sections are sufficient for the justification of the specification.

5.3.6 Reference Standards

The submission should provide the sources of reference standards or materials used to test the drug substance. Primary reference standards obtained from official sources such as the Schedule B compendia do not need further characterization. The submission should fully characterize and structurally elucidate any other primary standard (e.g., IR, UV, NMR, MS, etc.).

The submissions can use a secondary or in-house reference standard by providing a copy of its certificate of analysis and validating it against a suitable primary reference standard. The submission should provide copies of the IR and UV spectra of the secondary and primary reference standards run concomitantly. The submission should provide a brief description of the manufacturing process of the secondary reference standard, if it differs from the commercial process for the drug substance.

5.3.7 Packaging

5.3.7.1 Description and Specifications

The submission should provide a description of the container closure system or systems, including the identity of materials used for the primary packaging components with a brief description of the secondary packaging, if warranted. The choice of packaging materials should be based on protecting the drug substance from light and moisture, as well as the compatibility of the materials with the drug substance. Specifications for packaging materials should be relevant and include an identification test for the packaging materials that are in contact with the drug substance.

5.3.8 Stability

The sponsor should conduct stability studies, including stress, accelerated, and long-term stability studies, on the drug substance to establish appropriate packaging and storage conditions, and the re-test period. The ANDS should include the protocols used for the studies and the results obtained.

Note: If a DMF is used to support an ANDS, then a majority of the following information can be reproduced or referenced from the open part. You are advised that if the information within the DMF is found to be inconclusive, this may delay the approval of the ANDS.

5.3.8.1 Forced Degradation (Stress) Studies

The results of stress testing provide information on the intrinsic stability of the drug substance, potential degradation pathways, likely degradation products, and the stability indicating power of the analytical procedures. Stress testing is

normally carried out on one batch of the drug substance and generally includes the effect of heat, humidity, light, oxidation, and acid/base hydrolysis. The submissions should present the results in tabular form, including treatment conditions and quantitative results, which are normally assay and degradation products.

Note: If information on stress testing is available in the public domain, it may not be necessary to repeat the testing.

5.3.8.2 Accelerated and Long-term Studies

The submission should provide results of stability studies on a minimum of two batches of the drug substance stored at accelerated and long-term conditions. At the time of filing the ANDS, studies for a minimum of six months at each condition are required. The accelerated and long-term conditions depend on the recommended storage conditions, but would normally be 40°C ± 2°C / 75% ± 5% relative humidity (RH) for accelerated conditions and 25°C ± 2°C / 60% ± 5% RH for long-term conditions. If a failure to meet the acceptance criteria occurs at any time at the accelerated condition, additional testing should be conducted at the intermediate condition of 30°C ±2°C / 65% ± 5% RH.

Information on the stability lots should include date of manufacture, batch number and size, packaging, storage conditions, test intervals completed and to be completed, tests performed with acceptance criteria, and description and validation of analytical procedures, if different from those described in Subsection 5.3.5.2. The submission should present the results in tabular form, including quantitative results for all quantitative tests. The submission should provide a discussion of the results and the conclusions reached.

5.3.8.3 Proposed Storage Conditions and Re-test Period

The submission should provide proposed storage conditions and re-test period for the drug substance, based on the results of the stability studies. For drug substances that are shown to be unstable, it is more appropriate to establish a shelf-life (expiry period) rather than a re-test period. In certain cases, information available in the public domain may be sufficient to establish an appropriate re-test period, for example when a substantial body of evidence exists that establishes that the drug substance is inherently stable.

5.4 Drug Product

5.4.1 Description of the Drug Product

The submission should provide a detailed description of the drug product to be marketed in Canada, including the form in which it is to be sold, the strengths, appearance, type of container and closure system, proposed storage conditions, and expiration period. When applicable, the submission should also provide a description of the accompanying reconstitution diluent or diluents and their container and closure systems, and dosing devices. For reconstitution diluents that

are not commercially available in Canada or for which information has not been submitted and approved, the submission should include separately in the drug product section of the ANDS complete chemistry and manufacturing information on the diluent.

5.4.2 Pharmaceutical Development

The pharmaceutical development section of the submission should contain information on 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.

The studies to be described in this section are distinguished from routine control tests conducted according to specifications. Additionally, the sponsor should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance, and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached as a narrative to this section. Additional supportive data can be cross-referenced to the relevant sections as needed.

5.4.2.1 Formulation and Process Development

The submission should provide a brief summary describing the development of the drug product, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e., composition) described in Subsection 5.4.1 should be discussed. Results from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) should also be discussed, when appropriate.

5.4.2.2 Physicochemical Characteristics of the Drug Substance

The discussion of the physicochemical characteristics of the drug substance should include the possible influence of the drug substance solubility, particle size distribution, crystal form, or any other characteristic on the performance of the drug product.

5.4.2.3 Compatibility

This section of the submission should include a discussion of the compatibility of the drug substance with each of the excipients of the optimized formulation that was used to support the bioequivalence studies. These studies can be avoided if the sponsor of the generic drug product uses the approach of qualitative and quantitative analysis in developing their formulation that translates to reproducing the formulation of the CRP.

If the sponsor generates a formulation that does not comply with the approach of qualitative and quantitative analysis, then the sponsor should submit complete compatibility studies. These studies should examine the interaction of the active pharmaceutical ingredient (API) with each individual excipient. For combination

drug products, the sponsor should examine the interactions of API/API in combination with each excipient. Colour tests through visual examination are considered to be insufficient and testing should consist of chromatographic methods.

5.4.2.4 Physicochemical Characteristics of the Drug Product Relevant to Performance

The submission should address physicochemical characterisitics relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and immunological activity.

5.4.2.5 Microbiological Attributes

Where applicable, the submission should discuss the microbiological attributes of the dosage form, including the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the submission should address the integrity of the container closure system to prevent microbial contamination.

5.4.2.6 Container Closure System

The submission should discuss the suitability of the container closure system used for the storage, transportation, and use of the drug product. The discussion should consider choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug product (including sorption to container and leaching), safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

5.4.3 Manufacture

5.4.3.1 Manufacturers

The submission should provide the name, address, and responsibility of all sites, including those contracted, involved in the manufacture, packaging, labelling, testing, importing, storage, and distribution of the drug product. The address provided should be for the site where the activity takes place rather than the administrative offices.

5.4.3.2 Formulae

5.4.3.2.1 Unit Formula

Submission should provide the quantitative formula presented in tabular form, including for each component the amount on a per unit basis (e.g., mg/tablet, mg/mL) and percentage basis, the standard (e.g., USP, Ph.Eur., House, etc.), and the function (e.g., filler, binder, disintegrant, lubricant, etc.), as well as the total

weight or volume. The components should be listed by their proper, common, or compendial names, and their grades should be indicated, if applicable. The submission should provide the quantitative composition, including the standard for each component, for proprietary items such as capsule shells, colouring blends, and flavours. The quantitative composition can be provided in a DMF, but the qualitative composition should be included in the submission.

Alternatives or ranges for excipients are generally not accepted, but ranges may be accepted if supported by appropriate process validation data and, in extreme cases, comparative bioavailability studies.

Overages: All overages should be clearly indicated (e.g., "Contains 2% overage of the drug substance to compensate for manufacturing losses that are justified by process validation studies."). Any overage used to extend the shelf life of the drug product is considered to be unacceptable practice and will not be approved.

5.4.3.2.2 Batch Formula

The submission should provide the batch formula in tabular form for each proposed batch size, indicating the amount of each component on a per batch basis and the corresponding quality standard. The batch formula should include all components used in the manufacturing process regardless of whether the component appears in the final drug product (e.g., solvents, nitrogen, etc.). If the amount of active ingredient added to the batch formula does not correspond to the label claim (e.g., active ingredient added as a salt while label claim is as the base), the appropriate conversion factors should be indicated as a footnote to the table.

The following table provides an example of how to summarize unit and batch formulae as it relates to product development.

Table 1: Example Summary of Unit and Batch Formulae

Core tablets (components in technological order)	Unit		Clinical		Stability		Production	
	mg	%	kg	%	kg	%	kg	%
Active pharmaceutical ingredient	400.00	82.73	280.00	82.81	280.00	82.81	40.00	82.81
Maize starch	5.00	1.03	3.72	1.10	3.72	1.10	0.53	1.10
Micro Crystalline Cellulose (PH 302)	4.92	1.02	3.44	1.02	3.44	1.02	0.49	1.02
Povidone (PVPK-30)	20.00	4.14	14.00	4.14	14.00	4.14	2.00	4.14
Stearic acid	2.00	0.41	1.40	0.41	1.40	0.41	0.20	0.41
Maize starch	10.49	2.17	7.34	2.17	7.34	2.17	1.05	2.17
Micro Crystalline Cellulose (PH 302)	9.15	1.89	6.41	1.90	6.41	1.90	0.92	1.89
Sodium starch glycollate	4.92	1.02	3.44	1.02	3.44	1.02	0.49	1.02
Colloidal anhydrous silica	5.00	1.03	3.50	1.04	3.50	1.04	0.50	1.04
Purified Talc	3.92	0.81	2.74	0.81	2.74	0.81	0.39	0.81
Magnesium Stearate	4.60	0.95	3.22	0.95	3.22	0.95	0.46	0.95
Subtotal 1:	470.00	97.21	329.21	97.36	329.21	97.36	47.03	97.36
Film coating (components of two layers in technological order)								
Hypromellose (5 cps)	5.56	1.15	0.58	0.17	0.58	0.17	0.08	0.17
Ethyl Cellulose	0.13	0.03	0.14	0.04	0.14	0.04	0.02	0.04
Macrogol 6000	0.14	0.03	0.15	0.04	0.15	0.04	0.02	0.04
Purified Talc	0.19	0.04	0.20	0.06	0.20	0.06	0.03	0.06
Hypromellose (5 cps)	5.00	1.03	5.26	1.56	5.26	1.56	0.75	1.55
Purified Talc	0.38	0.08	0.40	0.12	0.40	0.12	0.06	0.12
Titanium dioxide	0.38	0.08	0.40	0.12	0.40	0.12	0.06	0.12
Macrogol 6000	1.72	0.36	1.80	0.53	1.80	0.53	0.26	0.53
Subtotal 2:	13.50	2.79	8.93	2.64	8.93	2.64	1.27	2.64
Grand total:	483.50	100.00	338.14	100.00	338.14	100.00	48.30	100.00

5.4.3.3 Manufacturing Process

5.4.3.3.1 Description

The submission should provide a flow diagram showing each step of the process, where materials enter the process, and where samples are taken for in-process testing. The submission should also provide a narrative summary of the manufacturing process, including packaging and labelling describing the sequence of steps. The summary should include the amount of ingredient added at each step, the equipment type and capacity, process parameters such as mixing times and speeds, processing temperatures, and any precautions necessary to ensure product quality, such as control of humidity, temperature, light, and maximum hold times, where necessary. The in-process testing should be indicated and it is recommended that the testing be presented in tabular form, including the process step, test conducted, and acceptance criteria.

5.4.3.3.2 Master Production Documents

The submission should provide copies of the drug product master production documents for each proposed strength, commercial batch size, and manufacturing site. The details in the master production documents should include, but not be limited to, the following items:

- 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);
- 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.);
- List of 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, etc.);
- Sampling plan with regard to
    - the steps where sampling should be done (e.g., drying, lubrication, and compression);
    - the number of samples that should be tested (e.g., blend drawn using a sampling thief from *x* number of different parts of the blender), and
    - the 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, etc.);
- Theoretical and actual yield; and
- Compliance with the GMP requirements according to the provisions of Part 2, Division 2 of the *Food and Drugs Regulations*.

5.4.3.3.3 Executed Production Documents

A minimum of two batches of each strength should be manufactured. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. The batches should be manufactured using a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral drug products, a pilot scale is generally considered, at a minimum, to be one-tenth that of a full production scale, whether tablets or capsules. Copies of the executed production documents should be provided for the batches used in the pivotal comparative clinical or bioavailability studies. Operators should ensure that any notations they make on the executed production documents are clearly legible.

5.4.3.4 Process Validation

Process validation should be conducted on all drug products, but the filing requirements differ depending on whether the drug product is sterile or non-sterile. Detailed guidance concerning process validation is available in the following documents issued by the HPFB Inspectorate.

- "Validation Guidelines for Pharmaceutical Dosage Forms" (GUIDE–0029)
- "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" (GUIDE–0008)
- "Process Validation: Moist Heat Sterilization for Pharmaceuticals"

Because of the nature of filing an ANDS, it is normally expected that process validation for solid oral drug products be completed prior to the distribution of a finished product and after the issuance of a Notice of Compliance that is intended to authorize the product for sale (prospective validation). Where this is not possible, as in the case of a new drug product recently marketed in other jurisdictions, it may be necessary to validate processes during routine production (concurrent validation). For long established processes and marketing in other jurisdiction that have been in use for some time without any significant changes, the process may also be validated according to an approved protocol (retrospective validation).

5.4.3.4.1 Sterile Products

For a sterile product, the submission should provide a copy of the process validation report, including protocol and results. The report should identify the critical steps, equipment, and process parameters that can affect the quality of the drug product, and define testing parameters, sampling plans, analytical procedures, and acceptance criteria. The drug product sterilization process should be validated. Since terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the drug product, if any other method of sterilization is selected, the submission should provide scientific justification for the selection. In addition to validating the drug product sterilization process, the submission should also provide reports on the validation of the processes for washing, treatment, sterilizing, and depyrogenating containers, closures, and equipment.

5.4.3.4.2 Non-sterile Products

For a non-sterile product, the submission should provide a copy of the process validation protocol, specific to the drug product. The protocol should

- identify the critical steps, equipment, and process parameters that can affect the quality of the drug product;

- define testing parameters, sampling plans, analytical procedures and acceptance criteria; and
- confirm that three consecutive production scale batches will be subjected to validation.

If process validation studies have already been completed, the submission should include a copy of the process validation report.

Note: For greater details in designing a process validation protocol, consult the HPFB Inspectorate, "Validation Guidelines for Pharmaceutical Dosage Forms" (GUIDE–0029).

5.4.3.5 Control of Excipients

5.4.3.5.1 Specifications

The submission should provide specifications for all excipients, including those that do not appear in the drug product (e.g., solvents, nitrogen, silicon for stoppers, etc.), and these specifications should be relevant to ensure that the performance of the quality characteristics of the drug product are maintained from the lots used in the bioequivalence studies to full scale production.

If the excipient complies with a Schedule B compendial monograph, it is acceptable for the submission to state that the excipient will be tested according to that standard. There is no need to reproduce the tests and acceptance criteria found in the standard. If the excipient is non-compendial or is compendial with additional tests or tighter limits, the submission should provide a copy of the specification.

5.4.3.5.2 Analytical Procedures and Validation

The submission should provide copies of analytical procedures and validation reports, where appropriate, for tests supplementary to those appearing in a Schedule B compendial monograph, as well as for all tests in specifications for non-compendial excipients.

5.4.3.5.3 Justification of Specifications

The submission should provide justification for tests and acceptance criteria supplementary to those appearing in a Schedule B compendial monograph, as well as for all tests in specifications for non-compendial excipients.

5.4.3.5.4 Excipients of Animal Origin

For excipients of animal origin, the submission should provide information concerning adventitious agents, including sources, specifications, descriptions of the testing performed, and viral safety data. or excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE) or Transmissible Spongiform Encephalopathy (TSE) agents, the submission should provide a letter of attestation with supporting documentation.

5.4.3.5.5 Novel Excipients

For excipients used for the first time in a drug product or by a new route of administration, the submission should provide full details of the manufacture and characterization of the novel excipient, as well as information required in the previous four subsections. The submission should also include cross references to any supporting clinical safety data.

5.4.4 Control of the Drug Product

5.4.4.1 Specifications

The submission should provide proposed regulatory specifications for release and shelf life testing. The specifications are a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. The specifications establish the 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 relevant critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as a condition of approval. The justification of specifications should be based on the lots used in the conduct of bioequivalence studies as the performance of the quality attributes should be identical between pre- and post-approval lots.

A copy of the drug product specifications from the sponsor, as well as from the company responsible for release testing, if different from the sponsor, should be provided, dated, and signed by authorized personnel (i.e., the person in charge of the quality control department). The submission should provide the specification reference number, version, and date for version control purposes. The standard declared by the sponsor could be a *Food and Drugs Act,* Schedule B compendial standard, manufacturer's or house standard, prescribed standard (e.g., Canadian Standard Drugs in Division 6 of the *Food and Drugs Regulations*), or a professed standard.

Although a Schedule B compendial monograph may exist, a sponsor can choose a manufacturer's standard as long as it complies with Section C.01.011 of the *Food and Drug Regulations*. Compliance with Section C.01.011 means that the acceptance criteria for potency and purity (i.e., limits on specified impurities) should be as tight as the most stringent acceptance criteria listed in the Schedule B compendial monographs. If the ANDS is for a non-official drug where no Schedule B compendial standard exists, a professed standard is used and the product labelling for such products does not carry any standard.

Tests for product appearance, identity and assay of the medicinal ingredients, and determination of degradation products are standard for all dosage forms. The other tests to be included in the specification will depend on the dosage form and route of administration. Proposed limits for degradation products that exceed the

VICH qualification threshold of 1.0% can be qualified by comparison with the CRP as discussed in Subsection 5.3.4 or by following the VICH guideline, "Impurities in New Veterinary Medicinal Products" (VICH GL 11), Attachment II, "Decision Tree for Safety Studies."

5.4.4.2 Analytical Procedures

The submission should contain copies of analytical procedures proposed for testing the drug product. It is not necessary to provide copies of Schedule B compendial analytical procedures unless the procedures are modified. Chromatographic analytical procedures should include system suitability testing (SST). For HPLC and GC procedures, the SST should include as a minimum, resolution and precision (minimum five replicates), but may also include tests such as number of theoretical plates and tailing factor. For TLC procedures, SST might include confirmation of sensitivity and component separation. For greater understanding of the details, definitions, and design of SST, sponsors should refer to the USP, General Chapter <621> Chromatography, which is found in the annual publication of the USP monographs.

5.4.4.3 Validation of Analytical Procedures

The submission should provide copies of the validation reports for the analytical procedures proposed for testing the drug product. The reports should include the protocol used, the results obtained for each validation characteristic, interpretation and discussion of the results, and conclusions reached. The choice of characteristics to be validated should be consistent with the type of analytical procedure and intended purpose.

Procedures drawn from Schedule B compendial monographs normally require at least partial validation since the composition of the product used for validation of compendial procedures is likely to be different from the composition (sample matrix) of the generic product. If a house procedure is developed to replace a compendial procedure for assay or determination of degradation products, the house procedure should be fully validated and its equivalency to the compendial procedure demonstrated.

Further guidance regarding the validation of analytical procedures is available in VICH guidance documents.

5.4.4.4 Batch Analysis

The submission should provide results of batch analyses, including certificates of analysis, for the batches used in the comparative *in vivo* or *in vitro* studies, as well as a minimum of two batches of each strength. The batch size should be at least 10% of full production scale. Bracketing and matrixing of proportional strengths can be applied. The batch number, size, and strength, as well as the date and site of manufacture should be included for each batch reported. The submission should supply quantitative results for quantitative tests. Content uniformity and dissolution results should include the mean, range, and relative standard deviation (RSD).

5.4.4.5 Justification of Specification

The justification of the specification should include the rationale for the inclusion or the exclusion of tests, discussion of the development of methods and acceptance criteria, and the rationale for differences from compendial tests, methods, or acceptance criteria. The justification of specifications should be based on the lots used in the conduct of bioequivalence studies as the performance of the quality attributes should be identical between pre- and post-approval lots.

5.4.5 Packaging

5.4.5.1 Description and Specifications

The submission should provide a description, including packaging materials and specifications, for each primary packaging component that comes into direct contact with the drug product and for functional secondary packaging components that act to protect the product or have a function in drug delivery. The tests to be included in the specification will depend on the packaging material, but would normally include a specific identity test such as IR, and tests related to performance such as thickness.

5.4.6 Stability

The submission should provide the results of stability testing performed to determine how the quality of the drug product varies with time under the influence of environmental factors such as temperature, humidity, and light. The submission should include information on the recommended storage conditions and shelf-life based on these studies.

5.4.6.1 Accelerated and Long-term Studies

The submission should include a stability protocol indicating storage conditions studied and providing information on accelerated and long-term conditions, time points at which samples are taken for analysis, and the tests to be conducted. Results should be provided for a minimum of two batches of each strength in each proposed container/closure system. Bracketing and matrixing can be applied if scientifically justified. For example, if the drug product has a common formulation (compressed to different tablet weights) for a number of strengths, then a minimum of one lot of each strength should be studied for stability. At the time of filing the ANDS, data covering a minimum of six months at the long-term and accelerated conditions should be included.

Normally, 25°C ± 2°C / 60% ± 5% RH would be the long-term condition and 40°C ± 2°C / 75% ± 5% RH would be the accelerated condition. Frequency of testing for the long-term condition would normally be every three months in the first year, every six months in the second year, and annually thereafter. Frequency of testing for the accelerated condition would normally be a minimum of three and six months, but more frequent testing during the first three months may be appropriate. If a failure to meet the acceptance criteria occurs at any time at the

accelerated condition, additional testing should be conducted at the intermediate condition of 30°C ±2°C / 65% ± 5% RH.

Stability results should be presented in tabular form and include batch number, date of manufacture, batch size, container/closure, storage conditions, test intervals completed and proposed, and tests performed with acceptance criteria. If there is more than one packaging format, such a blisters and bottles, then each format should be studied. Analytical procedures that differ from those described in Subsection 5.4.4.2 should be included along with appropriate validation data.

All studies should report appearance, assay, and degradation products, while the other tests to be conducted will depend on the dosage form and route of administration. The submission should supply quantitative results for quantitative tests. Some tests, such as sterility, particulate matter, and bacterial endotoxins, need not be performed at every test interval. For drug products that require reconstitution or dilution, the submission should supply stability results to support the proposed storage periods of the reconstituted or diluted product. Drug products containing preservatives to prevent oxidation or microbial activity should be studied at time zero and at the end of the proposed shelf life to ensure protection of the drug product and the submission should include the results of these studies. Where the antimicrobial preservative lower assay limit is less than 90%, preservative effectiveness studies at the proposed lower limit for preservative content should be conducted.

5.4.6.2 Proposed Storage Conditions and Shelf-life

The submission should provide the proposed storage conditions and shelf-life of the drug product in each commercial container/closure system based on the results of the stability studies. The storage conditions will normally include a temperature range such as 15 – 30°C and may include storage precautions such as “protect from light” or “protect from humidity,” depending on the results of the stability studies.

5.4.6.3 Stability Commitment

When the available long-term stability data does not cover the proposed shelf-life, the submission should make a commitment to complete the studies to the proposed shelf-life. If these studies were not conducted on production scale batches, the submission should make a commitment to place two production scale batches of each strength on stability, along with the stability protocol. Bracketing and matrixing can be applied in the same manner as stated earlier, if scientifically justified.

The submission should make a commitment to establish a continuing stability program of on-going studies for the product, along with a stability protocol.

5.5 Additional Information

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.

5.5.1 Stability of Medicated Feeds

The submission should provide the 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. 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, known as in-use studies, should be carried out at both the lowest and highest levels recommended.

The sponsor should perform assays on feed before and after pelletizing to determine the effects of pelletizing and include this data in the submission. These assays should be repeated 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.

5.5.2 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. The submission should provide data from the assays. 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.

5.5.3 Premixes Proposed for Concurrent Use

For premixes that are recommended for concurrent use, the submission should 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.

5.5.4 Feed Assay Validation

If a drug is to be administered as a medicated feed, the submissions should provide an acceptable method of analysis for the drug, when mixed in typical complete feeds at the recommended level. The submission should include the following information:

- A clear and concise description of the methodology;
- Method performance standards (i.e., recoveries, analytical ranges, limits of quantification and detection, and coefficients of variation for repeatability);
- Critical control points;

- Experimental designs and statistical plans;
- Raw data, chromatograms, tracings, calculated results, statistical results, and quality control for methods;
- Interference studies and documentation;
- Familiarization procedures for new analysts;
- Other related documentation such as ruggedness studies, confirmatory and trace level procedures, collaborative studies, and references; and
- 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.

5.5.5 Samples

The submission should provide samples for analysis, as described below:

- The active ingredient reference standard, in a sufficient quantity to validate the method, with a purity percentage indicated on the label;
- The technical product (10 g), with a purity percentage indicated on the label;
- The drug in finished pharmaceutical form (500 g);
- 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.
- Unmedicated feed blank (1 kg). Supply unmedicated samples of feed from each of the five feeds requested for medicated feed (above). The feeds are to be analyzed to verify the absence of the active ingredient or of interference.

When Agriculture and Agri-Food Canada is prepared to validate the method of analysis, it will request the samples.

5.6 Bioequivalence Studies with Canadian Reference Product

This section of the submission should discuss the studies comparing the ANDS product with the CRP. When bioequivalence studies were conducted to support the ANDS, the submission should simply reference the type of study conducted and where in the submission the results can be found. If the sponsor has requested a waiver from comparative *in vivo* studies, this section of the submission should provide the comparative *in vitro* data to establish pharmaceutical equivalence.

5.6.1 In Vivo Study Waivers

For drug products that may be eligible for an exemption of *in vivo* studies, if appropriate *in vitro* data is presented, refer to Subsection 6.2, “Criteria for Waivers for Immediate-Release Formulations”.

5.6.2 Pharmaceutical Equivalence

When the sponsor requests an *in vivo* waiver, the sponsor must present satisfactory information on pharmaceutical equivalence. In order to demonstrate pharmaceutical equivalence, the generic product and the CRP must be of the same dosage form and contain chemically equivalent drug substances (i.e., the same chemical structure and the same salt).

The demonstration of pharmaceutical equivalence should include the following information:

1. A side-by-side comparison of the formulations, both quantitative and qualitative, if this information is available for the CRP;
2. Comparative analytical testing of a minimum of two lots of generic product and CRP using the drug product specifications established for the generic product;
3. Comparative impurity profiles for a minimum of two lots of generic drug substance, generic drug product, and CRP using a methodology with adequate specificity;
4. Additional testing for solutions could include comparative pH, viscosity, specific gravity determinations, or any test that is relevant for comparison purposes;
5. For soluble powders, medicated premixes, and immediate-release solid oral dosage forms, information on comparative drug substance solubility should be included;
6. For powders intended to be administered as a solution, sponsors should perform comparative dissolution studies (i.e., time to complete dissolution) using the generic product and the CRP.
7. For immediate release solid oral dosage forms, sponsors can use comparative dissolution profiles in three dissolution media, including 0.1 N HCl or simulated gastric fluid without enzymes, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid without enzymes can be used. For drug products for which a USP monograph is available, the apparatus and rotation speed specified should be used. If no USP monograph is available, it would be appropriate to use the method proposed for the generic product. To support a request for an *in vivo* waiver, 12 dosage units of each product should be used in the dissolution study and a sufficient number of test points should be selected to characterize the dissolution profile (e.g., 10, 15, 20, and 30 minutes). The dissolution profiles obtained should be compared using the similarity factor (f_2) which is a measurement of the similarity in the percent dissolution between the two curves as determined by the following formula:

   where R_t and T_t are the percent dissolved at each point.

   The two dissolution curves are considered similar if the f_2 value is ≥50. In order to use mean values, the coefficient of variation should not be more than

20% at the early time points and not more than 10% at the other time points. If both the generic product and CRP dissolve ≥85% of label amount in ≤15 minutes using all three dissolution media, the profile comparison using the f_2 test is not necessary.

5.6.3 Canadian Reference Product

The CRP is to be used in all comparative studies. The most appropriate CRP and the one that must be used if it is available on the market is the first product to receive a Notice of Compliance (NOC) based on a full NDS. If this pioneer product is no longer available in Canada, the next approved product from another manufacturer that also received an NOC can be used. When the sponsor chooses to use a product from another manufacturer that has also received an NOC, VDD requests the sponsor to contact Health Canada to ensure agreement on the substitute CRP. The CRP must have Canadian labelling and a drug identification number (DIN), and be accompanied by proof of purchase in Canada.

5.6.3.1 Use of a Non-Canadian Reference Product

If bioequivalence studies were performed using a product that is not a CRP, the sponsor should demonstrate the equivalence of the product that is not the CRP with the CRP. The demonstration of equivalence should include the following information:

1. Documentation that the non-CRP contains the same medicinal ingredient(s) in the same concentration as found in the CRP marketed in Canada;
2. Documentation that the non-CRP is authorized for marketing by a health authority in a country using drug assessment criteria comparable to those used in Canada;
3. Documentation that the non-CRP is marketed in the country of origin by the same company or corporate entity that currently markets the same medicinal ingredient in the same dosage form in Canada, or that is marketed in the country of origin through a licensing agreement with the company or corporate entity that currently markets the product in Canada;
4. Copies of the labelling for the non-CRP to be used as a reference and of the CRP marketed in Canada;
5. To the extent possible and if the information is available, a side-by-side comparison of the formulations, both qualitative and quantitative;
6. Certificates of analysis for both products, analyzed using the specifications proposed in the ANDS for the generic product;
7. Information on additional testing of solutions, including pH, viscosity, and specific gravity, and any other test that is relevant in establishing equivalency;
8. For immediate release solid oral dosage forms, comparative dissolution profiles conducted as recommended under Subsection 5.6.2, number 7; and

9. Documentation that the non-CRP appears the same as the CRP marketed in Canada, with respect to colour and, in the case of immediate release tablets, shape, size, weight, and type of coating.

6. Part II, Clinical Requirements – Bioequivalence Studies

This part of the document provides guidance for conducting bioequivalence studies to register with the VDD generic versions of off-patent Canadian approved veterinary drugs and for other relevant applications when comparative bioavailability studies are required.

Sponsors are encouraged to consider pre-submission conferences to discuss comparative bioavailability/bioequivalence requirements and/or present study protocols to the CED for guidance on specific requirements prior to conducting such studies.

6.1 Bioequivalence

Bioequivalence is demonstrated when the rate and extent of absorption of two pharmaceutically equivalent formulations of drugs (test and reference) are sufficiently similar, within pre-determined allowable limits, when administered under similar experimental conditions. The underlying principle is that these products should be therapeutically equivalent if they show bioequivalence with respect to each other and, hence, be interchangeable in a clinical setting.

Bioequivalence studies are mostly conducted as pivotal studies to support applications for ANDS for generic veterinary drugs confirmed to be pharmaceutically equivalent to the CRP, as a means to preclude the need for safety and efficacy studies (see subsection C.08.002.1 (1) of the *Food and Drugs Regulations*).

Bioequivalence studies may also be conducted to support a New Drug Submission (NDS) or a Supplemental New Drug Submission (SNDS) for approval of an alternative dosage form, new route of administration, new strength, or a significant manufacturing change which may affect the rate or extent of drug absorption, of new or already approved formulations, respectively.

Because bioequivalence studies can demonstrate comparable animal safety with a reference product only in terms of the active ingredient, differences in excipients in product formulations and different product specifications may result in tissue irritancy and other adverse effects. Hence, sponsors may need to address animal safety aspects of a new product formulation by providing data from additional animal safety studies and/or providing relevant scientific rationale.

It is recommended that bioequivalence studies be conducted according to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) as detailed in the Organisation for Economic Cooperation and Development "Series on Principles of Good Laboratory Practice" or the Veterinary International Conference on Harmonization, "Consensus Guideline" (VICH Topic GL9).

6.2 Criteria for Waivers for Immediate-Release Formulations

6.2.1 When In Vivo Bioequivalence Studies May not be Necessary

In general, there must be an *in vivo* demonstration of a limited acceptable difference in the rate and extent of drug bioavailability associated with the test and reference formulations when administered at the same molar dose and under

the same experimental conditions. However, in certain circumstances, a waiver of *in vivo* bioequivalence studies may be requested for a pharmaceutically equivalent uncomplicated medicinal ingredient of an immediate-release dosage form, when scientifically justified and when accompanied by suitable *in vitro* data. *In vivo* bioequivalence studies are generally unnecessary if the product fulfils one or more of the following conditions:

1. The **formulations are identical** and bioavailability of the reference formulation has been adequately demonstrated in the target species. This condition generally applies to generic formulations that are produced by the same manufacturer as the reference product (same API source and manufacturing process). This may also include reformulated products by the original manufacturer that are identical to the original product except for colouring agents, flavouring agent, or preservatives, which are recognized as having no influence on bioavailability.
2. The product is to be administered as a **parenteral aqueous solution** (intravenous [i.v.], intramuscular [i.m.], subcutaneous [s.c.]) and contains the same concentration of the same active ingredient(s) and excipients as the reference product (differences in buffering agents and/or preservatives with the reference product may be acceptable). The pH and specific gravity of the solution should be the same as for the reference product. The product should not cause an injection site tissue reaction (s.c. and i.m.) that may potentially influence the rate and extent of absorption of the active ingredient and the maximum injection dose volume per injection site should be the same as for the reference product.
3. The product is to be administered as an **oral aqueous solution** and contains the same concentration of the same active ingredient(s), and the same or essentially the same concentration of the same excipients as the reference product, and the excipients do not affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g., polysorbate 80, polyethylene glycol, ethanol, surfactants or excipients that may affect transport proteins), solubility (e.g. co-solvents), membrane permeability or drug metabolism, and/or inactivate the active ingredient. Exceptions could be justified for colouring or flavouring agents which are not known to influence the absorption characteristics of the drug.
4. The product is to be administered as a solid oral immediate-release dosage form of **proportional multiple strengths** when *in vivo* bioequivalence (generic) or extensive clinical safety and efficacy data (innovator) has been demonstrated at the highest intended labelled dose and all of the following conditions are met:
   (a) The dosage strengths differ only by the mass of the active ingredient(s);
   (b) The active ingredient(s) is known to be associated with linear pharmacokinetics;
   (c) The composition of all formulations are qualitatively identical;

(d) The ratio between concentrations of active ingredient(s) and excipients among the different strengths is identical (proportional formulations);

(e) The dissolution profiles between all strengths are considered similar (refer to Subsection 5.6.2, "Pharmaceutical Equivalence").

5. The product is a **simple topical solution Category I** (dermal, ophthalmic, otic, and nasal) intended for local therapeutic effects only.
6. The product is as an **inhalant volatile anesthetic solution**.

Sponsors wishing to make a request for a waiver are encouraged to consult with the VDD for guidance as to the suitability and specific data requirements in a pre-submission conference, prior to submitting an application. A waiver request accompanied by a summary of the supportive *in vitro* data (including dissolution profiles- see Subsections 5.6.2 and 6.4), Certificates of Analysis, and a side by side comparison of the medicinal and non-medicinal ingredients of the test and reference products, should be included in the submission in lieu of Part III and Part IV of the *Guidance for Industry: Preparation of Veterinary New Drug Submissions*.

6.3 Conduct of *In Vivo* Bioequivalence Studies

6.3.1 General Considerations

6.3.1.1 Reference Product Selection

The selected CRP, as defined in C.08.001.1 of the *Food and Drugs Regulations*, must be the original off-patent approved pioneer (also known as innovator) product currently marketed and approved in Canada, for the same indications (claims, target species) and must contain the same concentration(s) of the active ingredient(s), as intended for the generic product. If this pioneer product is no longer available, then the first approved generic equivalent product can be used as long as it is currently marketed in Canada.

If bioequivalence studies are conducted in another regulatory jurisdiction, the CRP should be preferentially used as the reference product. A foreign-registered reference product may be used; however, the sponsor must provide evidence that the reference product formulation is qualitatively and quantitatively the same to that registered by the VDD, including the same potency, meeting the same compendial or other applicable standards of identity, strength, quality and purity (and where applicable, content uniformity), disintegration times, and dissolution rates (refer to Subsection 5.6.3).

The sponsor should provide certificates of analysis to confirm that the batches of the test and reference products used in the bioequivalence studies comply with product specifications. The sponsor should also provide proof of purchase of the

CRP (photocopy of CRP label or purchase invoice) including the DIN, expiry date, lot number, product name, and manufacturer.

The formulation of the test product used in the bioequivalence studies must be the same as the final formulation intended to be marketed.

6.3.1.2 Species Selection

To minimize variability that would not be attributed to the different drug formulations, selected animals should be clinically healthy and from a homogenous group (age, breed, weight, hormonal and nutritional status, level of production, etc). Weight range should be kept to a minimum to allow for the same total dose to be administered across subjects.

Because species selection is considered a factor that may potentially interact with the drug formulation, studies should be conducted for each major target species for which the reference product is approved for on the label.

If the drug is to be used in minor species, demonstrating bioequivalence in a relevant major species may be sufficient under the following conditions:

- Only species with minor physiological differences which do not produce important differences in drug absorption are considered (e.g., cattle and sheep); and
- Bioequivalence was confirmed in the major target species via a blood-level bioequivalence study rather than a pharmacological or a clinical end-point study.

The experimental subjects should be drug-free for a minimum of two weeks prior to the study or longer depending on the biological half-life of the active ingredients.

6.3.1.3 Dose Selection

Bioequivalence studies should be conducted at the same dose for the test and reference products. The dose should be the highest labelled dose approved for the reference drug for which the sponsor has demonstrated linear kinetics through published literature or a pilot study. This rule applies for products labelled for a single claim and labelled for multiple claims involving different pharmacological action (therapeutic and production claims), in the case of blood-level studies.

For drugs with a documented wide margin of safety and linear kinetics, it is also possible to conduct the *in vivo* bioequivalence study at higher than approved dose (two to three times the highest approved dose) to achieve measurable blood levels and avoid splitting tablets. Splitting (or shaving or filing) tablets is not considered acceptable by the CED, unless tablets are scored and dosing by half increments is representative of the clinical setting. In this case, the study report should provide tablet uniformity data as supportive data.

The potency of the test and reference products should be assayed prior to conducting the bioequivalence study to ensure compendial specifications are met.

Potencies of both products should be within 95 to 105% of nominal concentrations and the potency of the test and reference lots should not differ by more than ± 5% as normalization to account for any potency differences is considered unacceptable by the CED. Certificates of analysis should be provided for both the test and reference products.

6.3.1.4 Route of Administration

As per the *Regulations*, the route of administration must always be the same for the proposed generic product as for the CRP. When the test product is intended for more than one route of administration, all routes should be tested since generic and innovator products should be clinically interchangeable. If not all routes are tested, sponsors are encouraged to consult with the CED prior to filing an ANDS in order to discuss the suitability of a partial label (refer to Section 8. Labelling).

6.3.1.5 Fed vs. Fasted State

Feeding may either enhance or interfere with the active ingredient's absorption, depending on the characteristics of the active ingredient(s) and the formulation. Feeding may also increase the inter- and intra-individual variability in the rate and extent of absorption. For these reasons, a fasted state is recommended for conducting bioequivalence studies for immediate-release oral formulations unless it would be unsafe to administer the formulations without food or if the CRP label indicates that the product is limited to the administration in the fed state. Fasting and feeding conditions should be fully described in the protocol, giving careful consideration to the pharmacokinetics of the active ingredient(s) and animal welfare.

Both fasted and fed states are necessary for enteric coated and oral sustained release products, for drugs known to have a high bioavailability in the fed state, for drugs exhibiting non-linear kinetics, or a narrow therapeutic ratio.

The study protocol should provide the scientific rationale for conducting a bioequivalence study under fasting and/or feeding conditions.

6.3.1.6 Criteria for removal of subjects

Detailed criteria for removal of subjects from the bioequivalence study should be included *a priori* in the study protocol and adequately justified in the study report. Outliers can not be arbitrarily discarded simply to narrow the 90% CI or fit the pre-determined acceptance criteria for reasons other than a documented clinical (physiological or pathological problem) and/or a defined experimental error. Withdrawal of animals and deletion of data must be reported and adequately justified. No more than 5% of subjects in total can be excluded from an *in vivo* study. Unbalanced bioequivalence studies (unequal number of subjects per group) are not recommended.

6.3.1.7 Animal Welfare

The CED recommends that the sponsor consults the following website for the Canadian Council on Animal Care (CCAC) to ensure that all animal ethics requirements are respected when conducting *in vivo* bioequivalence studies <www.ccac.ca> and <www.sciencemag.org/cgi/reprint/312/5774/700.pdf>. A copy of the Animal Ethics Committee approval, as appropriate for each country in which the trial was undertaken, should be included in the study report.

6.3.1.8 Selection of the Bioequivalence Study

There are three types of *in vivo* studies available to directly or indirectly assess bioequivalence between the test and reference products: blood-level study, pharmacological end-point study, and clinical end-point study. Bioequivalence testing must be conducted using the most appropriate method available for the specific use of the product. The study protocol should justify the selection of the type of *in vivo* bioequivalence study.

For all three types of *in vivo* studies, the sponsor is encouraged to discuss the planned study protocol in advance with the CED to avoid the possible *post hoc* finding that the studies failed to meet applicable statutory or regulatory requirements and to find out if additional studies (e.g., palatability studies, tissue irritation studies) will be required.

6.3.2 Blood-level Study

A blood-level study is the bioequivalence study that is considered the most sensitive and accurate measure of the rate and extent of drug absorption. The blood-level study should be chosen over the pharmacological and clinical end-point studies, whenever possible, especially when drug concentrations can be readily measured in the blood.

Bioequivalence data is required for each active ingredient present in the product formulations. Since the parent compound is most sensitive to differences in formulations, it is accepted that bioequivalence studies should be solely based on the parent compound. In some situations, however, measurement of a metabolite may be necessary instead of the parent compound, if, for instance, the concentration of the parent compound is too low to be accurately measured (e.g., major difficulty in analytical method, the product is unstable in the biological matrix, or the half-life of the parent compound is too short). Bioequivalence determinations based on metabolites should be justified in each case, bearing in mind that the aim of a bioequivalence study is to compare the *in vivo* performance of the test and reference products.

6.3.2.1 Study Design Considerations

1. Single-dose studies

A single-dose study conducted at the highest labelled dose of the reference product is generally recommended for the demonstration of bioequivalence. The

study should be designed in such a manner that the formulation effect can be distinguished from other effects. A two-period, two-sequence crossover design is recommended as it eliminates a major source of variability (i.e., between subject differences in the rates of active ingredient absorption, clearance, and volume of distribution). The allocation of subjects to the treatment sequences should be randomized. The study protocol should provide the randomization scheme.

When the length of the washout period is incompatible with a crossover design (e.g., substances with very long half-lives or studies performed with growing animals) or when blood sampling is limited (e.g., poults, chicks, fish), a parallel group design could be considered; other study designs may be acceptable. The choice of the study design, however, should be justified in the study protocol.

2. Multiple-dose studies

Single dose studies are preferred as the potential to detect a difference in the rate of absorption is lower if the active ingredient has accumulated. Multiple dose studies should be scientifically justified and should be considered if, for example, the assay sensitivity is inadequate for accurate quantification by the analytical method of the active ingredient(s) after a single-dose administration, or for drug products with complex pharmacokinetics (e.g. modified-release dosage forms, non-linear kinetics), in addition to single dose studies.

3. Selection of the number of subjects

The number of subjects must be appropriate for statistical analysis and should be carefully estimated and justified in the protocol. Pharmacological and clinical end-point studies generally require more subjects than blood-level studies. Pilot studies or reference to scientific literature are recommended as a means of estimating the appropriate sample size for the pivotal *in vivo* bioequivalence study.

Sponsors are encouraged to consult Hauchke, D et al, 1999. *Sample size determination for proving equivalence based on the ratio of two means for normally distributed data*. Statistics in Medicine, 18: 93-105, for detailed information on how to determine the appropriate number of subjects for *in vivo* bioequivalence studies.

Failed bioequivalence studies may be used as pilot studies to support the design of more suitable pivotal *in vivo* bioequivalence studies. Results of failed studies should not be pooled with newly generated data to increase the sample size. Pooling of data should only be done under stringent statistical conditions of a "sequential analysis" and the intermediate evaluation of the dataset should be planned *a priori*.

6.3.2.2 Pharmacokinetic Considerations

1. Sampling time

The total number of sampling times will depend on the concentration-time profile curvature and the anticipated variability of the bioavailability data including pharmacokinetic (PK) variability, assay error, and differences between the test and reference products in absorption kinetics. A pilot study or reference to scientific literature may be needed to determine appropriate sampling times and duration depending on the drug's disposition.

For immediate-release formulations, the sampling period should adequately define the peak concentration and the extent of the absorption and elimination by extending to at least three terminal half-lives beyond the time to maximum concentration (Tmax). For modified-release formulations, the duration of sampling must be adequate to cover the entire absorption phase associated with the test and reference formulations.

Sampling times must be the same for the test and reference products to allow for proper statistical analysis.

2. Washout period

The duration of the washout period in a crossover study should be approximately 10 times the terminal half-life to ensure that 99% of the administered dose has been eliminated from the body. If more highly complex kinetic models are anticipated (e.g., active ingredient for which long withdrawal times have been assigned due to prolonged tissue-binding), or for an active ingredient with the potential for physiological carry-over effects, the washout period should be adjusted accordingly.

6.3.2.3 Pivotal parameters for blood-level studies

In general, in single-dose studies, the Area Under the Curve ($AUC_{0\text{-}LOQ}$ or $AUC_{0\text{-}t}$ and $AUC_{0\text{-}INF}$), the maximum concentration (Cmax), and the Tmax must be determined as bioequivalence is based on these pivotal PK parameters. In multiple-dose studies, bioequivalence is determined by estimating the Area Under the Curve ($AUC_{0\text{-}\tau}$), the maximum concentration at steady-state ($Cmax_{ss}$), the minimum concentration at steady-state ($Cmin_{ss}$; usually three sequential Cmin values are compared to confirm SS), and the time to maximum concentration at steady-state ($Tmax_{ss}$). To avoid potential bias, pivotal parameter comparisons should be based on observed rather than fitted data.

The comparison of the test and reference product value for the non-infinity estimate, $AUC_{0\text{-}LOQ}$ or $AUC_{0\text{-}t}$, provides the closest approximation of the measure of uncertainty (variance) and the relative bioavailability estimate associated with $AUC_{0\text{-}INF}$ (i.e., the full extent of product bioavailability), as long as the duration of sampling times is sufficiently long to demonstrate $AUC_{0\text{-}LOQ}/AUC_{0\text{-}INF} \geq 0.80$ for each subject. The study report should include individual $AUC_{0\text{-}LOQ}/AUC_{0\text{-}INF}$ results.

6.3.2.4 Statistical Analysis

To indicate product bioequivalence, the pivotal parameters must be associated with a 90% confidence interval (CI), which falls within a set of acceptable limits. This method is equivalent to a two one-sided test procedure with the null hypothesis of bio-inequivalence at a 5% significance level. An Analysis of Variance (ANOVA) is necessary to estimate the error variance needed for the calculation of the 90% CI, while taking into account sources of variation that can be reasonably assumed to have an effect on the response variable, such as formulation, period, sequence tested against animal-nested-in sequence effects, and where appropriate, gender and gender-by-formulation effects. The presence of a statistically significant sequence effect must be handled appropriately by re-designing the study protocol to minimize this effect or the first period of the crossover design may be analyzed as a parallel design, providing statistical power is still adequate for this study design.

Sponsors should provide ANOVA tables (including all *p* values) and summary statistics such as means, medians, geometric means, minimum and maximum concentrations, and coefficients of variation in the study report.

Sponsors are encouraged to consult Health Canada's *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies*, *Part A: Oral Dosage Formulations Used for Systemic Effect* and the United States Federal Drug Administration (FDA) Center for Veterinary Medicine (CVM) *Guidance for Industry #35: Bioequivalence Studies* for detailed information on 90% CI calculations and statistical requirements.

6.3.2.5 Bioequivalence Acceptance Intervals for PK Parameters

The following equations may be used in the calculations of the lower and upper bounds of the 90% CI for $AUC_{0\text{-}INF}$, $AUC_{0\text{-}t}$ and Cmax estimated from natural log-transformed data resulting from a cross-over study:

$$L = (\text{mean } \ln X_T - \text{mean } \ln X_R) - t_{nA+nB\,-\,2;\,0.05} \bullet s\,[½\,(1/n_A+1/n_B)]^{0.5}$$

$$U = (\text{mean } \ln X_T - \text{mean } \ln X_R) + t_{nA+nB\,-\,2;\,0.05} \bullet s\,[½\,(1/n_A+1/n_B)]^{0.5}$$

where L is the lower confidence bound, U is the upper confidence bound, T and R are the test and reference products respectively, n_A and n_B are the sample sizes for the test and reference products in each period respectively, X is the pivotal PK parameter (AUC or Cmax), and s is the square root estimator of the error variance σ^2 from the ANOVA table.

The calculated confidence bounds for each parameter are backtransformed (e^L and e^U) in order to be expressed on the original scale of measurement. The PK parameters to be tested, the 90% CI calculation method, and the 90% CI bounds must be stated *a priori* in the study protocol.

For AUC and Cmax, the acceptable criteria is that the Geometric Mean Ratio (GMR Test/Reference) and the 90% CI should be entirely contained within the limits of 0.80–1.25 or 80% to 125%, where $(e^L - 1) \times 100$ and $(e^U - 1) \times 100$ should fall within - 20% and + 25%.

A tighter acceptance interval may be needed in the case of substances with a narrow therapeutic range.

For Tmax, in general, a clinical assessment rather than a derived mathematical estimate is acceptable. However, for time-dependant drugs (early time of onset or rapid rate of absorption), an absolute interval of variation should be selected recognizing that a ± 20% variation for a Tmax of 10 minutes does not have the same impact as a ± 20% variation for Tmax of 120 minutes.

The study report should be sufficiently detailed to enable the PK and statistical analyses to be repeated. Failure to fall within these limits for any pivotal PK parameter results in a conclusion of bio-inequivalence.

6.3.2.6 Validation of the Bioanalytical Method

Submissions should present bioanalytical methods that are well characterized, fully validated, and documented to yield reliable results that can be satisfactorily interpreted. The determination of bioequivalence is dependent on reliable, precise, and accurate measurement of the active ingredient(s), or its metabolite(s), or both, as a function of time.

The main characteristics of a bioanalytical method essential to ensure the acceptability of the performance and the reliability of analytical results are:

(1) stability of the stock solutions and of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage;

(2) specificity;

(3) accuracy;

(4) precision;

(5) LOQ; and

(6) analytical system reliability.

The validation of a bioanalytical method should comprise the following two distinct phases:

1. Pre-study phase in which compliance of the assay with the characteristics listed above is verified.
2. Study phase in which the validated bioanalytical method is applied to the actual analysis of samples from the bioequivalence study to confirm the validity of the determinations. A calibration curve should be generated for each analyte in each analytical run and used to calculate the concentrations of the analyte in the unknown samples in the run. Several separately prepared quality control (QC) samples (low, medium and high concentrations) should be analyzed with the processed test samples at intervals based on the total number of samples. The QC samples (minimum 6 samples in each analytical run per concentration) should be stored frozen with the incurred samples.

All samples obtained for both the test and reference products should be analyzed using the same method and all procedures should be performed according to Standard Operating Procedures (SOPs). Any modification of the bioanalytical method before and during the analysis of study specimens may require adequate revalidation. Sponsors should report and justify all modifications.

6.3.3 Pharmacological End-point Study

Pharmacological end-point studies are used when a drug induces physiological changes over time related to its indications for use and when the measurement of the rate and extent of drug absorption in blood cannot be achieved, or when blood concentrations cannot be used as surrogate end-points for the demonstration of efficacy and safety of the particular pharmaceutical product in the target species (e.g., for drugs with local effects without systemic absorption).

Demonstration of bioequivalence between the test and reference products for any given pharmacodynamic (PD) effect does not guarantee the bioequivalence of other effects, as concentration-response curves may be different for different drug effects. Each label claim must be accompanied by the appropriate pharmacological end-point study.

6.3.3.1 Study Design

Pharmacodynamic assessment determines drug effect as a function of time, in a manner analogous to a PK assessment of drug blood concentration versus time. Timing and duration of effect monitoring and adequate dispersion of data over the entire effect range are important to ensure a representative characterization of the label claim.

If the generic product contains excipients that have the potential to cause tissue irritation or an active ingredient that may potentially cause adverse effects even if the blood concentration is not therapeutically important, the sponsor may need to provide additional safety and/or systemic absorption data to confirm animal safety and/or residue.

6.3.3.2 Selection of Pivotal Parameters

The clinical evaluation of the selected target parameters(s) should be appropriately validated and justified in the study protocol and summary report. The chosen pharmacological effect(s) should be amenable to accurate, precise, and reproducible quantification. Since PD assessment necessitates characterization of the drug effect as a function of time, the pivotal parameters for this type of study are generally Area Under the Effect Curve (AUEC), maximum effect (Emax), and corresponding time at maximum effect (tEmax).

Sponsors should include evidence that the PD comparisons are being generated within a portion of the profile where inequivalent exposure can be detected i.e. during the slope.

6.3.3.3 Statistical Analysis and Bioequivalence Acceptance Intervals

The number of subjects to be included in the study will depend on the variability of the target parameters and the acceptance range, and to ensure adequate statistical power, is usually much higher than the number of subjects in blood-level studies. The sponsor should provide scientific support (through published literature or pilot studies) for the calculation of the appropriate sample size in the study protocol.

Statistical considerations for the assessment of PD pivotal parameters (AUEC, Emax, and tEmax) are, in principle, the same as for corresponding PK parameters (refer to Subsection 6.3.2.3). However, the conventional acceptance range as applicable to blood-level studies is generally not appropriate (too large) in most cases. This range should therefore be defined *a priori* in the study protocol on a case-by-case basis. The sponsor is thus encouraged to contact the CED prior to conducting this type of study to discuss the acceptable confidence interval limits for the particular PD effect(s) of the active ingredient(s) to be tested.

6.3.4 Clinical End-point Study

The clinical end-point study is used when blood concentrations cannot be measured or are not relevant, and pharmacological effects over time cannot be monitored. A clinical end-point study is conducted by comparing the test product to the reference product and a negative control. This generally applies to, but is not limited to the following products: ectoparasiticides (topical administration), anthelmintics (oral administration with *in situ* gastrointestinal activity), locally active topical drugs (dermal, ophthalmic, otic and inhalant preparations), and intramammary products.

6.3.4.1 Study Design

Clinical end-point studies are generally well-controlled, double blinded studies using target animals in relevant feeding and husbandry conditions, with either naturally or experimentally induced disease. This type of study is generally conducted using a parallel group design with, at a minimum, three treatment groups (negative control(s), test, and reference products). The purpose of the negative control is to confirm the sensitivity and validity of the study.

The target parameter(s) or response(s) to be measured must be based on the labelled claims of the reference product. Demonstration of bioequivalence between the test and reference products for any given clinical response does not guarantee the bioequivalence of other clinical response or therapeutic effects. Each label claim should be accompanied by the appropriate clinical end-point study. The clinical evaluation of the selected target parameter(s) should be appropriately validated and justified in the study protocol as well as in the summary report. When applicable, it may be relevant to include safety end-points in the final comparative assessments.

The dose and duration selection should reflect common clinical use of the reference product and the experimental sensitivity. In the event of foreign-

conducted studies, environmental conditions (e.g., climate, pasture versus feedlot, etc.) and medical conditions (e.g., sources of parasite or bacteria) should be similar to those expected in Canada.

If the generic product contains excipients that have the potential to cause tissue irritation or an active ingredient that may potentially cause adverse effects even if the blood concentration is not therapeutically important, the sponsor may need to provide additional safety and/or systemic absorption data to confirm animal safety.

6.3.4.2 Statistical Analysis

When considering sample size, it is important to consider whether the pen or the individual animal is the appropriate experimental unit. When testing formulations with subjective claims (e.g., pain relief), the acceptable unit is the individual animal. The number of subjects to be included in the study depends on the variability of the target parameters and the acceptance range, and to ensure adequate statistical power, is usually much higher than the number of subjects in blood-level studies. The sponsor should provide scientific support (through literature or pilot studies) for the calculation of the appropriate number of subjects needed, in the study protocol.

Statistical analysis is used to compare the test and reference products. In addition, a traditional hypothesis test is performed comparing both the test and the reference products separately to a negative control. This hypothesis test is conducted to ensure that the study has adequate sensitivity to detect differences when they actually occur. If no significant improvement ($p > 0.05$) is seen in the parameter (i.e., the mean of the test and the mean of the reference products are either or both not significantly better than the mean of the negative control), the study will generally be considered inadequate to demonstrate bioequivalence. When both the test and reference products have been shown to be superior to the negative control, the determination of bioequivalence is generally based on pre-specified acceptance criteria taking into account the natural course of the disease, the efficacy of available treatments, and the chosen target parameter(s).

The sponsor is encouraged to contact the CED prior to conducting this type of study to discuss the acceptable criteria for establishing bioequivalence for the clinical effect(s) of the active ingredient(s) to be tested.

If the negative control is omitted for ethical or practical considerations, the omission should be justified in the study protocol. In this case, responses to the test and reference products should each provide a statistically significant improvement over baseline.

If the results are ordered by categorical data (e.g., excellent, good, fair, or poor), a non-parametric hypothesis of no difference between test product and negative control, and between the reference product and the negative control, should be performed.

6.4 Dissolution Testing

In vitro data generated from dissolution studies are generally used to support requests for waivers of *in vivo* bioequivalence studies for immediate-release solid oral dosage forms (refer to Subsections 5.6 and 6.2).

An *in vitro* test should not be used when the mean dissolution time is higher than the mean absorption time, as long dissolution times are difficult to extrapolate between *in vitro* and *in vivo* conditions.

The methodology and apparatus in accordance with pharmacopoeia requirements (Ph Eur, BP, USP, CSP) and the conditions of testing (pH, temperature, dissolution medium, stirring, etc.) should be clearly defined *a priori* in the study protocol. Replicates of measures should be taken to account for the variation inherent to the analytical method. A validated analytical method should be used with accuracy and precision within established acceptable limits. For rapidly dissolving products, it may be necessary to generate an adequate profile, such as sampling at five-minute intervals. Only one measurement should be considered after the 85% dissolution of both the test and reference products.

The similarity between dissolution profiles of the test and reference products should be demonstrated statistically using the similarity factor (f_2).

For detailed information on experimental design of dissolution studies, and calculation and interpretation of f_2, refer to Subsection 5.6.2, number 7.

6.5 Special Topics

6.5.1 Modified-Release Formulations

Modified-release dosage forms are drug products that differ from conventional immediate-release dosage forms in the rate at which the drug is released (disintegration, de-aggregation, dissolution, absorption). Due to the greater likelihood of an increase in inter-individual variability in bioavailability, including the possibility of dose-dumping, an increase in the risk of adverse effects such as gastrointestinal irritation, or of an accumulation when the drug is given in repeated doses at the recommended dose intervals, the sponsor should contact the CED for guidance on specific requirements prior to conducting bioequivalence studies for this type of dosage formulation.

Often, modified-release products are intended for single use and no accumulation between doses is expected. In these cases, single-dose bioequivalence data is normally sufficient to demonstrate similarity between products. For prolonged release formulations intended for repeated dosing (to reduce fluctuations during steady-state treatment or to reduce frequency of administration) where there is accumulation between doses, demonstration of bioequivalence should be based on a multiple-dose study (refer to subsections 6.3.2.1 and 6.3.2.3) in addition to the fasted and fed single dose studies.

Sponsors are encouraged to consult Health Canada's *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies*, *Part B: Oral*

Modified Release Formulations for detailed information on 90% CI calculations and statistical requirements.

6.5.2 Generic Formulations for Use in Feed or Drinking Water

A generic soluble powder of an uncomplicated medicinal ingredient for use in drinking water is generally eligible for a waiver of *in vivo* studies on the basis of the product being an aqueous oral solution at time of administration.

In order to be granted a waiver, *in vitro* data requirements for pharmaceutically equivalent soluble powders should include:

1) solubility data to ensure that, prior to administration, the product will go into solution under the range of physical conditions that a user of the product would typically encounter when adding the soluble powder to animal drinking water in the field; and
2) the product's formulation, to ensure that there is no difference between the generic and reference products likely to adversely affect the performance of the generic product by causing a direct pharmacological effect (e.g., altered GI transit time, membrane permeability, or drug metabolism), or by inactivating the active ingredient (e.g., chelating agent).

If a highly water soluble active ingredient present in a generic feed premix is shown to rapidly dissolve when exposed to a range of physiological pH values representative of *in vivo* conditions, it will likely go rapidly into solution when exposed to the fluids in the GI tract and effectively behave as an oral solution shortly after administration. Accordingly, the CED will consider waiver requests that include:

1) the demonstration of solubility across a pH range of 1.2 to 7.5 (low, medium and high); and
2) similar product formulation to ensure that there are no ingredients (including biomass) in the generic formulation that could adversely affect the performance of the generic product by causing a direct pharmacological effect (e.g., altered GI transit time, membrane permeability, or drug metabolism), or by inactivating the active ingredient (e.g., chelating agent).

6.5.3 Changes in Dosage Form, Strength, Route of Administration, API Source or Manufacturing Process

According to subsection C.08.002.1 (1) of the *Food and Drugs Regulations*, changes in dosage form, strength, route of administration, or condition of use of a generic product compared to the CRP would not fall within the eligibility criteria defined for filing an ANDS. The above changes to a proposed generic product in comparison to the CRP require the sponsor to apply as a new drug by filing an NDS. When sponsors propose minor formulation or manufacturing process changes, or a change in dosage form, strength, or route of administration to their own already approved innovator products, the above guidelines may be used to demonstrate that these proposed changes do not affect the rate and extent of

absorption of the active ingredients(s). In these cases, filing of a Supplemental New Drug Submission (SNDS) is generally acceptable.

6.6 Palatability Studies

For several dosage forms, a palatability study may be needed for the proposed new drug in order to permit label claims including "flavoured" and reference to taste or palatability. For chewable tablets and flavoured oral solutions, for example, sponsors should provide evidence of the palatability of their proposed formulation in the target species.

6.7 Study Report

The bioequivalence study report should include complete documentation of its protocol, conduct, and evaluation of the bioequivalence study and comparative dissolution study, according to the VICH "Consensus Guideline" (VICH GL9).

The incidence, severity and duration of adverse reactions and side effects observed during the bioequivalence study must be reported in the submission report. The probability that an adverse effect is drug-induced is to be judged by the principal investigator.

6.8 Pharmacovigilance Data

For a timely review, the CED requests sponsors provide a Periodic Summary Update (PSU) report, as part of their submission, in cases when the proposed drug formulation is currently marketed in other countries (refer to VICH Guideline 29: *Pharmacovigilance of veterinary medicinal products: management of periodic summary update reports (PSUs)*). If not submitted within the ANDS, a PSU report may be requested in a Minor Information Request (MIR) during review.

7. Part III, Human Safety Requirements

This section of the guidance document pertains to generic veterinary drugs used in food-producing animals. However, it may also be applicable to other animal species, if the proposed use of veterinary drugs in the ANDS is considered to have potential human health concerns. Human safety evaluations of ANDSs include safety assessment of drug residues in edible tissues and food products (milk, eggs, and honey) intended for human consumption, and under certain circumstances, evaluations of toxicological and microbiological safety data.

Sponsors are encouraged to consult the Human Safety Division of the VDD for specific human safety data requirements prior to submission of their applications.

7.1 Laboratory Animal Toxicity Studies

The toxicological data, including the acceptable daily intakes (ADI) established for the Canadian Reference Product (CRP), are applied to the generic versions of the CRP. Hence, laboratory animal toxicity studies are generally waived for an ANDS. However, under certain circumstances, for example, when new toxicological information has emerged regarding the safety of the active ingredients since the approval of the CRP, additional toxicity data may be required for the human safety assessment.

7.2 Microbiological Safety Studies

The microbiological safety studies apply only to veterinary antimicrobial products (e.g., antibacterials) and are generally waived for the generic products. However, the VDD regularly reviews the microbiological safety, including human health risks associated with antimicrobial resistance, of the approved antimicrobial products. For veterinary antimicrobial drugs identified for review, drug sponsors, including those of generic drug products, may be required to provide additional data for the microbiological safety assessments. This additional data may include the effects of the antimicrobial drugs on human gut microflora (e.g., determination of microbiological acceptable daily intake [mADI]) and on human health risks associated with antimicrobial resistance. Data relevant for such assessments are similar to those described in Subsection 9.2.1, "Veterinary Antimicrobial Products," *Guidance for Industry: Preparation of Veterinary New Drug Submissions* (Health Canada, 2007).

7.3 Residue Studies

This section provides guidance for situations or conditions under which waivers of the drug residue depletion studies could be granted. It also describes conditions under which the relevant studies will be required. Overall, the information submitted on residues should be sufficient to confirm or establish that the withdrawal period / withholding time of the generic drug product is identical to that of the CRP.

Requests for waiver of the residue depletion studies will be considered on a case-by-case basis. When a sponsor requests a waiver for residue depletion study requirements, an assessment of an ANDS is conducted to determine whether the generic drug product is

identical to the CRP. When a waiver cannot be granted, the residue depletion studies to confirm or establish that the withdrawal period of the generic product is the same as approved for the CRP will be required.

7.3.1 Situations and Conditions When the Residue Data Requirements Could Be Waived

For certain products for which the waivers of pharmaceutical equivalence and bioequivalence study requirements have been granted, residue data to confirm the withdrawal period assigned to the CRP will not be necessary. Please refer to Subsection 5.6 and Subsection 6.2 of this guidance document for the waiver requirements for pharmaceutical equivalence and bioequivalence, respectively. As described in Subsection 7.3.2 of this document, there are situations where an abbreviated depletion study (see Subsection 7.3.3 below) may be required even after granting pharmaceutical equivalence and bioequivalence of the generic products.

If bioequivalence is granted based on blood-level studies, which should cover the absorption, distribution, and elimination phases of the active ingredients vs. the time profile, and the assay method used is sensitive enough to measure the residue levels in blood for the entire withdrawal period established for the CRP, the residue depletion data requirements may be waived provided that the correlation data between the depletion of drug residue from plasma and target tissue is known.

The waiver of residue data requirements may be granted to medicated premix products or soluble powder oral dosage forms that are pharmaceutically equivalent to the CRP.

7.3.2 Situations and Conditions When the Residue Data Requirements Cannot Be Waived

In various situations, the residue depletion data requirements cannot be waived. The descriptions below specify the situations where sponsors must submit the data from an abbreviated residue depletion study (see Subsection 7.3.3) or a comprehensive residue depletion study (see Subsection 7.3.4 below).

In general, when the waivers for pharmaceutical equivalence or bioequivalence cannot be granted, a waiver for the residue depletion study requirements will also not be considered. In most cases, data from an abbreviated residue depletion study will be required to confirm the withdrawal period of the generic products.

An abbreviated residue depletion study is generally required in food-producing animals for the following product formulations:

- Non-aqueous products for injection by subcutaneous and/or intramuscular routes;
- Intra-mammary infusion in dry cows;
- Pour-on formulations;

- Implants; and
- Intra-ruminal devices.

For products where the formulation (e.g., pH, vehicle, excipients, etc.) differs from that of the CRP, and concerns about residue depletion are evident, data from abbreviated residue depletion studies to confirm the withdrawal period may still be required even though the generic product is considered to be pharmaceutically equivalent and the waiver of bioequivalence study requirements has been granted.

Some generic drug products may have the same plasma disposition profile as the CRP at the concentrations used in bioequivalence studies, but may have very different tissue disposition kinetics when followed out to the withdrawal period for the CRP. In these cases the submission must include data from an abbreviated residue depletion study. Similarly, differences in the location of injection sites or evidence of significant injection site tissue reaction might lead to altered tissue residue depletion pattern, which may result in the submission requiring data from an abbreviated residue depletion study.

In generic drug submissions where residue depletion studies are not waived, and when the CRP is indicated for use in more than one food-producing species, an abbreviated tissue residue depletion study will generally be required for each major food-producing species on the label. This is because the data derived from one animal species generally cannot be extrapolated to another species due to possible species differences in drug partitioning or binding in tissues. These differences could magnify a small variation in the rate and extent of drug absorbed into a large variation in marker residue concentrations in the target tissue.

For a CRP approved for use in major and minor species, data from an abbreviated residue depletion study from a major species on the label is generally sufficient for confirmation of withdrawal periods for all related minor species on the label.

In all cases where no residue data are available on file for the CRP, the ANDS must contain data from the tissue residue depletion studies to meet the current standards of the guidelines.

A sponsor seeking a shorter withdrawal period for the generic product must provide the data from a comprehensive residue depletion study to support the proposed shorter withdrawal period.

7.3.3 Abbreviated Residue Depletion Study

The purpose of an abbreviated residue depletion study is to confirm the withdrawal period of a generic version of the CRP.

This study should be conducted in a minimum of 6 animals (evenly mixed by sex) for large and medium sized animals (e.g., cattle, swine, sheep, etc.), 12 birds for poultry, 15-20 for fish, and 20 lactating dairy animals (e.g., cows, goats, and sheep), treated with the product at the same dose and using the same route and frequency of administration as recommended for the CRP. The study should

include a control (non-treated) animal. The concentration levels of the marker residue or residues in the target tissue, if known, at the recommended withdrawal period for the CRP, will need to be determined by using the validated analytical method (regulatory method).

A single-point statistical procedure will be used to determine the upper tolerance limit of residue concentrations with 95% confidence for 99% of the animal population, which should be below the established maximum residue limit (MRL) at the established withdrawal period for the CRP.

In case the residue levels in target tissue, if known, at the established withdrawal period for the CRP, exceed the established MRL, data from a comprehensive residue depletion study (see Subsection 7.3.4 below) should be provided as described in Subsection 9.3.2.2.3, "Drug Residue Depletion Studies," *Guidance for Industry: Preparation of Veterinary New Drug Submissions* (Health Canada, 2007).

7.3.4 Comprehensive Residue Depletion Study

The purpose of a comprehensive residue depletion study is to establish a withdrawal period for the generic drug product.

This study should be conducted in a minimum of 20 animals, divided into either four or five groups of four or five animals each. The study should include at least one control (non-treated) animal. Groups of animals are slaughtered at each of either four or five appropriately distributed and pre-selected time point intervals following the last administration of the test article. Edible tissues are then collected for marker residue analysis. For the purpose of establishing the withdrawal period, only marker residue in the target tissue, if known, would be analyzed.

For zero-day withdrawal periods, the residue depletion study requirements for the Veterinary New Drug Submissions (NDSs) as described in Subsection 9.3.2.1.2, "Metabolism Studies in the Intended Species," *Guidance for Industry: Preparation of Veterinary New Drug Submissions* (Health Canada 2007) shall apply.

A statistical procedure will be used to calculate the withdrawal period. The upper tolerance limit residue concentrations with 95% confidence for 99% of the animal population will be determined, which should be below the established MRL.

It is noted that to meet the current standards of the guidelines, data from a comprehensive residue depletion study in all the edible tissues may be requested where the MRL in tissues other than the target tissue are not available.

7.3.5 Analytical Methodology

When choosing analytical methods to determine marker residue concentration levels, sponsors should consider the approved method. If an analytical method other than the approved method of analysis is used, the sponsors of the generic products should provide method validation data with consideration of the analytical methodology requirements described in Subsection 9.3.2.2, "Residue Studies," *Guidance for Industry: Preparation of Veterinary New Drug Submissions* (Health Canada, 2007).

8. Labelling

All labels of the test product should be the same as the reference product labelled claims and instructions. Fewer or reduced claims (partial labels) compared to the CRP may be acceptable as long as the partial claim does not raise any potential safety, efficacy, and human safety concerns for the VDD.

The sponsor is requested to submit the most recent French and English versions of all the CRP labels (inner and outer labels and package inserts) along with the proposed French and English draft labels (hard copy and electronic format) for the generic drug product in the submission as per the provisions of Part C, Division 4 of the *Food and Drugs Regulations* and Health Canada's guidance document for labelling of veterinary drugs.

An attestation to the complete and accurate translation of the labels in the second official language (either French or English) is also required. The sponsor should submit the actual size label design, font, and layout of the label that will be used for final printing for review prior to marketing. A final printed copy of the labels must be submitted at the time of introduction of the test product on the Canadian market.

9. Appendices

Appendix I: References

Health Canada Documents (www.hc-sc.gc.ca)

Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms, March 7, 1996.

Canadian Reference Product, October 12, 1995.

Draft Guidance Document: Drug Master Files, September 5, 2008.

Food and Drugs Act and Regulations

Good Manufacturing Practices Guidelines, November 8, 2009.

Guidance for Industry: Bioequivalence Requirements: Critical Dose Drug, May 31, 2006.

Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A: Oral Dosage Formulations Used for Systemic Effects, October 8, 1997.

Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part B: Oral Modified Release Formulations, November 10, 1996.

Guidance for Industry: Preparation of Veterinary New Drug Submissions, March 19, 2007.

Guidance for Industry: Management of Regulatory Submissions, November 27, 2003.

Interpretation of "Identical Medicinal Ingredient", July 9, 2003.

Notice to Industry: Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption is Important (Rapid Onset Drugs), June 22, 2005.

Notice to Industry: Bioequivalence Requirements for Long Half-life Drugs, June 22, 2005.

Notice to Industry: Post-Notice of Compliance (NOC) Changes Guidance, December 3, 2009.

Post-Notice of Compliance (NOC) Changes: Framework Document, December 3, 2009.

Post-Notice of Compliance Changes: Quality Document, December 3, 2009.

Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document, December 3, 2009.

Submissions for Generic Topical Drugs, September 24, 1990.

Validation Guidelines for Pharmaceutical Dosage Forms, (GUIDE-0029).

United States Federal Drug Administration and Center for Veterinary Medicine Documents (www.fda.gov)

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products: General Considerations, March 2003.

Guidance for Industry #35: Bioequivalence Guidance, November 8, 2006.

Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002.

Guidance for Industry #171: Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles, October 6, 2008.

Veterinary International Cooperation on Harmonization Documents (www.vichsec.org)

"Consensus Guideline – Guidelines on Good Clinical Practices" (VICH Topic GL 9 (GCP)) (July 2001).

"Impurities in New Drug Substances" (VICH GL 10) (January 2008).

"Impurities in New Veterinary Medicinal Products" (VICH GL 11) (January 2008).

"Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients" (VICH GL 18) (July 2001).

"Pharmacovigilance of veterinary medicinal products: management of periodic summary update reports (PSUs)" (VICH GL 29), June 2007.

"Stability Testing for Medicated Premixes" (VICH GL 8) (June 2001).

"Stability Testing of New Drug Substances and Products" (VICH GL 3) (January 2008).

"Stability Testing: Photostability Testing of New Drug Substances and Products" (VICH GL 5) (May 2000).

"Stability Testing: Requirements for New Dosage Forms" (VICH GL 4) (May 2000).

"Validation of Analytical Procedures: Definition and Terminology" (VICH GL 1) (October 1999).

"Validation of Analytical Procedures: Methodology" (VICH GL 2) (October 1999).

"Guidance for Industry – Specifications: Test Procedures and Acceptance Criteria for New Veterinary drug Substances and New Medicinal Products: Chemical Substances" (VICH GL 39) (November 2006).

International Conference on Harmonisation Document (www.ema.europa.eu)

"Impurities: Guideline for Residual Solvents", July 1997.

Organisation for Economic Cooperation and Development Document (www.oecd.org)

"OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring", 1998.

Appendix II: List of Abbreviations and Acronyms

ANDS	Abbreviated New Drug Submission
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
AIF	Animal Ingredient Form
API	Active Pharmaceutical Ingredient
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BAN	British Approved Name
BE	Bioequivalence
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CAS	Chemical Abstracts Service
CCAC	Canadian Council on Animal Care
CED	Clinical Evaluation Division, VDD
CEP	Certificate of Suitability
CEPA	Canadian Environmental Protection Act
CF	Consumption Factor for organs, muscle, milk, eggs and honey
CFIA	Canadian Food Inspection Agency
CI	Confidence Interval
Cmax	Maximum or Peak Concentration
CPID-CE	Certified Product Information Document
CRP	Canadian Reference Product
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
DPIF	Drug Product Information Form
DS	Drug Substance
DSC	Differentia Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines and HealthCare

EMEA	European Medicines Agency
EP	European Pharmacopeia (see Ph.Eur.)
ESC	Experimental Studies Certificate
EU	European Union
F	Bioavailability
f_2	similarity factor
FDA	Food and Drug Administration of US
F&DA	Food and Drugs Act
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GL	Guideline
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
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
INN	International Non-proprietary Name
IR	Infrared
i.v.	intravenous
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	Material Safety Data Sheet
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	Organisation for Economic Cooperation and Development
OIE	Organisation mondiale de la sante animale
PD	Pharmacodynamic
Ph.Eur	Pharmacopoeia EU (see EP)
PK	Pharmacokinetic
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
RRT	Relative Retention Time
RSD	Relative Standard Deviation
SANDS	Supplemental Abbreviated New Drug Submission

SC	Santé Canada
s.c.	Subcutaneous
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	Half-life
Tmax	Time to reach the maximum 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
VABNDS	Veterinary ABNDS
VDD	Veterinary Drugs Directorate
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
VNDS	Veterinary NDS
WHMIS	Workplace Hazardous Materials Information System
XRD	X-ray Diffraction

Appendix III: Glossary of Terms

Abbreviated New Drug Submission (ANDS): a submission for a new drug where, in comparison with a Canadian Reference Product (CRP), the new drug

(a) is the pharmaceutical equivalent;

(b) is bioequivalent based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;

(c) has the same route of administration; and

(d) has conditions of use that fall within the conditions of use for the Canadian reference product.

When filing the ANDS, a manufacturer must ensure that it contains sufficient information and material to demonstrate that the generic product is pharmaceutically equivalent as well as bio-equivalent with the CRP. In the case of food-producing animals, the ANDS must confirm that the withdrawal period/withholding time is identical to that of the CRP. (Ref: Section C.08.002.1(1) of the *Food and Drugs Regulations*)

Bioavailability (F): the rate and extent of drug transfer from dosage form to blood.

Bioequivalence: is demonstrated when the rate and extent of absorption of two formulations of drugs (test and reference) are sufficiently similar, within pre-determined allowable limits, when administered under similar experimental conditions.

Canadian Reference Product (CRP): a drug

(a) for 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) that is acceptable to the Minister and 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) that is acceptable to the Minister and 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). (Ref: Section C.08.001.1 of the *Food and Drug Regulations*)

Drug: 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 where food is manufactured, prepared, or kept. (Ref: Section 2 of the *Food and Drugs Act*)

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

Essentially the same: For the purposes of this document, *essentially the same* would be interpreted as the amount (concentration) of each excipient in the test product to be within 10% of the amount (or concentration) of each excipient in the reference product. A side-by-side comparison of the qualitative and quantitative formulations for the test and reference products should be provided.

Generic Drug: for the purpose of this document, a generic drug is a drug formulation that contains the same active ingredient(s) at the same concentration and that has a comparable dosage form, route of administration, and labeled indications as the CRP.

Half-life (t½): the time taken for a drug concentration to decline by 50 percent in blood.

Identical: a generic drug product is considered identical to a reference product if it contains identical active (salt or ester of the same therapeutic moiety) and inactive ingredients in the identical dosage form and concentration, has identical physicochemical characteristics (pH, particle size distribution, crystalline form, molecular lattice structure, dissolution profile, etc.), identical use pattern (target animal species, dose rates, route of administration, withholding times), identical label claims and instructions, identical manufacturing quality and process, and identical source of the active pharmaceutical ingredient at the reference product.

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

Major Target Species: for the purpose of this document, the seven major target species in Canada are cats, dogs, cattle, horses, swine, chickens, and turkeys.

Manufacturer: a person, firm, partnership, or corporation that sells a food or drug under its own name, trade name, or other name, word, design, or mark it controls. (Ref: Section A.01.010 of the *Food and Drug Regulations*)

Medicated Premix (Feed Additive Drug): a drug specifically formulated for blending into animal feed.

Minor Formulation Changes: only include alterations to the excipients and not to the active ingredients. These alterations should produce no significant change in the physical or chemical characteristics of the product and no consequent improvement or reduction in performance. There should be no change in the basic activity of the product.

Narrow Therapeutic Range: a narrow therapeutic range (NTR) drug is a drug where the ratio of the lowest concentration at which clinical toxicity occurs, to the median concentration providing a therapeutic effect, is less than or equal to 2. Since small differences in the amount of NTR drug administered may result in more serious consequences than with 'uncomplicated' drugs, the required degree of assurance of the similarity of reference and subsequent-entry products is felt to be greater with NTR drugs than with 'uncomplicated' drugs.

New Drug: a drug that contains or consists of a new substance, 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 the safety and effectiveness of its use a drug in Canada. (Ref: Section C.08.001 of the *Food and Drugs Regulations*)

New Drug Submission (NDS): a submission that contains sufficient information and material to enable assessment of the safety and effectiveness of the subject new drug. The NDS 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. (Ref: Section C.08.002, and labelling as per Division 1 of Part C of the *Food and Drug Regulations*)

Notice Of Compliance (NOC): the document that is issued pursuant to section C.08.004 to the manufacturer of a drug when an NDS, ANDS, or SNDS complies with the *Food and Drug Regulations*. It includes the name, 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 ANDS, 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 mechanisms of action, their structure activity relationships, and their interaction with other drugs.

Pharmacokinetics (PK): the study of the time course of drugs including absorption, distribution, metabolism, and excretion.

Pharmacovigilance: for the purpose of these guidelines, pharmacovigilance refers to the reporting of adverse drug reactions and to 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, efficacy, and 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 authorities with worldwide recognition, such as the World Association for the Advancement of Veterinary Parasitology.

Protocol: 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: data resulting from the original observations and activities of a study. 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 is necessary for the reconstruction and evaluation of the study report.

Re-test period:
The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given medicinal product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a medicinal product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Sell: "sell," as defined in the *Food and Drugs Act*, does not necessarily require the exchange of money for commodity. "Sell" includes offer for sale, exposure for sale, or having in possession for sale or distribution, whether the distribution is made for consideration or not. For example, the distribution of free samples to health professionals is considered to be a sale. The *Food and Drug Regulations* prohibit the sale of a drug unless certain conditions have been met. (Ref: Section 2 of the *Food and Drugs Act*).

Shelf life (also referred to as expiration dating period):
The time period during which a medicinal product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Simple Topical Formulation – Category I: a solution containing the drug substance in which the solvent does not include inactive ingredients that may affect the penetration/absorption of the active ingredient(s) through the skin, and does not cause any tissue reaction (Ref: *Submissions for Generic Topical Drugs, September 24, 1990)*.

Sponsor: see Manufacturer.

Submission: documentation 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 (SANDS): a supplement to an ANDS with respect to matters that are significantly different to those contained in the ANDS, 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. (Ref: Section C.08.003 of the *Food and Drug Regulations*)

Supplemental New Drug Submission (SNDS): 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. (Ref: Section C.08.003 of the *Food and Drug Regulations*)

Therapeutic Equivalent: when a new drug, in comparison with the reference drug, is pharmaceutically equivalent and after administration in the same molar dose, their effects with respect to both efficacy and safety are interchangeable, as determined from appropriate blood-level, pharmacodynamic, clinical or *in vitro* studies.

Therapeutic Index: the ratio between the effective dose (optimum dose) and the toxic dose (lowest dose at which toxic signs are exhibited).

Uncomplicated Medicinal Ingredients: ingredients that do not exhibit a narrow therapeutic ratio or safety margin (does not require careful dosage titration or patient monitoring), a risk of serious undesired side effects, or complex pharmacokinetics (e.g., non-linear kinetics, modified release formulations).

Withdrawal Period: (for milk refer as the Withholding Time) this is the length of time that must elapse after treating an animal with a drug before the animal or its products can be marketed. Withdrawal Period/Withholding Time varies for different drugs, reflecting the amount of time needed for an animal to metabolize that drug and for the drug's concentration level in the animal tissue or product to decrease to a safe, acceptable level.