Health Canada Santé Canada

Post-Notice of Compliance (NOC) Changes: Guidance for quality of veterinary drugs

Canada

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Overview

Objectives

This guidance document has 3 main objectives:

1. To provide guidance for post-Notice of Compliance (NOC) quality changes specifically for veterinary drugs.
2. To assist with the classification of quality changes made to a new veterinary drug that has received a NOC pursuant to section C.08.004 of the *Food and Drug Regulations*(the Regulations).
3. To provide sponsors guidance with respect to the reporting category and the recommendations on the data to support a quality related change.

Scope and application

This guidance document applies to sponsors intending to make changes to new veterinary drugs that have received a NOC pursuant to Section C.08.004 of the Regulations.

This guidance document is not applicable to veterinary biologics regulated by the Canadian Food Inspection Agency (CFIA), such as biological vaccines. Refer to applicable CFIA guidelines and policies for veterinary biologics.

Consult Health Canada's Post-Notice of Compliance (NOC) Changes: Quality - Guidance for Biologics pertaining to products regulated by the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) when:

- biotechnological tools are used at any stage during the synthesis of the drug substance(s). For example:
    - DNA cloning
    - gene targeting
    - rDNA technology
- biological processes, such as fermentation, are used during the manufacturing of a veterinary drug product

We encourage sponsors to consult with the Veterinary Drugs Directorate (VDD) for specifics of the conditions, data requirements and submission classifications.

ICH Q8, ICH Q9, ICH Q10 and ICH Q11 apply to medicinal products for human use only. However, the related concepts are also useful in the context of veterinary drug products. We advise sponsors of veterinary drugs submissions to refer to these relevant ICH guidelines.

Read this guidance document in conjunction with:

- Post-Notice of Compliance (NOC) Changes: Framework Document - Guidance for Veterinary Drugs
- Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document - Guidance for Veterinary Drugs
- other related Health Canada guidance documents

Information regarding general submission requirements and target performance standards may be found in the Veterinary drugs - Management of regulatory submissions guidance.

Background

This guidance document replaces the guidance previously provided in Appendix 2: Quality Post-NOC Changes - Veterinary Drugs of the Guidance Document: Post-NOC Changes: Quality Document (2019). This document has been updated to provide clarity and consistency. It will be periodically updated with an emphasis on applying a science-based and risk-based approach to the pharmaceutical quality assessment of these products. Updated guidance documents are necessary to provide information to support quality changes to new drugs which apply a modernized, science-based, and risk-based approach to this area.

Document change log

- Appendix 2 of the Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document (2019) has been made into a separate document for veterinary drugs.
- The guidance has been reformatted to allow for web publishing.
- A complete Certified Product Information Document (CPID) is recommended for all quality-related post-NOC changes. Refer to a new section "Supporting data - Certified Product Information Document (CPID)" in the guidance.
- Comments received from the industry during consultation have been incorporated throughout the guidance.
- Change examples have been added, removed, or revised to clarify requirements and to address the request from industry for additional guidance. Notable areas where this guidance has been revised are:
    - New examples added to include separate requirements for starting materials, intermediates, and final drug substance
    - New example added for changes involving Certificate of Suitability (CEP)
    - New example added for changes involving container closure system
    - New example added for changes involving product in-use stability period
    - Merged examples as the same requirements are applied to all immediate release dosage forms including medicated premixes
    - Merged examples for the changes involving post-approval stability protocol
    - Several changes now have multiple categories of changes to allow industry more flexibility in submission of changes
    - Some conditions and supporting data for certain changes have been removed or revised to clarify the requirements
    - Supporting data concerning process parametric release has been revised to clarify the expectations.
    - Overall updates to the text have been made to provide more clarity of the requirements
    - References to related guidance documents have been added or revised (including VICH and ICH guidelines, and Health Canada's guidance on parametric release)

Note about guidance documents in general

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the relevant sections of the Regulations and other applicable guidance documents.

Related Links

- Veterinary drugs - Management of regulatory submissions guidance
- Post-Notice of Compliance changes: Framework document for veterinary drugs
- Post-Notice of Compliance changes: Guidance for safety and efficacy of veterinary drugs

Classification – reporting categories

Introduction

The following criteria are meant to provide guidance with respect to the classification of a quality related change. Specific change examples based on the application of these criteria are provided in the post-NOC change examples sections (for drug substances or drug product) of this guidance document.

We advise sponsors to exercise caution in classifying a series of changes for the same drug product intended to be implemented simultaneously or to be phased in sequentially. Although the individual changes may be classified at a particular reporting category (such as Notifiable Change), collectively, the changes may warrant a higher risk reporting category (such as Supplement). Refer to the multiple changes section for more information.

If the submission has been inappropriately classified, we will notify the sponsor at the screening stage. Contact the Veterinary Drugs Directorate for assistance in classifying a change or a series of changes.

Email: vdd.skmd.so-dgps.dmv.cp@hc-sc.gc.ca

Level I: Supplements

Level I: Supplements (major quality changes) are changes to a new drug that:

- are "significantly different" as it relates to the matters specified in C.08.003 (2) of the Regulations **and**
- have the potential to have an adverse effect on certain factors of the drug product, as they may relate to its safety or effectiveness. These factors are:
    - purity
    - quality
    - potency
    - identity
    - strength

In general, a change that is supported by extensive documentation or requiring extensive assessment of the supporting documentation would be considered a Level I: Supplement (major quality change. For example, a change supported by in vivo studies. This gives Health Canada the opportunity to apply the principles of risk management by having the necessary time for an appropriate assessment of the documentation.

This assessment will consider:

- any potential impact upon market availability
- the adverse effects on the drug product's:
    - purity
    - quality
    - potency
    - identity
    - strength

The changes included in this reporting category shall be filed, along with the recommended supporting data, to Health Canada as a:

- Supplement to a New Drug Submission (SNDS) **or**
- Supplement to an Abbreviated New Drug Submission (SANDS)

The sponsor may not implement the change until a NOC has been issued.

Level II: Notifiable Changes

Level II: Notifiable Changes (moderate quality changes) are changes that have a moderate potential to have an adverse effect on certain factors of the drug product, as they may relate to its safety or effectiveness, but do **not** require an issuance of NOC. These factors are:

- purity
- quality
- potency
- identity
- strength

File changes included in this reporting category to Health Canada as a Notifiable Change, along with the recommended supporting data. Sponsors should not implement any Level II changes until a No Objection Letter (NOL) has been issued.

Level III: Annual Notification

Level III: Annual Notification (minor quality changes) are changes that have minimal potential to have an adverse effect on certain factors of the drug product, as they may relate to its safety or effectiveness. These factors are:

- purity
- quality
- potency
- identity
- strength

The sponsor may implement the changes included in this reporting category without the prior review of the data supporting such a change by Health Canada. Submit all Level III changes using the Post-Notice of Compliance Changes: Notices of Change of Veterinary Drugs: Level III Form:

- at the time the proposed change is implemented **or**
- during the annual drug notification period in accordance with C.01.014.5 of the Regulations

Level IV Changes: record of changes

Level IV (Quality only) changes are changes to a new drug that are **not**:

- Level I, Level II or Level III
- expected to have an adverse effect on certain factors may relate to the safety or effectiveness of the drug product. These factors are:
    - purity
    - quality
    - potency
    - identity
    - strength

The sponsor may implement changes included in this reporting category without prior review by Health Canada. The changes should:

- be retained as part of the drug product's record by either the sponsor or the manufacturer
- comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the Regulations

A list of examples of Level IV changes is provided in Appendix 3 of this guidance document.

Documentation

Introduction

This section provides general information on documentation, including supporting data common to each reporting category. For other specific documentation requirements, refer to the post-NOC change examples sections (for drug substance or drug product). They include recommendations on the supporting data for a given change, either to be submitted to Health Canada or maintained by the sponsor. An adequate rationale is required when supporting data cannot be provided.

Supporting data

Certified Product Information Document

The Certified Product Information Document (CPID) provides an accurate record of technical data in the drug submission at the time the NOC is issued. It is intended to serve as an official reference document during the course of post-approval inspections and post-approval change evaluations as performed by Health Canada. The document helps expedite the review process and facilitate the management of future post-approval changes. Refer to the VDD's Certified Product Information Document (CPID) template for the following scenarios and provide the required document(s) as outlined:

1. When proposing changes to products with a currently approved CPID

Provide an electronic copy (Microsoft Word document with tracked changes) of the revised CPID with the updated sections affected with the proposed change.

2. When proposing changes to products with no approved CPID

Provide an electronic copy of the CPID in Microsoft Word format. Use tracked changes for the sections affected with the newly proposed changes that have not been previously approved by Health Canada. Include a statement under the administrative summary table on the title page to confirm that the information on the CPID is accurate, complete, and consistent with the quality information approved for the product.

A complete CPID should be submitted at the filing of Level I or Level II changes. Should you have any questions or concerns, contact the assigned Regulatory Project Managers (RPMs) or SKMD at vdd.skmd.so-dgps.dmv.cp@hc-sc.gc.ca.

Level I and Level II changes

Provie all data recommended to support the change with the submission. Submit data as indicated below.

Provide a detailed rationale when you cannot submit recommended supporting data.

Supporting data common to Level I and Level II changes

Where applicable, include in the submission package for Level I and Level II Quality changes:

- a covering letter that includes a brief narrative description and rationale of the change(s)
- a list of changes describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used along with a table outlining the currently approved and the proposed information
- an electronic copy (Microsoft Word document with tracked changes) of:
    - Package Insert
    - a sample of the inner and outer labels to reflect any proposed changes **and**
    - the relevant Certified Product Information Document (CPID)

Recommendations are also included in Post-NOC Change Examples sections outlining the specific information to support the various quality changes. Noted that common information is not repeated for the various change examples provided in this guidance document.

When cross-references are made to previously submitted information, details on the cross-referenced information should be indicated in the covering letter. For example:

- brand name of the drug product
- manufacturer or sponsor's name
- submission type
- control number
- date approved

Certificate of Suitability (CEP)

We encourage the use of Certificates of Suitability to the monographs of the European Pharmacopoeia (CEPs) issued by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe (EDQM) to support changes to the drug substance used in pharmaceuticals for veterinary use. Also, the use of Transmissible Spongiform Encephalopathy (TSE) CEPs may be provided to support raw materials, auxiliary materials and reagents at risk of transmitting BSE/TSE agents. Contact the Veterinary Drugs Directorate for further guidance.

With respect to the Health Canada Guidance Document Use of Certificates of Suitability as supporting information in Drug Submissions (2017/08/21) , sponsors should note:

- The term Master File (MF) used in Section 4 is synonymous with the term Active Substance Master File (ASMF).
- If the company has a current valid Certificate of Suitability (CEP), and they can provide all the attestations as per the guidance document (Section 2.1), they are encouraged to submit a CEP in support of the information for the drug substance. The minimum information required is described in Section 2.2 of the guidance document.
- The ASMF should be provided in all cases mentioned under Section 2.3 of the guidance document.

Level III changes

Sponsors should not submit any data generated in support of a Level III change with the Post-Notice of Compliance Changes (Level III) Form. Health Canada can request this data, which sponsors must make available within 30 calendar days.

Any Level III changes that have been implemented should be annotated in the affected documents. Dates of implementation should be:

- clearly identified (for example, Package Insert and CPID)
- filed with the next Level I - Supplement or Level II - Notifiable Change that necessitates a label or quality change as well

Level III changes submitted annually during the sponsor's Annual Drug Notification period should include:

- All Level III changes implemented for each new drug that has received a NOC **and** that have occurred in the preceding 12 months should be compiled using the Post-Notice of Compliance (NOC) Changes: Level III form
- A completed Post-Notice of Compliance (NOC) Changes: Level III form for each drug that has received a NOC

Only submit a copy of the revised annotated labels, Package Insert and/or CPID with the filing of the next Level I - Supplement or Level II - NC that necessitates a label change or quality change as well. Clearly identify the dates of implementation for these Level III changes.

Level IV changes

The quality changes included in this category should:

- be retained as part of the product's record by either the sponsor or the manufacturer
- comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the Regulations

Annotate these changes in the affected documents (such as Package Insert and CPID) with the filing of the next submission that necessitates a label or quality change as well.

Clinical data

A number of changes outlined in this guidance document include recommendations for supporting clinical or comparative bioavailability data.

The nature of a change and the related conditions fulfilled for that change, as well as the type of product and its characteristics would generally dictate the need for clinical data. Product characteristics can include:

- indications
- formulation
- dosage form
- pharmacokinetic profile
- physicochemical properties

In certain situations, where specific criteria are met, sponsors may submit a request for a waiver of in vivo (clinical) studies. This is also known as biowaiver.

Clinical data may take the form (or be a combination) of:

- palatability studies
- pharmacovigilance data
- in vivo laboratory studies
- field safety or efficacy trial data
- comparative bioavailability studies
- published articles from literature, as deemed appropriate to support a particular change

Clinical data may be required for each major species included in the indications when a veterinary drug product is intended for use in more than one animal species if the change and/or the product is not eligible for a biowaiver.

Sponsors should consult the Veterinary Drugs Directorate for specific questions, alternatives, or for additional information on biowaivers and in vivo bioavailability/bioequivalence studies.

Comparative in vitro studies

Several changes outlined in this guidance document include recommendations for supporting comparative in vitro studies (such as comparative dissolution studies). Where an in vitro comparison is recommended to support a Post-NOC Change, compare the product manufactured according to the same formulation and manufacturing process used in the pivotal clinical and/or comparative bioavailability studies approved for the original drug submission. For example, including batch formula or manufacturing process. This is called the "approved product" in this guidance document.

Alternative approaches to this recommendation may be acceptable if scientifically justified. For example, a comparison to a sponsor's marketed product (rather than the product used in the pivotal clinical and/or comparative bioavailability studies) could be justified if a significant body of information has been established for the marketed drug product. For the purposes of this document, a significant body of information for the marketed drug product is likely to exist after a reasonable number of batches of the drug product will be marketed during the specified period of time (for example, a minimum of 10 batches).

Sponsors should refer to the General Chapters available in the current Schedule B pharmacopoeia for general dissolution and drug release specifications. For example, United States Pharmacopeia (USP) <711>, USP <724>, European Pharmacopeia (Ph.Eur.) 2.9.3.

Appendix 1 also outlines recommendations for conducting and assessing comparative dissolution profiles (such as conditions or similarity).

Stability testing

If stability studies are recommended to support a change, these studies should be conducted in accordance with applicable VICH and Health Canada guidance documents, for example:

- VICH GL3 - Stability testing of new veterinary drug substances and medicinal products
- VICH GL8 - Stability testing for medicated premixes
- VICH GL5 - Stability Testing: Photostability Testing of New Drug Substances and Products
- VICH GL4 - Stability Testing: Requirements for New Dosage Forms
- VICH GL45 - Quality: Bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products
- VICH GL51 - Quality: Statistical evaluation of stability data
- VICH GL58 - Stability Testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV

In case where accelerated stability studies are not routinely performed due to the nature of the product, provide a rationale.

Pharmaceutical development and quality by design

The International Council for Harmonisation (ICH) has developed the Q8 guideline: Pharmaceutical Development and Q8 Annex. They describe respectively the suggested contents for the 3.2.S.2.2 to 3.2.S.2.6 sections and for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the Common Technical Document (CTD) format.

The pharmaceutical development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. Provide the pharmaceutical development information for a veterinary drug submission as outlined in section 6.4.2 of Guidance for Industry: Preparation of Veterinary New Drug Submissions.

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support establishing the design space, specifications, and manufacturing controls.

The applicant proposes the design space, which is subject to regulatory assessment and approval. Working within the design space is not considered as a change that would require prior approval but should be documented with the requisite Change Controls where necessary. Movement outside of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

For example, some of the Post-NOC Changes that are listed in this guidance document as Level I or Level II may not require approval prior to implementation if they are within the approved design space.

A sponsor may also establish a new design space for an existing product. Once approved, this would provide the advantage of limiting the necessity to file future submissions for changes within the ranges of the design space.

If proposed and approved, record the details of the design space in the Certified Product Information Document (CPID). We encourage sponsors to discuss with Health Canada when considering the establishment of a design space.

Multiple changes

Multiple Level II (Quality) changes to the same drug product may be filed in a single submission provided those changes are related or supported by the same information. If the changes are related, the sponsor should indicate the association between the proposed changes. The sponsor should ensure that the documentation for each change complies with the requirements of the corresponding section of the guidance. For submissions that include multiple changes, the sponsor should clearly specify which supporting data supports which change.

If there are too many changes filed within the same submission or major issues are identified with a change which would require extensive time to review, Health Canada may divide the changes into separate submissions.

If the same change is applicable to multiple drugs, the same supporting data package may be used but a separate submission is required for each drug product.

Examples (drug substance)

Introduction

The change examples provided in this guidance are not considered to be exhaustive such as to cover all possible situations. When in doubt as to the classification or supporting documentation, sponsors should contact the Veterinary Drugs Directorate for clarification.

The change examples presented below are intended to assist with classifying changes made to the quality information. The information summarized in the tables provides recommendations for:

- The conditions to be fulfilled for a given change to be classified as either a Level I, II, or III change. If the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example:
    - if the conditions recommended for a Level II - Notifiable Change are not fulfilled, the change is considered a Level I - Supplement
    - if the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of an NDS or an ANDS
- The supporting data for a given change, either to be submitted to Health Canada and/or maintained by the sponsor. Where Master Production Documents are required, make these documents available in an official language (English or French), or a translation from the original language.
- The reporting category (such as Supplement, Notifiable Change or Annual Notification).

Health Canada reserves the right to request additional information or material as deemed appropriate, or to define conditions not specifically described in this document. Sponsors should contact the directorate when a change that may have the potential to impact product quality is not found in the tables.

Although the Common Technical Document (CTD) format is not applicable to veterinary drugs submissions, but for convenience, the change examples are organized according to the structure of the CTD.

3.2.S.1 General information

1. Change in the drug substance name/nomenclature

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the drug substance name/nomenclature	1	1,2	Annual Notification

Conditions

1. Confirmation that the information on the drug substance has not changed as a result of the change. For example, cross reference(s) should be provided to the previously approved drug submission, including:
    - brand name of the drug product
    - manufacturer or sponsor's name
    - submission type
    - control number
    - date approved

Supporting data

1. Package Insert and Inner and Outer Labels, if applicable
2. (S.1.1) Information on the proposed nomenclature of the drug substance, for example:
    - chemical name(s)
    - compendial name (Schedule B of the Food and Drug Regulations)
    - evidence that the proposed name for the drug substance is recognized, such as:
        - British Approved Names (BAN)
        - United States Adopted Names (USAN)
        - Recommended International Non-Proprietary Name (INN)

3.2.S.2 Manufacture

2. Changes to starting materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a manufacturing site	None	1-6	Notifiable Change
	1-4	1-6	Annual Notification
b. Changes to the route of synthesis (such as reagents), with or without a change in manufacturing site	None	1-6	Notifiable Change
	1-4	1-6	Annual Notification

Conditions

1. No changes to the specifications for the starting material other than addition of tests to the specifications or tightening of acceptance criteria.
2. Analytical methodology (HPLC, LC-MS-MS) has been used to survey the impurity profile of the starting material and ensure that purging of impurities from subsequent drug substance manufacturing steps has occurred.
3. The manufacturing process for the drug substance that is performed under Good Manufacturing Practices (GMP) has at least 3 synthetic steps prior to the final salt production or purification steps.
4. There is no change in the route of synthesis of the non-commercial starting material (including reagents) other than the addition of purification steps and/or changes to solvents that are VICH GL18(R) class 2 or 3. The impurity profile of the drug substance remains the same (no new impurities above the VICH GL10(R) identification threshold and no new identified impurities).

Supporting data

1. (S.2.3) Name and address of starting material manufacturer.
2. (S.2.3) Specifications for starting material.
3. (S.2.3) Route of synthesis of a non-commercially available starting material. Note: Route of synthesis would include basic information about the synthetic reactions that are used (such as a flow chart) and would include reagents and solvents but would not involve detailed information about the

reaction conditions or process. For fermentation or semi-synthetic processes, it would involve a similar level of detail.

4. (S.2.3, S.4.4) Analytical data to support consistent impurity profiles between the previously authorized and new starting material, and between drug substance manufactured with the previously authorized and new starting material.
5. (S.2.5, S.2.6, S.3.2) The new source(s) of starting material (or reagents/catalysts or solvents) have been used during drug substance manufacture, validation (if applicable), and technology transfer (if applicable). For sterile drug substances, applicable process validation studies are successfully completed to manufacture commercial size batches of the drug substance. Potential impurities not routinely tested have been confirmed to be absent from the impurity profile of the drug substance by either testing, risk analysis, or knowledge of fate/purge of impurities.
6. (S.2.6) Risk assessments and justification of changes that any changes are minor or insignificant. The assessment discusses those changes that result in changes to the specifications of the starting material, related intermediate or the final drug substance. The impact assessment considers potential for any new impurities, carry-over of all impurities and whether changes to the starting material specifications are needed.

3. Changes to drug substance intermediates

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a manufacturing site	None	1-7	Notifiable Change
	1-4	1-7	Annual Notification
b. Changes to specifications	None	4,5	Notifiable Change
	1,2	4	Annual Notification
c. Changes to the manufacturing process, with or without change in manufacturing site	None	1-7	Notifiable Change
	1-4	1-7	Annual Notification

Conditions

1. A written quality agreement is in place between the intermediate manufacturer and the drug substance manufacturer.
2. No changes to the specifications for the intermediate other than addition of tests to the specifications or tightening of acceptance criteria.
3. Analytical methodology (HPLC, LC-MS-MS) has been used to survey the impurity profile of the intermediate and ensure that purging of impurities from subsequent drug substance manufacturing steps has occurred.

4. There is no change in the route of synthesis of the intermediate (including reagents, solvents or process conditions). The impurity profile of the intermediate remains the same (no new unidentified impurities above the VICH GL10 identification threshold, and no new identified impurities).

Supporting data

1. (1.2.5) Evidence of Good Manufacturing Practices (GMP) compliance status and/or Establishment Licence (EL) information. For more information, refer to the Notice: Submission Filing Recommendations for Veterinary Drugs - Good Manufacturing Practices and Drug Establishment Licences
2. (S.2.1) Name and address of the intermediate manufacturer.
3. (S.2.2) Route of synthesis of the intermediate.
4. (S.2.4) Specifications for the intermediate.
5. (S.2.4, S.4.4) Analytical data to support consistent impurity profiles between the previously authorized and new intermediate, and between drug substance manufactured with the previously authorized and new intermediate.
6. (S.2.5, S.2.6, S.3.2) The new source(s) of intermediate (or new sources of reagents/catalysts or solvents have been used during drug substance manufacture, validation, and technology transfer (if applicable). Applicable process validation studies are successfully completed to manufacture commercial size batches of the drug substance. Potential impurities not routinely tested have been confirmed to be absent from the impurity profile of the drug substance by either testing, risk analysis, or knowledge of fate/purge of impurities. Validation reports demonstrate equivalency of processes.
7. (S.2.6) Risk assessments and justification of changes (including those that result in changes the specifications of the related intermediate or the final drug substance).

4. Changes to the drug substance manufacturing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a manufacturing site	None	1-8	Supplement
	2-4	1,3-8	Notifiable Change
	1-4	1,3-8	Annual Notification
b. Addition of testing (such as release, stability) site	None	1,4,6,7	Notifiable Change
	5 or 6	1,4,6,7	Annual Notification
c. Deletion of a manufacturing site	None	None	Annual Notification

Conditions

1. No major changes in the drug substance synthesis. That is, it uses the same:
    - starting material
    - intermediates
    - solvents
    - reagents
    - purification/isolation process
    - process conditions and controls
    - analytical methods
    - specifications
2. Where materials of human or animal origin are used in the process:
    - the change of source is supported by a valid Transmissible Spongiform Encephalopathy (TSE) Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM), **or**
    - the source of the material from the new supplier has been previously authorized for viral safety or TSE risk by:
        - the Pharmaceutical Drugs Directorate (PDD) **or**
        - the Biological and Radiopharmaceutical Drugs Directorate (BRDD)
3. The change does not concern a sterile drug substance.
4. The change concerns drug products containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).
5. The analytical method(s) for the new testing site is/are equivalent to the analytical method(s) in the compendial drug substance monograph (Schedule B of the Food and Drug Regulations).
6. All analytical tests and equipment are equivalent to previously validated /registered methods.

Supporting data

1. (1.2.5) Evidence of GMP compliance status and/or Establishment Licence (EL) information. For more information, refer to the Notice: Submission Filing Recommendations for Veterinary Drugs - Good Manufacturing Practices and Drug Establishment Licences.
2. For sterile drug substances, evidence of validation of the sterilization process.
3. (S) A complete Active Substance Master File (ASMF) or drug substance information relevant to the change for the proposed site.
4. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing, packaging and testing.
5. (S.2.3) For drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents [such as ruminant origin], information and evidence that the material does not pose a potential BSE/TSE risk should be provided where available. For example:
    - name of manufacturer
    - species and tissues from which the material is a derivative
    - country of origin of the source animals
    - its use and previous acceptance
6. (S.4.3) Copies and summaries of method validation reports / method transfer reports, which demonstrate equivalency of analytical procedures used by the currently approved and proposed sites.
7. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and comparative analytical data in a tabular format, for at least 1 pilot scale batch of the currently approved and proposed sites.

8. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance at the new site into the long-term stability program (bracketing and matrixing with justification would be acceptable for multiple strength products).

5. Changes to the drug substance when the manufacturing site has a valid Certificate of Suitability (CEP)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition of a manufacturing site or a change to the manufacturing process	1	1-5	Annual Notification
b. Replacement of a currently approved ASMF with a CEP	1,2	1,2	Annual Notification

Conditions

1. A valid Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM), along with the annexes and all attestations as described in Health Canada's guidance document "Use of Certificates of Suitability as Supporting Information in Drug Submissions".
2. No significant change to the drug substance information approved by Health Canada in the ASMF.

Supporting data

1. (1.2.3) A copy of the Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM) which is current and valid (the CEP has not been suspended or withdrawn). If the CEP is in lieu of an Active Substance Master File (ASMF), the declaration of access box shows the drug product manufacturer's name. The changes to the drug substance have been accepted by the EDQM as part of the certification procedures. Annexes and all attestations as described in Health Canada's guidance document "Use of Certificates of Suitability as Supporting Information in Drug Submissions".
2. (1.2.5) Evidence of Good Manufacturing Practices (GMP) and/or Establishment Licence (EL) information. For more information, refer to the Notice: Submission Filing Recommendations for Veterinary Drugs - Good Manufacturing Practices and Drug Establishment Licences.
3. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing.
4. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and comparative analytical data in a tabular format, for at least 1 pilot scale batch of the currently approved and proposed sites (processes).
5. (P.8.2) An updated post-approval stability protocol and stability commitment to place the first commercial scale batch of the drug product manufactured using the drug substance manufactured at the new site or using the new process into the long-term stability program (bracketing and matrixing with justification would be acceptable for multiple strength products).

6. Change in the manufacturing process for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the manufacturing process for the drug substance	1	1-10	Supplement
	1-4,7,8	1-5,7,8,10	Notifiable Change
	1-8	1-5,7,8,10	Annual Notification

Conditions

1. No change in the identicality of the drug substance in accordance with the Health Canada's Interpretation of identical medicinal ingredient.
2. No change in the physical state of the drug substance. For example:
    - crystalline
    - amorphous
    - solid
    - semi-solid
    - liquid
    - gas
3. For low solubility drug substances, no change in the polymorphic form or no change in the particle size distribution of the drug substance.
4. Where materials of human or animal origin are used in the process:
    - the change of source is supported by a valid Transmissible Spongiform Encephalopathy (TSE) Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM), **or**
    - the source of the material from the new supplier has been previously authorized for viral safety or TSE risk by:
        - the Pharmaceutical Drugs Directorate (PDD) **or**
        - the Biological and Radiopharmaceutical Drugs Directorate (BRDD)
5. No Level I or Level II changes in the drug substance specifications.
6. No change in the route of synthesis (intermediates remain the same), physical characteristics, and impurity profile of the drug substance (no new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within VICH limits).
7. The change does not concern a sterile drug substance.
8. The change concerns drug products containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).

Supporting data

1. (S) Updated or new Master File (MF) (with a Letter of Access) or relevant drug substance information.
2. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
3. (S.2.3) Information on the quality and controls of the materials used in the manufacture of the proposed drug substance, as applicable. For example, raw materials, starting materials, solvents, reagents, catalysts. If the information is proprietary, reference should be made to the restricted part

of the MF, or the proprietary information may be submitted by the drug substance manufacturer directly to VDD.

4. (S.2.3) For drug substances or intermediates manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (such as ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk should be provided where available. For example:
    - name of manufacturer
    - species and tissues from which the material is a derivative
    - country of origin of the source animals
    - its use and previous acceptance
5. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance. If the information is proprietary:
    - reference should be made to the restricted part of the MF, **or**
    - the proprietary information may be submitted, by the drug substance manufacturer, directly to VDD
6. (S.2.5) For sterile drug substances, evidence of validation of the sterilization process.
7. (S.3.1) Evidence for elucidation of structure, where applicable.
8. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and comparative analytical data in a tabular format, for at least 1 pilot scale batch of the currently approved and proposed processes.
9. (S.7.3) Results of 2 batches with a minimum of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing of the proposed drug substance.
10. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of the drug product, manufactured using the proposed drug substance, into the long-term stability program (bracketing and matrixing with justification would be acceptable for multiple strength products).

7. Change in the batch size for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the batch size for the drug substance	None	1-3	Notifiable Change
	1-7	1,3	Annual Notification

Conditions

1. No change in the proportionality of the raw materials.
2. Changes to the method of manufacture are only those necessitated by change in batch size (for example, use of different-sized equipment).
3. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
4. No Level I or Level II changes in the drug substance specifications.
5. Up to 10-fold scale-up or scale-down compared to the approved batch size.
6. The change concerns drug products containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).
7. The change does not concern a sterile drug substance.

Supporting data

1. (S.2.2) A brief narrative description of the proposed manufacturing process(es).
2. (S.2.5) For sterile drug substances, evidence of validation of the sterilization process.
3. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a tabular format, for at least 1 pilot scale batch.

8. Change in the controls for the materials used in the manufacture of the drug substance or controls performed at critical steps in the process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in the controls for the materials used in the manufacture of the drug substance (such as raw materials, starting materials, solvents, reagents, catalysts)	None	1-4	Notifiable Change
b. Change in the controls performed at critical steps in the process	1-3	1,2,4	Annual Notification

Conditions

1. No Level I or Level II changes in the drug substance specifications, such as:
    - no new impurity above 0.1%
    - no change in the approved total impurity limit
    - residual solvents within VICH limits
2. The change does not affect the sterilization procedures of a sterile drug substance.
3. The change concerns drug products containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).

Supporting data

1. (S.2.3) Information on the quality and controls of the materials (such as raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance. If the information is proprietary:
    - reference should be made to the restricted part of the MF, **or**
    - the proprietary information may be submitted by the drug substance manufacturer, directly to VDD
2. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance. If the information is proprietary:
    - reference should be made to the restricted part of the MF, **or**
    - the proprietary information may be submitted by the drug substance manufacturer, directly to VDD
3. (S.2.5) For sterile drug substances, evidence of validation of the sterilization process.
4. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for at least 1 pilot scale batch of the drug substance manufactured with the current and proposed methods.

3.2.S.3 Characterisation

There are no quality change examples for this section at the present time that have not been addressed in other sections.

3.2.S.4 Control of the drug substance

9. Change regarding the standard claimed for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in the standard claimed for the drug substance (for example, from a Professed to a Schedule B pharmacopoeial standard or from one Schedule B standard to a different Schedule B standard).	1-3	1-4	Annual Notification
b. Change in the specification for the drug substance to comply with an updated Schedule B pharmacopoeial monograph	1,2	1-3	Annual Notification

Conditions

1. The change is made exclusively to comply with the pharmacopoeia.
2. No Level I or Level II changes to the specifications [functional properties of the drug substance, such as particle size distribution, polymorphic form].
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specification.

Supporting data

1. (S.4.1) Updated, QC approved, proposed drug substance specification.
2. (S.4.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
3. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a tabular format, for at least 1 batch if new tests and/or analytical methods are implemented.
4. (S.4.5) Justification of the proposed drug substance specification (for example, demonstration of the suitability of the monograph to control the drug substance, including impurities).

10. Change in the specification for the drug substance involving test and acceptance criteria

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. For sterile drug substances, replacing the sterility test with alternate microbiological methods or process parametric release	None	1-8	Supplement
b. Deletion of a test	None	2,7,8	Notifiable Change

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
	1,5	2,7,8	Annual Notification
c. Replacement of a test	1-7	2-5,7,8	Annual Notification
d. Addition of a test	1,3,4,6,7	2-5,7,8	Annual Notification
e. Relaxation of an acceptance criterion	None	2,7,8	Notifiable Change
	1,4,6,7	2,7,8	Annual Notification
f. Tightening of an acceptance criterion	1,2,4,6,7	2,7,8	Annual Notification

Conditions

1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the impurity profiles that impacts safety of the drug substance. Acceptance criterion for any Class 3 residual solvent is within the VICH limits (the relaxation of an acceptance criterion for a Class 1 or 2 solvent should be filed as a Notifiable Change).
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The change does not concern sterility testing.
7. The change concerns drug products containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).

Supporting data

1. (S.2.5) Evidence of validation of the sterilization process.
2. (S.4.1) Updated, QC approved, proposed drug substance specification.
3. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
4. (S.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
5. (S.4.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
6. (S.4.4) Description of the batches, certificates of analyses, or batch analysis report and summary of results, of a sufficient number of batches (minimum of 10 batches) to support the process parametric release.
7. (S.4.5) Justification of the proposed drug substance specification (such as test parameters, acceptance criteria or analytical procedures). For Process Parametric Release (PPR), provide a

thorough risk assessment that identifies the risks of manufacturing and releasing non-sterile product and the proposed management plan. For further information on requirements for obtaining authorization for PPR, consult Health Canada's Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

8. (P.2) Where appropriate (such as for a change in particle size limit for a poorly soluble drug substance), comparative, multi-point dissolution profiles in the release medium for 1 batch of the drug product using material from the approved and change drug substance specifications.

11. Change in the specification for the drug substance involving analytical procedures

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Deletion of an analytical procedure	None	1,5	Notifiable Change
	5	1,5	Annual Notification
b. Replacement of, alternate, or additional analytical procedure	None	1-5	Notifiable Change
	1-4	1-5	Annual Notification
c. Change from a House analytical procedure to a Schedule B analytical procedure, a change from an approved compendial analytical procedure to an harmonized compendial procedure, or from one Schedule B standard to a different Schedule B standard).	None	1,3-5	Annual Notification

Conditions

1. The method of analysis is based on the same analytical technique or principal and no new impurities are detected.
2. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not concern sterility testing.
5. The deleted analytical procedure is an alternate and equivalent method.

Supporting data

1. (S.4.1) Updated, QC approved, proposed drug substance specification.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of method validation reports, if new analytical procedures are used.
4. (S.4.3) Comparative analytical results demonstrating that the approved and proposed analytical procedures are equivalent.
5. (S.4.5) Justification of the proposed drug substance specification.

3.2.S.6 Container closure system

12. Change in the primary container closure system(s) for the storage and shipment of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1-3	Notifiable Change
	1,2	2,3	Annual Notification

Conditions

1. Results demonstrate that the proposed container closure system is at least equivalent to the approved container closure with respect to its relevant properties (such as including results of transportation or interaction studies, if appropriate).
2. The drug substance is not sterile or the change does not affect sterilization parameters of a sterile drug substance.

Supporting data

1. (S.2.5) Evidence of process validation for the sterilization process, if different from the current process.
2. (S.6) Information on the proposed container closure system (for example, description, materials of construction, specifications).
3. (S.7.3) Results of a minimum of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing of the drug substance in the proposed container closure system.

3.2.S.7 Stability

13. Change in the re-test period (or shelf-life) for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Extension	None	1-4	Notifiable Change
	1-2	1-4	Annual Notification
b. Reduction	1	1-4	Annual Notification

Conditions

1. The drug substance meets the approved stability specification.
2. Full long-term stability data is available covering the proposed re-test period (or shelf-life) and is based on stability data generated on at least 3 commercial scale batches.

Supporting data

1. (S.7.1) Summary of stability testing and results (for example, studies conducted, protocols used, results obtained).
2. (S.7.1) Proposed storage conditions and re-test period (or shelf-life, as appropriate).
3. (S.7.2) Updated post-approval stability protocol and stability commitment.

4. (S.7.3) Results of stability testing generated on at least 2 pilot and/or commercial scale batches with stability data to support the proposed re-test period or shelf-life.

14. Change in the storage conditions for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition/deletion of a cautionary statement or relaxation/tightening of a temperature criterion (for example, from 15-25 ˚C to 15-30 ˚C).	None	1	Annual Notification

Conditions

None

Supporting data

1. (S.7.3) If applicable, stability testing results to support the change to the storage conditions on at least 2 lots (pilot or commercial scale).

Examples (drug product)

3.2.P.1 Description and composition of the drug product

15. Addition of a dosage form or strength

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition of a dosage form or strength	None	1-14	Supplement

Conditions

None

Supporting data

1. (1.5) Supporting clinical or comparative bioavailability data, in vitro in vivo correlation (IVIVC) data (or a request for a waiver of in vivo studies).
2. (1.2.5) Evidence of GMP compliance status and Establishment License (EL) Information. For more information, refer to the Notice: Submission Filing Recommendations for Veterinary Drugs - Good Manufacturing Practices and Drug Establishment Licences
3. (1.2.6) Letters of Access if Master Files (MFs), are submitted for new excipients.
4. Package Insert and Inner and Outer Labels.
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (such as choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing (such as multi-point dissolution profiles in the release medium for solid dosage units) for the approved and proposed products, discussion of any in vitro and/or in vivo studies.
7. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
8. (P 3.5) Process validation data on 3 consecutive commercial batches and /or QC approved Process validation protocol of the proposed drug product. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches per year). In addition, for a sterile drug product, evidence of validation for the sterilization process.
9. (P.4) Control of Excipients, if new excipients are proposed (such as specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
10. (P.5) Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), Batch Analyses (certificate of analyses for a minimum of 1 pilot scale batch per strength).
11. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
12. (P.8.1) Stability Summary and Conclusions (minimum of 2 pilot scale batches), results of a minimum of 6 months of accelerated (or intermediate as appropriate) and 6 months of long-term testing of the proposed drug product; bracketing and matrixing approaches for multiple strengths and packaging components could be applied, if scientifically justified.
13. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
14. (R.1) Executed Production Documents for at least 1 pilot scale batch of each new dosage form or strength.

16. Change in the composition of a solution dosage form

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the composition of a solution dosage form	2	1-13	Supplement
	1,3,4,5,7	2-13	Notifiable Change
	1,3-8	2-13	Annual Notification

Conditions

1. The changes in excipients of the approved and proposed drug products are considered to be qualitatively the same and quantitatively essentially the same (as defined in the Health Canada guidance document Pharmaceutical Quality of Aqueous Solution).
2. The proposed excipient(s) does/do not function to affect the absorption of the drug substance.
3. The proposed excipient(s) does/do not function as a preservative or preservative enhancer.
4. No Level I or Level II changes in the specifications of the proposed excipient(s) or the drug product.
5. No change to the physical characteristics of the drug product (such as viscosity, pH, osmolality).
6. The change does not concern a sterile drug product.
7. The change concerns a drug product containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).
8. The proposed colouring agent (if applicable) is permitted by the Canadian regulations (refer to the section C.01.040.2 of the *Food and Drug Regulations*).

Supporting data

1. Literature data or evidence to confirm that the change does not affect the absorption of the drug substance.
2. Supporting palatability data when a flavouring agent has been added, removed or replaced.
3. (1.2.6) Letters of Access if Master Files (MFs), are submitted for new excipients, when applicable.
4. Package Insert and Inner and Outer Labels, when applicable.
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (such as choice of excipients, compatibility of drug substance and excipients), comparative testing on the physicochemical properties for the approved and proposed products, results of preservative effectiveness testing (if applicable).
7. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
8. (P.3.5) Process validation data on 3 consecutive commercial batches and /or QC approved Process validation protocol of the proposed drug product. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches per year). In addition, for a sterile drug product, evidence of validation for the sterilization process.
9. (P.4) Control of Excipients (for example, specifications with justification).
10. (P.5) Batch Analyses (certificate of analyses for a minimum of 1 pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions: results of a minimum of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing for at least 2 pilot scale batches of the proposed drug product.

12. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
13. (R.1) Executed Production Documents for at least 1 pilot scale batch of each strength of the proposed product.

17. Change in the composition of an immediate release dosage form (including a medicated premix)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the composition of an immediate release dosage form (including a medicated premix)	4	1-13	Supplement
	1-5	2-13	Notifiable Change
	1-7	2-13	Annual Notification

Conditions

1. The changes in the excipients are considered to be qualitatively the same.
2. The quantitative changes in excipients, expressed as percentage (w/w) of total formulation, are less than or equal to the ranges outlined in Appendix 2.
3. The change does not affect the performance characteristics of the drug product.
4. The proposed excipient(s) does/do not function to affect the absorption of the drug substance.
5. No Level I or Level II changes in the specifications of the proposed excipient(s) or the drug product.
6. The change concerns a drug product containing drug substances that are discrete chemical entities (the drug substance is not a polymer or polymeric complex).
7. The proposed colouring agent (if applicable) is permitted by the Canadian regulations (refer to the section C.01.040.2 of the *Food and Drug Regulations*).

Supporting data

1. Literature data or evidence to confirm that the change does/do not affect the absorption of the drug substance.
2. Supporting palatability data when a flavouring agent has been added, removed or replaced
3. (1.2.6) Letters of Access if Master Files (MFs) are submitted for new excipients.
4. Package Insert and Inner and Outer Labels, when applicable.
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (such as choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing for the approved and proposed products (for example, depending on the solubility and permeability of the drug (refer to Appendix 1), multi-point dissolution profiles in either the release medium or in multiple media covering the physiological pH range), discussion of any in vitro and/or in vivo studies, results of preservative effectiveness testing (if applicable).
7. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
8. (P.3.5) Process validation data on 3 consecutive commercial batches and /or QC-approved Process validation protocol of the proposed drug product. Concurrent validation would be acceptable for low

volume drug products (for example, only 2 batches per year). In addition, for a sterile drug product, evidence of validation for the sterilization process.

9. (P.4) Control of Excipients, if new excipients are proposed [such as specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations].
10. (P.5) Batch Analyses (certificate of analyses for a minimum of 1 pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of 2 pilot scale batches): results of a minimum of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing of the proposed drug product (bracketing or matrixing approaches for multiple strengths and packaging components could be applied, if scientifically justified).
12. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
13. (R.1) Executed Production Documents for 1 batch representative of each strength of the proposed product.

18. Addition, deletion or replacement of micro tracer used in a medicated premix

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition, deletion or replacement of micro tracer used in a medicated premix	1	1-4	Annual Notification

Conditions

1. The proposed micro tracer is pre-tested to confirm stability in the drug premix, and there is no change in the stability protocol, stability tests, and stability commitment of the medicated premix.

Supporting data

1. Justification of the addition/removal or replacement of the micro tracer (for example, demonstration of the suitability of the new micro tracer to control the medicated premix, including batch to batch consistency). Justification that there is no "statistically significant" deviation from complete mixing.
2. Information supporting adequacy of batch-to-batch cleanout of the mixer and other feed manufacturing equipment.
3. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, process validation data and/or QC approved Process Validation Protocol. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches per year).
4. (R.1) Executed Production Documents for one batch representative of each strength of the proposed product.

19. Change to the composition of a modified release dosage form

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change to the composition of the release controlling agent in a modified release dosage form	None	1-12	Supplement
	1,2	1-12	Notifiable Change

Conditions

1. The change is within parameters established by an in vitro in vivo correlation previously approved by Health Canada.
2. No changes in the specification of the drug product other than appearance or changes to comply with a Schedule B monograph.

Supporting data

1. (1.5) Supporting clinical or comparative bioavailability data (the supporting clinical or comparative bioavailability data may be waived if an acceptable in vitro in vivo correlation has been established and approved).
2. (1.2.6) Letters of Access if Master Files (MFs) are submitted for new excipients.
3. Package Insert and Inner and Outer Labels, when applicable.
4. (P.1) Description and composition of the dosage form.
5. (P.2) Discussion of the components of the drug product (for example, choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing, for example:
    - depending on the mechanism for drug release (extended or delayed)
    - drug release profiles in multimedia or using different agitation speeds) for the approved and proposed products
    - discussion of any in vitro and/or in vivo studies
    - results of preservative effectiveness testing (if applicable)
6. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
7. (P.3.5) Process validation data on 3 consecutive commercial batches and /or QC approved Process validation protocol of the proposed drug product. In addition, for a sterile drug product, evidence of validation for the sterilization process. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
8. (P.4) Control of Excipients, if new excipients are proposed (for example, specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
9. (P.5) Batch Analyses (certificate of analyses for a minimum of 1 pilot scale batch per strength).
10. (P.8.1) Stability Summary and Conclusions (minimum of 2 pilot scale batches). For example, results of a minimum of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing of the proposed drug product.
11. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
12. (R.1) Executed Production Documents for 1 batch of each strength.

20. Change to product markings, involving a change in embossing, debossing, or engraving (except scorelines/break lines) or a change in imprinting

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change to product markings, involving a change in embossing, debossing, or engraving, except scorelines/break lines (for example, plain tablet to engraved, engraved to plain, change in engraving), or a change in imprinting (for example, plain tablet/capsule to imprinted tablet/capsule)	1,2	1-3	Annual Notification

Conditions

1. The change does not affect the stability or performance characteristics (such as release rate) of the drug product.
2. Changes to the drug product specifications are those necessitated only by the change to the markings.

Supporting data

1. Package Insert and Inner and Outer Labels.
2. (P.5) Specification(s) and Batch Analysis (such as Certificate of Analysis for 1 batch per strength).
3. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).

21. Change in scoring configuration

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition of a scoreline	1,3	1-6	Notifiable Change
b. Deletion of a scoreline	1-4	1,4-6	Annual Notification

Conditions

1. The change does not affect the stability or performance characteristics (such as release rate) of the drug product.
2. Changes to the drug product specifications are those necessitated only by the change to the scoring.
3. The change does not concern a modified release drug product.
4. Addition or deletion of a score line to a generic product is consistent with a similar score line in the innovator product (Canadian Reference Product).

Supporting data

1. Package Insert and Inner and Outer Labels.
2. (P.2) Comparative, multi-point dissolution profiles for the approved and proposed products performed using the release conditions.
3. (P.2) Demonstration of the uniformity of the dosage units of the split tablets.
4. (P.5) Specification(s) and Batch Analysis (such as Certificate of Analysis for 1 batch per strength).

5. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6. (R.1) Executed Production Documents for 1 batch representative of each strength of the proposed product.

22. Change in shape or dimensions of tablets, capsules, suppositories, or pessaries

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in shape or dimensions of tablets, capsules, suppositories, or pessaries	1,2	1-6	Notifiable Change
	1-3	1-6	Annual Notification

Conditions

1. No change in the qualitative and quantitative composition and mean mass or fill weight.
2. Changes to the drug product specifications are those necessitated by the change to the drug product shape or dimensions.
3. The change does not concern a modified release drug product or does not affect the performance characteristics (such as release rate) of the drug product.

Supporting data

1. Package Insert and Inner and Outer Labels, when applicable.
2. (P.2) Discussion of the differences in manufacturing process(es) between the approved and proposed products and the potential impact on product performance
3. (P.2) Comparative, multi-point dissolution profiles for the approved and proposed products performed using the release conditions.
4. (P.5) Specification(s) and Batch Analysis (such as Certificate of Analysis for 1 batch per strength).
5. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6. (R.1) Executed Production Documents for 1 batch representative of each strength of the proposed product.

23. Change in diluent

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. replacement or addition of a diluent for a lyophilized powder or concentrated solution	None	1-11	Supplement
	1	2,4,8	Notifiable Change
b. deletion of a diluent	None	2	Annual Notification

Conditions

1. Diluent is commercially available with a valid Drug Identification Number (DIN).

Supporting data

1. (1.2.6) Letters of Access if Master Files (MFs) are submitted for new excipients.
2. Package Insert and Inner and Outer Labels.
3. (P.1) Description and composition of the diluent.
4. (P.2) Discussion of the components of the drug product, as appropriate (such as choice of excipients, compatibility of the drug product with the diluent).
5. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, process validation data and/or QC approved Process Validation Protocol, and testing standards for the diluent if it is included with the product. Concurrent validation would be acceptable for low volume drug products (such as only 2 batches per year).
6. (P.4) Control of Excipients, if new excipients are proposed (such as specifications, confirmation that none of the excipients are prohibited by the *Food and Drug Regulations*).
7. (P.5) Batch Analyses (such as Certificate of Analysis for a minimum of 1 pilot scale batch of the diluent, if it is included with the product.
8. (P.7) Discussion (including description, materials of construction on the container closure system, compatibility studies with the diluent).
9. (P.8.1) Stability Summary and Conclusions: results for 2 pilot scale batches of a minimum of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing of the diluent.
10. (P.8.2) Updated post-approval stability protocol and stability commitment for the diluent if it is included with the product.
11. (R.1) Executed Production Documents for 1 batch of the diluent if it is included with the product.

3.2.P.2 Pharmaceutical development

24. Change in the approved design space

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Establishment of a new design space	None	1	Supplement
b. Expansion of the approved design space	None	1	Supplement
c. Reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space)	None	1	Notifiable Change
d. Process parametric release	None	1	Supplement

Conditions

None

Supporting data

1. (P.2) Pharmaceutical development data to support the establishment or changes to the design space (including changes to process parametric release for sterile products). For changes to Process Parametric Release (PPR), provide a thorough risk assessment that identifies the risks of manufacturing and releasing non-sterile product and the proposed management plan. For further information on requirements for obtaining authorization for PPR, consult the Health Canada's Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

3.2.P.3 Manufacture

25. Replacement or addition of a drug product manufacturer / manufacturing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Production of a modified release, product with a complex matrix (such as emulsions, extended release parenterals, implants) or sterile product	None	1-10	Supplement
	1	2-10	Notifiable Change
b. Production of an immediate release product (for example, tablet, capsule, liquids, semi-solids)	None	2-10	Notifiable Change
	1-4	2-5,7-10	Annual Notification

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
c. Primary packaging	2,3	2,5	Annual Notification
d. Testing (such as release, stability)	None	2,5,7-9	Notifiable Change
	5 or 6	2,5,7-9	Annual Notification
e. Storage and distribution	1-3	2,3,5	Annual Notification

Conditions

1. No change in the Batch Formula, Description of Manufacturing Process, Equipment Class and Process Controls, Controls of Critical Steps and Intermediates, or Drug Product Specifications.
2. No Level I change in the container closure system.
3. The proposed facility has a current satisfactory Canadian GMP rating as determined by the Health Product Compliance Directorate, ROEB, GMP screening acceptance notice (at "Day 90") from the ROEB, or is already included in the Establishment License.
4. 3 consecutive production scale batches have been successfully validated as per QC approved process validation protocol, and technical transfer and/or process validation reports at the proposed site are available. Concurrent validation would be acceptable for low volume drug products (such as only 2 batches manufactured per year).
5. The analytical method(s) for the new testing site is/are equivalent to the analytical method(s) in the compendial drug product monograph (Schedule B of the *Food and Drug Regulations*).
6. All analytical tests are equivalent to previously validated /registered methods.

Supporting data

1. (1.5) Supporting clinical or comparative bioavailability data (or a request for a waiver of in vivo studies) (the supporting clinical or comparative bioavailability data may be waived if an acceptable in vivo/in vitro correlation has been established).
2. (1.2.5) Evidence of GMP compliance status and Establishment License (EL) Information. For more information, refer to the Notice: Submission Filing Recommendations for Veterinary Drugs - Good Manufacturing Practices and Drug Establishment Licences.
3. (P) Confirmation that information on the drug product has not changed as a result of the submission (for example, other than change in site).
4. (P.2) Comparative in vitro testing (such as multi-point dissolution profiles in the release medium for solid dosage units, comparative diffusion test results for semi-solids) for one batch of each strength of the approved and of the product produced at the new site (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified). See Appendix 1 for additional detail.
5. (P.3.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing, packaging, testing, storage and/or distribution.

6. (P.3.5) Process validation data on 3 consecutive commercial scale batches of the product at the new site and/or QC approved process validation protocol; in addition, for a sterile product, evidence of validation for the sterilization process. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
7. (P.5.3) Copies and summaries of method validation reports / method transfer reports, which demonstrate equivalency of analytical procedures used by the currently approved and proposed sites.
8. (P.5.4) Certificate of analyses for at least 1 commercial scale batch (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the product produced and/or tested at the new site (as applicable) into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Executed Production Documents for at least 1 commercial scale batch of each strength of the proposed product.

26. Change in the batch size for the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Increase in batch size beyond a factor of 10 times for a modified release drug product	None	1-7	Supplement
b. Increase in batch size beyond a factor of 10 times for an immediate release drug product	1-5	2,3,5-7	Annual Notification
c. Increase in batch size, up to and including a factor of 10 times	4	2,3,5-7	Annual Notification
d. A downscaling in the batch size	1-3,5	2-7	Annual Notification

Conditions

1. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size, (such as use of different sized equipment.)
2. The change should not be a result of unexpected events, resulting in failure to meet specifications, arisen during manufacture, or because of stability concerns.
3. The change in batch size is in comparison to the pivotal clinical/biobatch, or to the approved and validated commercial scale batches.
4. 3 consecutive production scale batches have been successfully validated as per QC approved process validation protocol. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
5. The change does not affect the sterilization procedure of a sterile drug product.

Supporting data

1. (1.5) Supporting clinical or comparative bioavailability data (or a request for a waiver of in vivo studies).
2. (P.2) Comparative in vitro testing (for example, multi-point dissolution profiles in the release medium for solid dosage units, comparative diffusion test results for semi-solids) for one batch of each strength of the approved and at the proposed scale.
3. (P.3.2) Batch formula of the proposed dosage form.
4. (P.3.5) Process validation data on 3 consecutive production scale batches of the proposed drug product and /or QC approved process validation protocol. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year). Confirmation that the reference batch size has been previously validated, as per approved process validation protocol; in addition, for sterile products, evidence of validation for the sterilization process.
5. (P.5.4) Description of the batches and summary of results for at least 1 commercial scale batch at the proposed scale.
6. (P.8.2) Updated post-approval stability protocol (QC approved) and stability commitment to place the first commercial scale batch of each strength at the proposed scale into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
7. (R.1.2) Executed Production Documents for at least 1 commercial scale batch of each strength of the proposed product.

27. Change in the drug product manufacturing process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the drug product manufacturing process	None	1-8	Supplement
	1-5	2-8	Notifiable Change
	1-8	2,3,5-8	Annual Notification

Conditions

1. The change does not affect the performance of the drug product.
2. The manufacturing processes for the approved and proposed products use the same principles and the same classes of equipment (note: a change from wet to dry granulation, from direct compression to wet/dry granulation, or vice versa, would be considered in principle).
3. Changes to equipment, operating procedures and process controls are minor/non-critical. The equipment used to produce the proposed product may vary in capacity, but are of the same class and operating principles.
4. The change is not the result of unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
5. The change does not involve the packaging or labelling where the primary packaging provides a metering and/or delivery function.
6. 3 consecutive commercial scale batches have been successfully validated as per QC-approved process validation protocol (this condition could be waived with justification for minor/non-critical

changes as outlined in Condition #3). Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
7. The change does not concern a modified release drug product.
8. The change does not affect the sterilization procedure of a sterile drug product.

Supporting data

1. (1, 5) Supporting clinical or comparative bioavailability data.
2. (P.2) Discussion of:
    - the development of the manufacturing process, where applicable
    - comparative in vitro testing for the approved and proposed products, such as:
        - multi-point dissolution profiles in the release medium for solid dosage units
        - particle size distribution
        - comparative diffusion test results for semi-solids
    - any in vitro and/or in vivo studies, where applicable
3. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
4. (P.3.5) Process validation data on 3 consecutive production scale batches of the drug product and or QC approved process validation protocol. For sterile products, evidence of validation and/or evaluation studies for the sterilization process. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
5. (P.5) Specification(s) (if specification(s) have changed), Batch Analyses (certificate of analyses for at least one commercial scale batch per strength).
6. (P.8.1) Stability Summary and Conclusions:
    - For a major change to the manufacturing process (for example, change in equipment class or manufacturing principles), results for 2 pilot scale batches of a minimum of:
        - 3 months of accelerated (or intermediate as appropriate) **and**
        - 3 months of long-term testing of the proposed drug product (bracketing and matrixing may be applied, if scientifically justified)
    - For a minor change to the manufacturing process (such as a change in mixer stirring speed), stability data at the time of filing would not be necessary (see P.8.2 below). Bracketing and matrixing may be applied, if scientifically justified.
7. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
8. (R.1.2) Executed Production Documents for at least 1 commercial scale batch of each strength of the proposed product.

28. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Deletion of a test	1,4,5	1,4	Annual Notification
b. Replacement or addition of a test	1-4,6	1-4	Annual Notification
c. Relaxation or tightening of an acceptance criterion	1,4	1-4	Annual Notification

Conditions

1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria (applies to replacement, not to addition of a test, where applicable).
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not affect the sterilization parameters or procedures of a sterile drug product.
5. The deleted analytical procedure has been demonstrated to be redundant with respect to the remaining analytical procedures (such as colour), and does not pertain to a critical quality attribute of the product (such as blend uniformity, weight variation).
6. The replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Supporting data

1. (P.3.3) Description of the proposed process controls or acceptance criteria of the critical steps and intermediates.
2. (P.3.5) Process validation data and /or QC approved Process validation protocol of the proposed drug product. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
3. (P.5.4) Description of the batches, and certificate of analyses for at least 1 commercial scale batch.
4. (R.1.2) Executed Production Documents for at least 1 batch of each strength of the proposed product or Master Production Documents.

29. Change in the approved protocol for process validation and/or evaluation studies

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the approved protocol for process validation and/or evaluation studies	1,2	1	Annual Notification

Conditions

1. The change does not concern a modified release drug product.
2. The change does not affect the sterilization procedures of a sterile drug product.

Supporting Data

1. (P.3.5) QC approved revised process validation and/or evaluation studies. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).

3.2.P.4 Control of excipients

30. Change in the source of an excipient

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in the source of an excipient from a vegetable, synthetic source, or non-TSE (such as animal) to a TSE risk (such as animal) source, or from a TSE risk (such as animal) to a different TSE risk (such as a different animal) source	None	2-4	Notifiable Change
	1,2	2-4	Annual Notification
b. Change in the source of an excipient from a TSE risk (such as animal) source to a vegetable or synthetic source	None	1,3	Annual Notification

Conditions

1. There is no qualitative or quantitative change in the excipient.
2. The change of source is supported by a valid Transmissible Spongiform Encephalopathy (TSE) Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM), or excipient is obtained from a previously approved source.

Supporting data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in terms of physico-chemical characterization of the proposed excipient with the approved excipient.
4. TSE Certificate of Suitability (CEP) issued by the EDQM, if available, or satisfactory BSE/TSE risk assessment on proposed excipient.

3.2.P.5 Control of drug product

31. Change regarding the standard claimed for the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in the standard claimed for the drug product (for example, from a Professed to Schedule B pharmacopoeial standard)	1,2	1-5	Annual Notification
b. Change in the specification for the drug product to comply with an updated Schedule B pharmacopoeial monograph	1,2	2-5	Annual Notification

Conditions

1. The change is made exclusively to comply with the Schedule B pharmacopoeia monograph.
2. No change to the specification that results in a potential impact on the performance of the drug product.

Supporting data

1. Package Insert and Inner and Outer Labels.
2. (P.5.1) Updated, QC approved, proposed drug product specification.
3. (P.5.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
4. (P.5.4) Description of the batches, certificates of analyses, and summary of results, for at least 1 batch (minimum pilot scale) of the drug product tested according to the proposed specification.
5. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program. Bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified.

32. Change in the specification for the drug product tests and acceptance criteria

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. For sterile products, replacing the sterility test with alternative microbiological methods or process parametric release	None	1,2,5,7-9	Supplement
b. Deletion of a test	1,4-7	2,8,9	Annual Notification
c. Replacement or addition of a test	1-4,6-8	2-6,8,9	Annual Notification

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
d. Relaxation of an acceptance criterion	None	2,5,6,8,9	Notifiable Change
	1,4,6-8	2,5,6,8,9	Annual Notification
e. Tightening of an acceptance criterion	1,4,6,7	2,8,9	Annual Notification

Conditions

1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria (applies to replacement, not to addition of a test, where applicable).
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No changes in the impurity profile that impacts safety of the drug product. Acceptance criterion for any Class 3 residual solvent is within the VICH limits (the relaxation of an acceptance criterion for a Class 1 or 2 solvent should be filed as a Notifiable Change).
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests and does not impact the safety or overall quality of the product [for example, removal of an organic volatile solvent test after at least 10 commercial scale batches tested and meet approved acceptance criteria, or provide valid scientific justification].
6. The change to the specifications does not affect the performance of the drug product.
7. The change does not concern sterility testing.
8. The relaxed criterion is in accordance with a Schedule B compendial monograph.

Supporting data

1. (P.3.5) Process validation data. Concurrent validation would be acceptable for low volume drug products (for example, only 2 batches manufactured per year).
2. (P.5.1) Updated, QC approved, proposed drug product specification.
3. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
4. (P.5.3) Copies or summaries of method validation reports, if new analytical procedures are used.
5. (P.5.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
6. (P.5.4) Description of the batches, and summary of results, for at least 1 (minimum pilot scale) of the drug product tested according to the proposed specification.
7. (P.5.4) Description of the batches, and summary of results, of a sufficient number of batches (at least 10 commercial scale batches) to support the process parametric release.
8. (P.5.6) Justification of the proposed drug product specification (for example, demonstration of the suitability to control the drug product, including degradation products). For Process Parametric Release (PPR), a provide a thorough risk assessment that identifies the risks of manufacturing and releasing non-sterile product and the proposed management plan. For further information on

requirements for obtaining authorization for PPR, consult the Health Canada's Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

9. For drug products that contain a drug substance that is not a discrete chemical entity (the drug substance is not a polymer or polymeric complex), demonstration that consistency of quality and of the production process is maintained.

33. Change in the specification for the drug product regarding analytical procedures

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Deletion of an analytical procedure	5	1,6	Notifiable Change
	5,6	1,6	Annual Notification
b. Replacement, alternate, or additional analytical procedure	None	1-6	Notifiable Change
	1-5	1-6	Annual Notification
c. Change from a House analytical procedure to a Schedule B analytical procedure, a change from an approved compendial analytical procedure to an harmonized compendial procedure, or from one Schedule B standard to a different Schedule B standard).	1,3	1-6	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. The method of analysis is based on the same analytical technique or principal and no new impurities are detected (Refer to VICH GL11 for impurity thresholds).
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The change does not concern sterility testing nor does it impact the dissolution test condition (such as apparatus, speed, medium) for a modified release product.
6. The deleted analytical procedure has been demonstrated to be redundant with respect to the remaining procedures and does not impact the safety or overall quality of the product (for example, removal of an organic volatile solvent test after at least 10 commercial scale batches tested and meet acceptance criteria, or provide valid scientific justification).

Supporting data

1. (P.5.1) Updated, QC approved, proposed drug product specification.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.

4. (P.5.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
5. (P.5.4) Description of the batches, and summary of results, for at least 1 batch (minimum pilot scale) of the drug product tested according to the proposed specification, if applicable.
6. (P.5.6) Justification of the proposed drug product specification (for example, demonstration of the suitability to control the drug product, including degradation products), if applicable.

34. Change of specification for a veterinary drug product used in food producing animals

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change of specification for a veterinary drug product used in food producing animals	None	1-8	Supplement
	4,6	1,4,5,8,9	Notifiable Change
	1-5	1,4,5,8,9	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
3. Acceptance criteria for degradation products and any Class 3 residual solvents are within the VICH GL 10, VICH GL 11 and VICH GL 18 limits, where applicable (the relaxation of an acceptance criterion for a Class 1 or 2 solvent should be filed as a Notifiable Change).
4. The change to the specifications does not result in a potential impact on the performance of the drug product (for example, solubility, release rate, dissolution).
5. The change does not concern sterility testing.
6. The change does not affect the withdrawal period (or withholding time for milk) of the veterinary drug product.

Supporting data

1. (P.5.1) Updated, QC approved, proposed drug product specification.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
5. (P.5.4) Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least 1 batch (minimum pilot scale) of the drug product tested according to the proposed specification.
6. (P.5.4) Description of the batches, certificates of analyses, and summary of results, in a tabular format, of a sufficient number of batches (at least 10 commercial scale batches) to support the process parametric release, where applicable.
7. (P.5.6) Justification of the proposed drug product specification (for example, demonstration of the suitability of the monograph to control the drug product, including degradation products). For Process Parametric Release (PPR), provide a thorough risk assessment that identifies the risks of

manufacturing and releasing non-sterile product and the proposed management plan. For further information on requirements for obtaining authorization for PPR, consult the Health Canada's Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

8. For drug products that contain a drug substance that is not a discrete chemical entity (the drug substance is not a polymer or polymeric complex), demonstration that consistency of quality and of the production process is maintained.
9. Confirmation that the withdrawal period (or withholding time for milk) has not been affected as a result of the change.

3.2.P.7 Container closure system

35. Change from an approved single-dose container to multi-dose container including in-use stability period

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change from an approved single-dose container to multi-dose container including in-use stability period	1	1-6	Notifiable Change

Conditions

1. The change does not involve a functional container closure system (for example, pre-filled auto injector).

Supporting data

1. Package Insert and Inner and Outer Labels.
2. (P.2) Information demonstrating suitability of the proposed container/closure system for its intended use (evidence that it is meeting the relevant pharmacopoeial tests, for example:
    - USP <661> Plastic Packaging Systems and their materials of construction
    - USP <1663> and <1664> Extractables and Leachables
    - USP <87> Biological Reactivity Tests, In Vitro
    - USP <88> Biological Reactivity Tests, In Vivo, as applicable
    - USP <381> Elastomeric Closures for Injections
    - USP <671> Containers - Performance Testing
    - Description of any additional treatments such as sterilization and depyrogenation of the components
3. (P.7) Information on the proposed container closure system, as appropriate [such as description, materials of construction of primary/secondary packaging components, performance specifications].
4. (P.3.5) For sterile products, process validation and/or evaluation studies, or provide equivalency rationale. For a secondary functional container closure system, validation testing report.
5. (P.8.1) Summary of stability testing and results [such as studies conducted, protocols used, results obtained].
6. (P.8.3) Stability test results from:
    - accelerated testing (usually a minimum of 3 months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; **and**
    - 3 months of real time/real temperature testing on 3 drug product batches stored in the proposed container, or longer if less than 3 time points are available (including the zero time point), as well as commitment to notify Health Canada of any failures in the ongoing long-term stability studies.

Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to VICH GL45).

36. Replacement or addition of a primary container closure system and change to the package size

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a primary container closure system	None	1-6	Notifiable Change
	1-4	1,2,4,6	Annual Notification
b. Change in the package size involving change in the fill weight / fill volume	None	1-7	Notifiable Change
	1-4	1,2,4-7	Annual Notification
c. Change in the package size involving a change in the number of units (such as tablets, ampoules) per package	None	1-6	Notifiable Change
	1-4	1,2,4-6	Annual Notification

Conditions

1. The change does not concern a sterile product.
2. No change in the type of container closure or materials of construction.
3. The change does not concern a container closure that functions to meter the drug product.
4. The change is consistent with the posology and treatment duration.

Supporting data

1. Package Insert and Inner and Outer Labels, when applicable.
2. (P.2) Information demonstrating the suitability of the proposed container closure system for its intended use (evidence that it is meeting the relevant pharmacopoeial tests, such as:
    - USP <661> Plastic Packaging Systems and their materials of construction
    - USP <1663> and <1664> Extractables and Leachables
    - USP <87> Biological Reactivity Tests, In Vitro
    - USP <88> Biological Reactivity Tests, In Vivo, as applicable
    - USP <381> Elastomeric Closures for Injections
    - USP <671> Containers - Performance Testing
    - Description of any additional treatments such as sterilization and depyrogenation of the components

For changes to functional packaging, data to demonstrate that the functioning of the new packaging is equivalent to that previously approved.

3. (P.3.5) For sterile products, evidence of the sterilization process for the container closure system and validation data of the manufacturing process for the new additional package size, where applicable.
4. (P.7) Information on the proposed container closure system (such as description, materials of construction of primary packaging components, specifications, including results of transportation studies, if appropriate).
5. (P.8.1) Stability Summary and Conclusions, results of a minimum 2 pilot scale batches, of 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. Bracketing and matrixing approaches can be used for multiple strengths and packaging components if scientifically justified.
6. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
7. Rationale for the additional package size.

37. Change in qualitative and/or quantitative composition of any primary or functional secondary container closure component

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in qualitative and/or quantitative composition of any primary or functional secondary container closure component	None	1-6	Notifiable Change
	1,2	1,2,4,6	Annual Notification

Conditions

1. The proposed packaging is at least as protective as the approved packaging.
2. The change does not impact the sterilization procedure of a sterile drug product.

Supporting data

1. Package Insert and Inner and Outer Labels, when applicable.
2. (P.2) Information demonstrating suitability of the proposed container/closure system for its intended use (evidence that it is meeting the relevant pharmacopoeial tests, such as:
    - USP <661> Plastic Packaging Systems and their materials of construction
    - USP <1663> and <1664> Extractables and Leachables
    - USP <87> Biological Reactivity Tests, In Vitro
    - USP <88> Biological Reactivity Tests, In Vivo, as applicable
    - USP <381> Elastomeric Closures for Injection
    - USP <671> Containers - Performance Testing
    - Description of any additional treatments such as sterilization and depyrogenation of the components
3. (P.3.5) For sterile products, process validation and/or evaluation studies.
4. (P.7) Information on the proposed container closure system (such as description, materials of construction of primary packaging components, specifications, including results of transportation studies, if appropriate).

5. (P.8.1) Stability Summary and Conclusions; results of a minimum of 2 pilot scale batches, 3 months of accelerated (or intermediate as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies.
6. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of each strength of the proposed product into the long-term stability program (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).

38. Change in the specification for a primary or functional secondary container closure component

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the specification for a primary or functional secondary container closure component, involving deletion, replacement or addition of a test or; relaxation or tightening of an acceptance criterion	None	1,2	Notifiable Change
	1,2	1,2	Annual Notification

Conditions

1. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
2. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.

Supporting data

1. (P.7) Updated QC approved proposed specifications, including justification.
2. (P.7) Description of the analytical procedure and, if applicable, validation data.

3.2.P.8 Stability

39. Change in the shelf-life for the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Extension	None	1-4	Notifiable Change
	1-2	1-4	Annual Notification
b. Reduction	1	1-4	Annual Notification

Conditions

1. The drug product meets the approved stability specification.
2. Full long-term stability data *is* available covering the proposed shelf-life and *is* based on stability data generated on at least 3 commercial scale batches.

Supporting data

1. (P.8.1) Summary of stability testing and results (such as studies conducted, protocols used, results obtained).
2. (P.8.1) Proposed storage conditions and shelf-life.

3. (P.8.2) Updated post-approval stability protocol and stability commitment.
4. (P.8.3) Results of stability testing (full long-term stability data covering the proposed shelf-life generated on at least 3 commercial scale batches of each strength for each approved packaging format/size), if applicable. Bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified.

40. Change in the product in-use stability period

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Extension or addition	1	1,2	Notifiable Change

Conditions

1. No change to the container closure system.

Supporting data

1. Package insert, Inner and Outer Labels
2. Results of in-use stability tests that simulates the condition of use and lasts the duration of the intended in-use stability period. Tests results should be provided for physical, chemical and microbial properties of the product. The analytical procedures used in the studies should be described and fully validated and a minimum of 2 pilot scale batches should be used in the study. One of the batches should be approaching the end of its shelf life.

41. Change in the storage conditions for the drug product or the diluted or reconstituted product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition of a cautionary statement	1	1,2	Annual Notification
b. Deletion of a cautionary statement	None	1,2	Notifiable Change
c. Relaxation of a temperature criterion	None	1,2	Notifiable Change
d. Tightening of a temperature criterion	1	1,2	Annual Notification

Conditions

1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.

Supporting Data

1. Package Insert and Inner and Outer Labels.
2. (P.8.3) If applicable, stability testing results to support the change to the storage conditions.

42. Change to the post-approval stability protocol for commitment or ongoing batches

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition of a time point at any time, or deletion of time points beyond the approved shelf-life	1	1-4	Annual Notification
b. Changes to comply with a relevant VICH guidance (such as deletion of a time point from previously approved stability protocol, or change in storage conditions)	1	1-5	Annual Notification

Conditions

1. No significant changes to the stability data (as defined in VICH GL 3: "Stability Testing of New veterinary Drug Substances and Medicinal Products" and VICH GL 8: "Stability Testing for Medicated Premixes").

Supporting Data

1. (P.8.1) Summary of stability testing and results (such as studies conducted, protocols used, results obtained).
2. (P.8.1) Proposed storage conditions and shelf-life.
3. (P.8.2) Updated post-approval stability protocol and stability commitment.
4. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment.
5. (P.8.3) Results of stability testing (full long-term stability data covering the proposed shelf-life generated on at least 3 commercial scale batches, bracketing and matrixing could be applied, if justified).

3.2.R.2 Devices

43. Change of an approved device used for administration of a veterinary drug

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition or replacement of a drug administration device that is *not* an integrated part of the primary packaging of a veterinary drug product	3,6	1-3,6	Notifiable Change
	1-6	1,3,6	Annual Notification
b. Deletion of a drug administration device that is not an integrated part of the primary packaging of a veterinary drug product	3	1,3,6	Annual Notification
c. Change in an approved multi-dose administration device for an injectable veterinary drug product	4	1-6	Annual Notification

Conditions

1. No change in the type of drug administration device or materials of construction.
2. No change in the function, suitability, and accuracy of the device.
3. The required dose of the veterinary drug product must still be accurately delivered in line with the approved posology and the results of such studies should be available.
4. The change should be consistent with the posology and treatment duration.
5. The change does not concern a sterile drug product.
6. No change in the strength, pharmaceutical form, or route of administration of the drug product

Supporting data

1. Package Insert and Inner and Outer Labels, when applicable.
2. Data demonstrating the suitability and compatibility of the materials of construction of the device system (such as extractable/leachable testing, permeation testing, biological reactivity tests light transmission, as applicable).
3. Information on the proposed measuring device system (such as description, materials of construction of primary packaging components, specifications, including results of transportation studies, if appropriate).
4. (P.8.1) Stability summary for a moderate change to the drug administration device system (such as different materials of construction); where applicable, in-use stability studies for multi-dose veterinary drugs.
5. (P.8.2) Updated post-approval stability protocol.
6. Reference to certificate of analysis, or other manufacturer standards for the device, where applicable, demonstrating the delivered dose (accuracy, precision) of the proposed device.

44.Change to a device used for the administration of an extended release veterinary drug

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change to a device used for the administration of an extended release veterinary drug [such as addition, deletion, replacement of, or change in materials of construction of an extended release device (such as for intraruminal boluses used for continued release) of a veterinary drug product].	None	1-7	Supplement
	3-5	1,3-7	Notifiable Change
	1-6	1,3-7	Annual Notification

Conditions

1. No change in the type of or materials of construction (such as composition of glass bolus).
2. No change in the shape or dimensions, function, suitability, and accuracy
3. The required dose of the veterinary drug product must still be accurately delivered in line with the approved posology and the results of such studies should be available.
4. The change should be consistent with the posology and treatment duration.
5. No change in release of the drug product into the digestive system and no impact on bioavailability of the active medicinal ingredient.
6. The new device is free from BSE / TSE agent (such as encapsulated gelatin).

Supporting data

1. Package Insert and Inner and Outer Labels, when applicable.
2. (1, 5) Supporting clinical or comparative dose delivery data, where applicable.
3. Data demonstrating the suitability of the materials of construction of the device system (such as extractable/leachable testing, permeation testing, biological reactivity tests, light transmission, as applicable). For changes to dose administering device, data to demonstrate that the delivered dose with the new device is equivalent to that previously approved.
4. (P.7) Information on the proposed dose delivery system (such as description, materials of construction of components, specifications, including results of transportation studies, if appropriate).
5. (P.8.1) Stability Summary and Conclusions, where applicable, results of in-use stability studies for multi-dose veterinary drugs.
6. Reference to certificate of analysis, or other manufacturer standards for the device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.
7. TSE Certificate of Suitability (CEP) issued by the EDQM, if available, or satisfactory TSE risk assessment on material of construction of the device.

45. Minor changes to a device used for the administration of an extended release veterinary drug

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in specification limits of an administration device for a veterinary drug (such as changes in balling gun used for intraruminal boluses to control drug product rate of release).	None	1-4	Notifiable Change
	1	1,4,5	Annual Notification
b. Minor change to an approved test procedure	1	3-5	Annual Notification
c. Addition of a new test parameter	None	1,4	Annual Notification

Conditions

1. Any change should be within the range of currently approved limits.

Supporting data

1. Package Insert and Inner and Outer Labels, when applicable.
2. Data demonstrating the suitability of the materials of construction of the measuring device system [such as extractable/leachable testing, permeation testing, biological reactivity tests, light transmission, as applicable]. For changes to measuring device, data to demonstrate that the measuring of the new device is equivalent to that previously approved.
3. (P.3.5) For sterile products, process validation data and/or evaluation studies, where applicable.
4. (P.7) Information on the proposed dose delivery system [such as description, materials of construction of components, specifications, including results of transportation or interaction studies, if appropriate; detailed description, drawing and composition of the device material and manufacturer specification].

5. Reference to certificate of analysis, or other manufacturer standards for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.

Appendices

Appendix 1: Recommendations for conducting and assessing comparative dissolution profiles

Recommendations when conducting comparative dissolution profiles:

- The resulting comparative dissolution profiles should be considered *similar* using the following equation which defines a similarity factor (f_2):
  $f_2 = 50 \text{ LOG } \{[1+1/n \Sigma^n_{t=1} (R_t-T_t)^2]^{-0.5} x\ 100\}$
  where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the 2 dissolution profiles are *similar*.
- At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the % coefficient of variation at the earlier point should be not more than 20% and at other time points should be not more than 10%.
- The dissolution measurements of the 2 products (such as test and reference, pre- and post- change, 2 strengths) should be made under the same test conditions. The dissolution time points for both the profiles should be the same, for example, for immediate release products: 15, 30, 45 and 60 minutes, for extended release products: 1, 2, 3, 5 and 8 hours.
- Adequate sampling should be performed until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.
- Because f_2 values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution of the product.
- If the individual data for both the test and reference products show more than 85% dissolution within 15 minutes, the profiles are considered *similar*(no calculations are necessary).
- When multi-media dissolution profiles are recommended, these studies should be performed in at least 3 media covering the physiological range (pH 1.2 - 6.8), for example water, 0.1N HCl, and pharmacopoeial buffer media for the test and reference products.
- When delayed-release products (for example, enteric coated) are being compared, it is acceptable to consider either multi-point testing in the acid phase as one of these media, or alternatively for coated products, to compare testing in 3 media once the coating disintegrates (such as pH 4, 5 and 6.8).

Summary of dissolution documentation

Drug permeability/solubility	Comparative dissolution data
Case A: High permeability, high solubility drugs	Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below).
Case B: Low permeability, high solubility drugs	Multi-point dissolution profile should be performed in the submission/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

Drug permeability/solubility	Comparative dissolution data
Case C: High permeability, low solubility drugs	Multi-point dissolution profiles should be performed in at least 3 media covering the physiological range (pH 1.2 - 6.8), for example, 0.1N HCl, and pharmacopoeial buffer media for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached.

Solubility

Solubility is calculated based on the minimum concentration of drug, milligram/ millilitre (mg/mL), in the highest therapeutic dose, determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5°C). *Highly water soluble drugs* are those with a dose/solubility volume of less than or equal to 250 mL. *Highest dose* is the highest approved therapeutic dose for the drug substance in Canada. If not currently approved in Canada, it should be the highest therapeutic dose proposed in the regulatory submission.

Example: Compound A has as its lowest solubility at 37± 0.5°C, 1.0 mg/mL at pH 6.8, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL).

Permeability

Evidence should be provided to justify the degree of permeability claimed for the drug substance. This could include information from published literature and/or data from experimental and/or clinical studies.

Appendix 2: Changes to excipients

Excipient		Percent excipient (w/w) out of total target dosage form core weight
Filler		±5.0
Disintegrant	• Starch • Other	• ±3.0 • ±1.0
Binder		±0.5
Lubricant	• Ca or Mg Stearate • Other	• ±0.25 • ±1.0
Glidant	• Talc • Other	• ±1.0 • ±0.1
Film Coat*		±1.0

Excipient	Percent excipient (w/w) out of total target dosage form core weight
* where the film coat is for appearance only and not intended affect the release rate or stability characteristics of the drug.	

Notes:

- These percentages are based on the assumption that the drug substance in the product is formulated to 100.0% of label/potency. The total additive effect of all excipient changes should be not more than 5.0%.
- Multi-functional Excipients: If an excipient provides multiple functions (for example, microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (±3.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification, including supporting data to demonstrate that the wider range will not affect the other function of the excipient should be provided.
- Bracketing: If different strengths of an immediate release solid oral dosage form have differences in the proportion of excipients which exceed those in the above table, but within the progression of strengths, the changes are incremental, a comparative bioavailability study should be performed on the lowest and highest strengths. Incremental changes are those in which proportions of excipients increase or decrease successively from the lowest to the highest strengths in the range.
- If different strengths contain different excipients, or if the differences in the proportion of excipients exceed those defined in the above table and are not incremental within the progression of strengths, comparative bioavailability studies should be performed on each strength.
- Pharmacokinetic Considerations: It should be noted that the pharmacokinetic characteristics of the medicinal ingredient (such as linear kinetics or non-linear kinetics with greater than or less than proportional increases in area under the curve (AUC) with increasing dose), will also be taken into consideration during the evaluation of a request for a waiver of the requirement to conduct clinical or comparative bioavailability studies on the basis of proportionality of additional proposed strength(s) to the strength used in the in vivo studies.

Appendix 3: Examples of Level IV changes

- Non-critical changes to the licensed application including spelling mistakes, editorial changes made to documents such as Validation Summaries and/or Reports, Analytical Procedures, SOPs, Production Documentation Summaries, QOS, for added clarity that have no impact to affect the safety, efficacy and quality of the product.
- Change in stopper cap colour for an injectable product.
- Modification to pretreatment stages of a WFI system, including purified water systems used solely for pretreatment in WFI production.
- Change in the floor plan that does not affect production process or contamination precautions.
- Addition of vial reject chute.
- Change in the in-process controls performed at non-critical manufacturing steps or change to a non-critical manufacturing area (see Glossary).
- Rooms upgrades, such as installation of improved finishes on floors/walls.
- Addition of a new GMP storage warehouse for raw materials, master and working cell banks and drug substance.
- Installation of non-process-related equipment or rooms to improve the facility, such as warehousing refrigerators or freezers.

- Replacement of equipment with an identical equipment.
- Change in specifications for a compendial raw material to comply with an updated Schedule B pharmacopoeial standard/monograph.
- For veterinary biologics, with the exception of a potency assay or a bioassay, transfer of the QC testing activities for a pharmacopoeial assay to a different laboratory within the same building, to a different building within the same company or to a different company listed on the sponsor's establishment licence.
- Change in supplier for non-critical excipients.
- Change in tertiary packaging components of drug substance or drug product that do not affect stability.
- Change in the name of the drug product manufacturing site.

Appendix 4: Glossary

Acronyms

ASMF

Active Substance Master File

ANDS

Abbreviated New Drug Submission

BRDD

Biologic and Radiopharmaceutical Drugs Directorate

BSE

Bovine Spongiform Encephalopathy

CQA

Critical Quality Attribute

CTD

Common Technical Document

DMF

Drug Master File

EDQM

European Directorate for the Quality of Medicines of the Council of Europe

EL

Establishment Licence

GMP

Good Manufacturing Practices

HC

Health Canada

HVAC

Heating, Ventilation, Air Conditioning

ICH

International Council for Harmonisation

INN

International Non-proprietary Name

IVIVC

in-vitro, in-vivo correlation

NC

Notifiable Change

NDS

New Drug Submission

NOC

Notice of Compliance

PDD

Pharmaceutical Drugs Directorate

QC

Quality Control

Q8(R2)

ICH guideline entitled "Pharmaceutical Development"

Q9(R1)

ICH guideline entitled "Quality Risk Management"

Q10(R1)

ICH guideline entitled "Pharmaceutical Quality System"

Q11

ICH guideline entitled "Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)"

SANDS

Supplement to an Abbreviated New Drug Submission

SNDS

Supplement to a New Drug Submission

TSE

Transmissible Spongiform Encephalopathy

VDD-CPID

Veterinary Drugs Directorate Certified Product Information Document.

VDD-QOS

Veterinary Drugs Directorate Quality Overall Summary

VICH

International Council for Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

WFI

Water for Injection

WHO

World Health Organization

Definitions

Adjuvant:

Component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses. Adjuvant may be of pharmaceutical origin (chemical/synthetic adjuvant) or of biological origin (biological adjuvant).

Batch:

A quantity of drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, produced according to a single production order and as attested by the signatories to the order. In the case of continuous manufacture, a batch corresponds to a defined fraction of the production that is characterised by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Biological auxiliary material:

Raw material from a biological source which is intended to be used as a processing aid in the fabrication of the drug. It may be absent from the drug or may remain as an impurity in the drug at the end of the manufacturing process (for example, biological additives used to supplement cell culture medium in production fermenter, human antithrombin III used to complex and remove human thrombin).

Biological starting material:

Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (such as plasma derivatives, ascitic fluid, bovine lung) or indirectly (such as cell substrate, host/vector production cells, eggs, viral strains).

Carrier:

An edible material (such as calcium carbonate, rice hull, corn cobs, gluten) to which drug substances are added to form a homogenous drug premix or is used to dilute the drug premix (or medicated premix) to form medicated feed.

Certificate of suitability (CEP):

A certificate of compliance of a substance with the relevant requirements of the European Pharmacopoeia monographs for use in medicinal products issued by the European Directorate for the Quality of Medicine of the Council of Europe (EDQM).

Container closure system:

The sum of packaging components that together, contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Change-over procedure:

A logical series of validated steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins.

Closed process/closed system:

Process equipment or process step in which the product is not exposed to the external environment. A closed system requires that the quality of materials entering or leaving the system and the manner in which these materials are added/removed from the system is carefully controlled.

Critical manufacturing step:

A manufacturing process/step that may result in a potential change in the purity/impurity profile or due to the nature of the starting materials or resulting product/intermediate, requires containment within a specially designed manufacturing area or production facility, for example, the development and preparation of cell banks and seed lots, initial propagation, scale-up, blood and plasma pooling and fractionation, fermentation, harvesting, inactivation, purification, addition of adjuvants or preservatives, the conjugation and pooling of bulk concentrates and the final preparation of drug product including concentration/diafiltration, formulation, sterile filtration, filling and lyophilization.

Critical process parameter:

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Quality Attribute:

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Delayed release:

Release of a drug (or drugs) at a time other than immediately following oral administration.

Dilute drug premix:

A drug for veterinary use that results from mixing a drug premix with a feed as defined in section 2 of the *Feeds Act*, to such a level that at least 10 kg of the resulting mixture is required to medicate one tonne of

complete feed, as defined in section 2 of the *Feeds Regulations* , 1983, with the lowest approved dosage level of the drug.

Design space:

The multidimensional combination and interaction of input variables (such as material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Different host/media-type:

Mammalian cells or any micro-organisms involved in the manufacture of a drug substance which are different from the existing hosts in the facility or use a cell culture or fermentation medium with significantly differing composition.

Discrete chemical entity:

A single molecular entity with a known chemical structure.

Dosage form:

A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses.

Drug product:

The dosage form in the final immediate packaging intended for marketing.

Drug substance:

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Drug substance intermediate:

A material produced during steps in the synthesis of a drug substance that must undergo further molecular change or processing before it becomes a drug substance

Equivalency of method:

The proposed analytical method has been validated and demonstrated to be equivalent to the approved method in terms of suitability for its intended use.

Equivalent equipment:

Equipment with similar design and same operating principle and fabricated with product-contact material of same or higher grade quality. Equivalent equipment should give a product of same quality as the one processed by the previous equipment.

Excipient:

Anything other than the drug substance in the dosage form.

Extended release:

Extended release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (for example, as a solution or an immediate release dosage form).

Facility:

A building in which a specific manufacturing operation or multiple operations take place.

Feed ingredient:

Any substance or mixture of substance that is assessed or evaluated as being acceptable for use in feeds.

Feed microtracers:

Microtracers are uniform stainless steel particles coloured with codified food dyes and incorporated into a drug premix (medicated premix). Microtracers are used in feed assays to establish correlation between drug and microtracer recoveries to give an easy and rapid method for semi quantitative detection of the medicated premix in the medicated feed, and the validation of mixing process in a field environment.

Fermentation train:

Equipment and conditions involved in the stepwise expansion of the cell culture process.

Functional secondary packaging:

Packaging material not in direct contact with the product that provide additional protection or serve to deliver the product.

HVAC (Heating, Ventilation, and Air Conditioning):

Industry term for the systems and technology responsible for the heating, ventilation, and air conditioning in buildings. HVAC systems regulate comfort (temperature and humidity), energy efficiency, and air quality.

Immediate release dosage forms:

Dosage forms that allow the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

In-process control:

Check performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as part of in-process control.

Interchangeable:

Where such status is indicated, any of the official texts from JP, EP, or USP can be substituted one for the other (appropriately referenced) in the ICH regions for purposes of the pharmaceutical registration/approval process. Using any of the interchangeable methods, an analyst will reach the same accept or reject decisions irrespective of which PDG pharmacopeia is used.

Medicated feed:

A mixed feed that contains a medicating ingredient [2.(1) of the *Feeds Regulations*, 1983].

Medicated premix (or drug premix):

A drug for veterinary use to which a drug identification number has been assigned, where the directions on its label specify that it is to be mixed with feed as defined in section 2 of the *Feeds Act*. (C.01A.001 of the *Food and Drugs Regulations*). It is a veterinary drug product prepared in advance with a view to the subsequent manufacture of medicated feeds.

Modified release dosage forms:

Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

Multi-product facility:

A facility where more than one product of the same type or products from different classes are fabricated (such as pharmaceutical and biological drugs).

Non-critical area:

Area that does not encompass process steps.

Non-critical excipient:

Excipient with no active function, for example, a solution used to adjust pH.

Non-critical manufacturing step:

A manufacturing process/step that has no impact upon purity and impurity profile or requires no specific facility considerations, for example, buffer and media preparation, storage of intermediates, and packaging (note that some biological drugs may require critical temperature and/or light control during packaging).

Open system:

Any steps in a manufacturing process where in-process materials or components are exposed to the external environment.

Pilot scale:

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Presentation:

Container that contains the drug product. The container may be used directly or indirectly in the administration of the drug (such as vials, pre-filled syringes, pre-filled pens).

Primary container closure component:

Packaging material in direct contact with the product.

Proposed drug substance/drug product:

Drug substance and/or drug product manufactured using a process incorporating the proposed change(s).

QC approved documents:

"QC approved" means approved by the person in charge of the quality control department.

Reprocessing:

Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications.

Schedule B pharmacopoeia:

Pharmacopoeia listed in Schedule B of the Food and Drugs Act (such as United States Pharmacopeia, European Pharmacopoeia).

Shelf-life (also referred to as expiration period):

The time period during which a drug product or drug substance is expected to remain within the approved shelf-life specification, provided that it is stored under the conditions defined on the container label.

Starting material:

A starting material is a raw material, intermediate, or a drug substance that is used in the production of a drug substance and that is incorporated as a significant structural fragment into the structure of the drug substance.

Strength:

Quantity of medicinal ingredient in a particular dosage form. For solution, concentration of the active pharmaceutical ingredient multiplied by the fill volume.

Release controlling excipient (or agent):

An excipient in the final dosage form whose primary function is to modify the duration of release of the active drug substance from the dosage form.

Unexpected events:

"Unexpected events arising during manufacture or because of stability concerns" refers to unexpected events resulting in a failure to meet specifications.

Validation:

The documented act of demonstrating that any procedure, process, and activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

Withdrawal period:

The length of time between the last administration of a drug to an animal and the time when tissues or products collected from the treated animal for consumption as food contain a level of residue of the drug that would not likely cause injury to human health.

Withholding time:

The length of time, specified in 12-hour milking intervals, up to a maximum of 8 intervals (96 hours) that must elapse after treating a lactating animal with a veterinary drug before milk can be collected for human consumption.