Health Canada Santé Canada

Guidance Document

Post-Notice of Compliance (NOC) Changes: Quality Document

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Document change log

Date	Nature of and/or reason for change:	Location
September 15, 2009	• Administrative changes	• Whole document
September 15, 2011	• Administrative changes • Appendix 1: Revised to eliminate Notifiable Changes as a reporting category	• Appendix 1
October 15, 2013	• Appendix 1 to 4: Revisions or clarifications for various quality changes, • All changes to veterinary drugs were deleted from Appendix 1 and consolidated into Appendix 2, • Appendix 2: Addition of changes to an approved drug administration device for a veterinary drug • Appendix 7: Additional examples of Level IV changes, and • Appendix 8: Addition of one definition.	• Appendices 1, 2, 3, 4, 7, 8
December 2014	• Appendix 1 - change #2 was deleted and a modification was made to the conditions in change #23.	• Appendix 1
February 2016	• Appendix 1, 2, 3 - further revisions or clarifications for various quality changes. • Appendix 8 - addition of acronyms and definitions.	• Appendices 1, 2, 3, 8
October 14, 2016	• Appendix 1 - the conditions and supporting data for changes 2a and 2b were made. • Appendix 2 - correction to the previously approved description for change 27b were made to the English (pdf and html) and French (html) versions.	• Appendices 1, 2

November 28, 2018	• Appendices 1, 2, 3, 4 - addition, deletion or modification to the description of some of the quality changes, the conditions to be fulfilled, the reporting categories, and the supporting data required. • Appendix 7 - addition of an example, modification of existing examples. • Appendix 8 - revision to an existing acronym and the addition of new acronyms. • Rewording of various sections to add clarity to existing text and to provide consistency with notices or policies that have been issued since the last update. • Updating text to reflect Health Canada's adoption of ICH guidelines or annexes (e.g., Q4B, Q8 and Q11). • Clarifying when Level III changes should be filed and what documentation should be submitted.	• Appendices 1, 2, 3, 4, 7, 8
July 31, 2019	Appendix 1 • Section 2 -addition of a reference • Change #2: o Multiple changes to the conditions to be fulfilled, the reporting categories, and the supporting data required for Supplements and Annual Notifications, o Addition of new changes that are considered Annual notifications. • Change #3 o Revisions to the conditions to be fulfilled and supporting data. • Change #4: o Clarification of the conditions to be fulfilled and the	Section 2 Appendices 1, 2

	supporting data required for a Supplement and an Annual Notification. • Change #16 o Change to condition 1 to allow for changes in colour or flavour and addition of supporting information for the change, o Changes to the supporting data for a Supplement and an Annual Notification. Appendix 2 • Change #2(a), #2(b) and #27(d) – addition of supporting data #7 • Change #28 – clarification has been added to Condition #5 • Change #29 o Revision of the conditions in the French language version to better reflect the content of the English version of the guidance document, o The number of conditions to be fulfilled for Annual Notifications has been corrected to read 1-8. • Change #48 – the word “auditif” replaced with the word “auriculaire” in the French version.	

Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

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

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

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1. Introduction

1.1 Objectives

(a) To assist with the classification of quality changes made to a new drug that has received a Notice of Compliance (NOC).

(b) To provide sponsors with recommendations on the data to support a change which would be considered sufficient to allow a determination of the impact of the change on the quality of the new drug as it relates to safety, efficacy and/or effective use of the new drug.

1.2 Scope and application

This guidance document applies to sponsors intending to make changes to new drugs that have received a NOC pursuant to Section C.08.004 of the Food and Drug Regulations. This may include pharmaceuticals, biologics and radiopharmaceuticals for human use and pharmaceutical, radiopharmaceutical and certain biotechnological products for veterinary use[1].

In the absence of a guidance specific to Quality changes to drugs which were approved through a Drug Identification Application - Biologics (DIN-B drugs), this guidance document applies to those products. This guidance also applies to those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold.

This guidance document should be read in conjunction with the associated Health Canada guidance documents entitled Post-Notice of Compliance (NOC) Changes: Framework Document and Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document as well as other related Health Canada guidance documents. Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance documents: Guidance for Industry: Management of Drug Submissions and Applications for drugs intended for human use and Guidance for Industry: Management of Regulatory Submissions for drugs intended for veterinary use.

It is recommended that the principles established in this guidance document be applied to similar Quality changes that occur during the development of the drug and the recommended supporting data be included with the initial New Drug Submission (NDS) or Abbreviated New Drug Submission (ANDS).

1.3 Background

The first version of Health Canada's Post-Notice of Compliance Changes – Quality Document was finalised in 2009. This document has been periodically updated and has an emphasis on applying a science-based and risk-based approach to the pharmaceutical quality assessment of these products. As such, updated guidance documents continue to be needed on the information to support quality changes to new drugs which apply a modernized, science-based, and risk-based approach to this area.

Sponsors are advised to consult the associated Post-Notice of Compliance (NOC) Changes: Framework Document for further background information, including a list of policies and guidance documents that have been superseded.

2. Guidance for implementation

2.1 Reporting categories

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 Appendix 1 (Human Pharmaceuticals), Appendix 2 (Veterinary drugs), Appendix 3 (Biologics) and Appendix 4 (Schedule C drugs) that follow. For assistance in classifying a change, sponsors are advised to contact Health Canada. Contact information is provided in Guidance for Industry: Management of Drug Submissions (drugs for human use) or the Guidance for Industry: Management of Regulatory Submissions (drugs for veterinary use).

Sponsors are advised 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 [for example (e.g.), Notifiable Change], collectively the changes may warrant a higher risk reporting category (e.g., Supplement). Sponsors are advised to contact Health Canada for specific guidance regarding filing requirements in such cases.

2.1.1 Level I - Supplements (major quality changes)

Level I - Supplements (Major Quality Changes) are changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

In general, a change that is supported by extensive documentation and/or requiring extensive assessment of the supporting documentation would be considered a Level I - Supplement (Major Quality Change) (e.g., a change supported by in vivo studies). This is to allow 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 take into consideration any potential impact upon market availability as well as the adverse effects on the identity, strength, quality, purity, or potency of the drug product.

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 a Supplement to an Abbreviated New Drug Submission (SANDS). The change may not be implemented by the sponsor until a NOC has been issued.

For supplements for conventional Human Pharmaceuticals, the guidance document Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) should be consulted for additional information on supporting data related to the change.

2.1.2 Level II - Notifiable Changes (moderate quality changes)

Level II - Notifiable Changes (Moderate Quality Changes) are changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

Note: All Level II - Notifiable Changes referred to in this document are not applicable to Human Pharmaceuticals.

The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a Notifiable Change. All Level II changes should not be implemented by the sponsor until a No Objection Letter (NOL) has been issued.

2.1.3 Level III - Annual Notification (minor quality changes)

Level III - Annual Notification (Minor Quality Changes) are changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

The changes included in this reporting category may be implemented by the sponsor without the prior review by Health Canada of the data supporting such a change. All Level III changes should be submitted using the Post-Notice of Compliance Changes: Notices of Change (Level III) Form. Supporting data for the Level III changes recommended in this guidance document should *not* be submitted; however, the data should be available to Health Canada within thirty (30) calendar days, if requested at any time.

Specific details about when to file the Level III changes are provided in Section 2.1.3 of the Post-Notice of Compliance (NOC) Changes: Framework Document.

2.1.4 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 and are not expected to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The changes included in this reporting category may be implemented by the sponsor 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 and comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the Food and Drug Regulations. A list of examples of Level IV changes is provided in Appendix 7.

3. Documentation

3.1 General information

The associated Post-Notice of Compliance (NOC) Changes: Framework Document should be consulted for details regarding the filing of submissions and annual notifications to Health Canada. Documentation recommended in Section 2.2.3.3 of the aforementioned guidance should be included with a Supplement or Notifiable Change (NC) filing and documentation in Section 2.2.4 should be included with the corresponding Annual Notification.

The change examples presented in Appendix 1 (Human Pharmaceuticals), Appendix 2 (Veterinary drugs), Appendix 3 (Biologics) and Appendix 4 (Schedule C drugs) are intended to assist with the classification of changes made to the Quality information. The information summarized in the tables provides recommendations for:

(a) The conditions to be fulfilled for a given change to be classified as a Level I, II, or III change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the

conditions recommended for a Level II - Notifiable Change are not fulfilled, the change is considered a Level I - Supplement. Similarly, if any of the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of an NDS or an ANDS.

(b) The supporting data for a given change, either to be submitted to Health Canada and/or maintained by the sponsor. Where applicable, the corresponding modules of the Common Technical Document (CTD) for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided, and
(c) The reporting category (e.g., Supplement, Notifiable Change or Annual Notification).

As previously mentioned, it is equally important to note that 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 Health Canada when a change that may have the potential to impact product quality is not found in the tables.

For convenience, the change examples are organized according to the structure of the Common Technical Document (CTD).

For the recommendations for the conditions, supporting data, and reporting categories for changes that are specific to drugs for veterinary use (e.g., premixes, boluses), sponsors should contact the Veterinary Drugs Directorate (VDD) of Health Canada.

3.2 Supporting data - Level I and Level II changes

All data recommended to support the change should be provided with the submission. Where applicable, these data should be provided in the format defined by the International Council for Harmonisation (ICH) Common Technical Document (CTD). A Quality Overall Summary (QOS) and Comprehensive Summary: Bioequivalence (CS:BE) should also be completed and provided, where applicable. For Veterinary Drug Submissions, data should be provided in the format of the Guidance for Industry: Preparation of Veterinary New Drug Submissions. Refer to existing Health Canada guidance documents for further detail regarding individual product recommendations.

When recommended supporting data cannot be submitted, a detailed rationale should be provided.

Supporting Data Common to Level I and Level II Changes

The following should be included, where applicable, in the submission package for Level I and Level II Quality changes:

(a) A covering letter that includes a brief narrative description and rationale of the change(s);

(b) 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[2];

(c) Where applicable, an annotated and non-annotated electronic copy of:

(i) the relevant Certified Product Information Document (CPID) (e.g., CPID-CE, CPID-B or CPID-R)

(ii) the Product Monograph or Package Insert (for Veterinary drugs), and

(iii) a sample of the inner and outer labels (Level I changes require label mock-ups while Level II changes require written text in place of mock-ups) to reflect any proposed changes.

(d) An annotated and non-annotated electronic copy of the relevant Health Canada Quality Overall Summary template (QOS), or the revised sections of the QOS. A document clearly detailing the proposed changes may be submitted in lieu of an annotated QOS (Module 2.3).

In addition to the above common information, recommendations are included in Appendices 1, 2, 3 and 4 outlining the specific information to support the various quality changes. It should be noted that the common information is not repeated for the various changes outlined in the appendices.

When cross-references are made to previously submitted information, details on the cross-referenced information should be indicated in the covering letter (e.g., brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved).

Certificate of Suitability (CEP)

While 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) may be provided to support changes to the drug substance used in pharmaceuticals for humans use (Appendix 1- Human Pharmaceuticals) and pharmaceuticals for veterinary use (Appendix 2 - Veterinary Drugs). They are not accepted for Biologics (Schedule D drugs) nor Radiopharmaceuticals (Schedule C drugs). However, for Biologics (Schedule D drugs), 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. Sponsors are encouraged to contact the appropriate Directorate for further guidance.

Production documents (Executed and Master Batch Records)

For Biologics (Schedule D drugs) and Radiopharmaceuticals (Schedule C drugs), in contrast of the requirements for a NDS, production documents are no longer required at time of filing to support any post-NOC changes. However, these may be requested during review and should be available within 15 days upon request.

3.3 Supporting data - Level III changes

Any data that may have been generated by the sponsor in support of a Level III change should not be submitted with the Post-Notice of Compliance Changes (Level III) but should be available to Health Canada within thirty (30) calendar days, if requested.

Any Level III changes that have been implemented should be annotated in the affected documents with the dates of implementation clearly identified (e.g., Product Monograph/Package Insert or CPID) and filed with the next Level I - Supplement or Level II Notifiable Change that necessitates a label or quality change as well.

Specific details about what information to file for Level III changes are provided in Section 2.2.4 of the Post-NOC Changes: Framework Document.

3.4 Supporting data - 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 and comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the Food and Drug Regulations. These changes should be annotated in the affected documents (e.g., Product Monograph/ Package Insert or CPID) with the filing of the next submission that necessitates a label or quality change as well.

3.5 Comparative studies

3.5.1 Comparative in vivo studies

A number of changes outlined in Appendices 1, 2, 3 and 4 include recommendations for supporting comparative in vivo studies (e.g., comparative bioavailability studies for Pharmaceuticals, bridging clinical studies for Biologics).

Sponsors should consult the ICH Q5E guideline and applicable Health Canada guidance documents when conducting comparative in vivo studies.

3.5.2 Comparative in vitro studies

A number of changes outlined in Appendices 1, 2, 3 and 4 include recommendations for supporting comparative in vitro studies (e.g., comparative dissolution studies). Where an in vitro comparison is recommended to support a Post-NOC Change, the comparison should be made to 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 (e.g., including batch formula, manufacturing process). This is referred to as the "approved product" in the appendices.

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 (e.g., 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 [e.g., United States Pharmacopeia (USP) <711>, USP <724>, European Pharmacopeia (Ph.Eur.) 2.9.3].

In addition, Appendix 5 outlines a number of recommendations for conducting and assessing comparative dissolution profiles (e.g., conditions, similarity).

3.6 Stability testing

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

(a) Stability Testing of New Drug Substances and Products [Q1A(R2)]

(b) Stability Testing: Photostability Testing of New Drug Substances and Products (Q1B)

(c) Stability Testing: Requirements for New Dosage Forms (Q1C)

(d) Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (Q1D)

(e) Evaluation of Stability Data (Q1E)

(f) Stability Testing of Biotechnological/Biological Products (Q5C).

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

3.7 Pharmaceutical development and quality by design

The International Council for Harmonisation (ICH) has developed two guidelines, Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities) and Q8: Pharmaceutical Development and Q8 Annex which 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. The Pharmaceutical Development information for a veterinary drug submission should be provided 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 the establishment of the design space, specifications, and manufacturing controls.

Design space is proposed by the applicant, and 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 Appendices 1, 2, 3 and 4 of this guidance document as Level I - Supplements (Major Quality Changes) or Level II - Notifiable Changes (Moderate Quality Changes) may not require approval prior to implementation if they are within the approved design space.

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

If proposed and approved, the details of the design space should be recorded in the Certified Product Information Document (CPID). Sponsors are encouraged to discuss with Health Canada when considering the establishment of a design space.

3.8 Consistency lot testing

For Biologics (Schedule D drugs) and for Radiopharmaceuticals (Schedule C drugs) that have a biologic drug substance, Health Canada usually requests consistency samples to support the information provided in Level I or Level II Changes. The consistency samples should be representative of the revised process/proposed change(s) and should come from three to five consecutively manufactured lots. Sponsors are encouraged to discuss consistency lot testing requirements prior to the submission of Level I or Level II changes and this will be confirmed during the review process. Sponsors are also encouraged to consult the Health Canada guidance document "Lot release program for Schedule D (Biologic) drugs" for further guidance.

3.9 On-site evaluation (OSE)

For Biologics (Schedule D drugs) and for Radiopharmaceuticals (Schedule C drugs) that have a biologic drug substance, an on-site evaluation (OSE) may be conducted by Health Canada to support the information provided in Level I or infrequently in Level II Changes. Sponsors are encouraged to discuss OSE requirements prior to the submission of Level I or Level II changes; the requirement for an OSE will be confirmed during the review process.

3.10 Multiple changes

Multiple Level II (Quality) changes to the same drug product may be filed in a single submission provided those changes are related and/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.

3.11 Interchangeable pharmacopoeial texts

The International Council for Harmonisation (ICH) has developed a guideline, Q4b: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions which describes a process for the evaluation and recommendation of selected pharmacopoeial texts to facilitate their recognition by regulatory authorities for use as interchangeable in the ICH regions. Where the ICH Q4B annexes have been adopted by Health Canada, such changes should be reported as a change from a House analytical procedure to a Schedule B analytical procedure (see Appendix 1- Human Pharmaceuticals, change numbers 9c and 32c) with supporting analytical method validation data, where appropriate.

4. Appendices

Appendix 1: Quality Post-NOC Changes (human pharmaceuticals)

Appendix 1 for Human Pharmaceuticals was developed using risk- and science-based principles. One of the key assumptions is that the company would gain significant amount of experience and knowledge on the product during its commercial manufacturing in the post-approval part of the lifecycle. This experience and knowledge would enable the company to perform the required risk assessment on the post-NOC change under consideration to evaluate the potential impact on quality, safety and efficacy in determining if the change would be Level I or III. However, if the company needs to make the change before gaining significant experience and knowledge (e.g., before making commercial batches) the company should consider submitting a supplement.

For implementing any post-NOC change as an Annual Notification at the manufacturing and testing site of the drug substance and drug product, the site should have a Good Manufacturing Practices (GMP) compliant rating acceptable to Health Canada. This is a fundamental and overarching principle of GMP based on which the Annual Notification process was developed (where there is reliance on the company's quality system and GMP).

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

(a) The conditions to be fulfilled for a given change to be classified as either a Level I, or III change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Level III - Annual Notification are not fulfilled, the change is considered a Level I - Supplement. However, in such a case the supporting data for a Supplement will remain the same as for an Annual Notification. Similarly, if any of the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of an NDS or an ANDS;

(b) 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, these documents should be available in an official language (English or French), or a translation from the original language. Where applicable, the corresponding modules of the Common Technical Document (CTD) for the supporting data have been identified in brackets;

c) The reporting category (e.g., Supplement or Annual Notification).

For convenience, the change examples are organized according to the structure of the Common Technical Document (CTD).

Multiple Changes related to the same pharmaceutical drug product falling in the category of Level I - Supplement changes can be filed in a single submission if those changes are related and/or are supported by the same data.

The information provided in the Level III form which is submitted at the time of implementation or annually during the Annual Drug Notification period will be audited applying principles of risk management. Sponsors will be required to address any comments arising from such

assessments in the time frame notified in the communication from Health Canada. Sponsors will be required to refile the information as a Level I - Supplement if it is deemed to be the proper classification for the change notified by the sponsor. It is expected that the company will perform a full assessment of the proposed change and document the justification as per the change control process of its quality system. It is recommended that the justification for the proposed change to Level III is summarised in a manner to facilitate efficient review (e.g., comparison table of existing versus proposed change).

3.2.S Drug substance

3.2.S.1 General information

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Change in the name of the drug substance	1	1-2	Annual Notification
Conditions			
1. Confirmation that the information on the drug substance has not changed as a result of the change [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved].			
Supporting Data			
1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels. 2. (S.1.1) Information on the proposed nomenclature of the drug substance [e.g., chemical name(s), compendial name] and evidence that the proposed name for the drug substance is recognized [e.g., Recommended International non-proprietary name (INN), United States Adopted Names (USAN), British Approved Names (BAN)].			

3.2.S.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Replacement or addition of a manufacturing site and/or manufacturer involving:			
a. Production of the starting material,	1 -3, 8, 12	5, 6, 7, 9	Annual notification
	None	5, 6, 7, 9	Supplement
b. Production of the intermediate or drug substance	1-2,6, 8-10	1-7, 9-10	Annual Notification
	1, 4, 6, 8-10	1-7, 9-10	Annual Notification
	None	Refer to Quality Guidance[3]	Supplement
c. The change is supported by a valid Certificate of Suitability (CEP)	1, 4-6, 9	2-6, 10-12	Annual Notification
	1, 4, 5, 7, 9	2, 4-6, 10-12	Annual Notification

	1, 2, 5-6, 9	2-6, 10-12	Annual Notification
	1, 2, 5, 7, 9	2, 4-6, 10-12	Annual Notification
	None	Refer to CEP and Quality Guidances[4]	Supplement
d. Substituting of an ASMF with a valid CEP for the drug substance	11	4, 11	Annual Notification
e. Testing [e.g., release, stability]	None	2, 5, 8, 9	Annual Notification
3. Deletion of a manufacturing site or manufacturer for the starting material, intermediate, or drug substance	None	None	Annual Notification

Conditions

1. The change concerns active pharmaceutical ingredients (APIs) that are discrete chemical entities (i.e., the API is not a polymer or polymeric complex).
2. All results of testing of all drug substance CQAs including the impurity profile (including mutagenic impurities) and particle size distribution and polymorphic form/crystallinity indicate that the drug substance is the same as previously authorized. (e.g. no change in the polymorphic form and no change in the impurity profile that impacts the safety of the drug substance).
3. No Level 1 changes in the drug substance synthesis (i.e. the same starting material, intermediates, solvents, reagents, purification/isolation process, process conditions and controls, analytical methods and specifications are used).
4. The drug product (DP) dosage form is a solution OR the API is fully dissolved in the manufacturing process OR the drug substance is a soluble drug substance as defined by dose/solubility volume in physiological pH 1.2-6.8 (see Quality Guidance Document) and is used in an immediate release product.
5. The change of source is supported by a valid Certificate of Suitability (CEP) issued by the EDQM and there is documented assurance that the manufacturing process to be followed is identical to the one evaluated by the EDQM.
6. An Active Substance Master File (ASMF) for the same site has been submitted to Health Canada.
7. The API from the specific site associated with the valid CEP has been previously been approved by TPD for any other drug product manufactured by your company.
8. The proposed new site is a subsidiary of the currently authorised drug substance or drug product manufacturer, under the same corporate structure / pharmaceutical quality system or is a contract manufacturer working for the authorized manufacturer under a signed agreement and has an equivalent pharmaceutical quality system. An equivalent quality management system is an acceptable quality management system as audited and documented by the authorised drug substance/drug product manufacturer. A written quality agreement is in effect between the contractual parties. Technology transfer to the new site was done with full transfer of complete and detailed manufacturing information for the previously authorized starting material and drug substance manufacturing process to the new site (i.e. the equivalent of the Restricted Part of an ASMF is transferred to the new site) and validation of the transfer

is complete. Documented evidence is available demonstrating successful completion of technology transfer to the new site of manufacture and testing for the previously authorized process, with no changes to the previously authorized starting material(s). Validation requirements are satisfied prior to use of drug substance batches from the new site in commercial drug products. Health Canada has a record of the site being used by the manufacturer of the API in any other product from your company or an ASMF has been submitted for the new site.

9. The new/proposed drug substance manufacturing building has a Drug Establishment Licence (DEL) for drug substance fabrication, or was successfully added to Drug Establishment Licence of the Canadian importer.
10. Where materials of human or animal origin are used in the process, the change of source is supported by a valid TSE Certificate of Suitability (CEP) issued by the EDQM or the source of the material from the new supplier has been previously authorised by TPD or BGTD for viral safety or TSE risk.
11. When a MF is being replaced by a CEP, the API from the specific site associated with the valid CEP has been previously been approved by TPD for any other drug product manufactured by your company and the API manufacturing site is listed on your company's DEL.
12. No change in the route of synthesis of the starting material, including reagents, solvents or process conditions. No change in the specifications for the starting material. The impurity profile of the starting material remains the same and testing of potentially mutagenic impurities has confirmed absence or the change is supported by a CEP.

Supporting Data

1. (1, 5) Where materials of human or animal origin are used in the process, the change of source is supported by a valid TSE Certificate of Suitability (CEP) issued by the EDQM or the source of the material from the new supplier has been previously authorized by TPD for viral safety data or TSE risk assessment .
2. (1.2.5) For sterile manufacturing, evidence of GMP and/or Establishment Licence (EL) information [Conformation of a satisfactory GMP rating by the Health Product Compliance Directorate of the Regulatory Operations and Regions Branch (RORB)], and (S.2.5) process validation and/or evaluation studies for sterilization. For drug substance testing sites evidence of GMP and/or EL information [e.g. Confirmation of a satisfactory GMP rating by the Health Product Compliance Directorate of the Regulatory Operations and Regions Branch (RORB)].
3. (S) Where applicable, updated or new ASMF (with a Letter of Access for the Drug Product (DP) manufacturer provided in Module 1), any relevant information on the starting material, intermediate or drug substance to be provided where available.
4. A copy of the Certificate of Suitability (CEP) issued by the EDQM which is current and valid CEP (i.e. not been suspended or withdrawn). If the CEP is in lieu of an 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.
5. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing.
6. (S.3) New sources of materials have been used during validation, technology transfer (if applicable) and process validation studies are successfully completed to manufacture commercial size batches of the drug substance. Potential impurities not routinely tested (including potentially mutagenic impurities) have been confirmed to be absent from the impurity profile of the API. Validation reports demonstrate equivalency of processes.
7. (S.2.3) For starting materials, intermediates or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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) should be provided where available.

8. (S.4.3) Copies or summaries of validation reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site or method transfer reports, which demonstrate equivalency of analytical testing results between the approved and proposed sites.
9. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for one batch each of the currently approved and proposed starting material, intermediate or drug substance sites.
10. (S.7.3, P.8.2) For changes that could affect the stability of the drug substance, stability studies have been initiated and at least 3 months of accelerated stability data on the new drug substance is available. Where the route of synthesis of the drug substance has been substantially changed or for drug products where stability issues are known (e.g. due to poorly stable drug substances) or where the changes may affect manufacturing or performance of the drug product, an 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).
11. The drug product manufacturer has received a copy of the CEP and annexes as well as all attestations from the drug substance manufacturer in accordance with the guidance document "Use of Certificates of Suitability as supporting information in Drug Submissions". The attestations have been assessed by the drug product manufacturer to ensure that the drug substance will be produced in accordance with the CEP.
12. The drug product has been fully validated using the new source of drug substance and there is no change in any Critical Quality Attribute for the drug product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
4. Change in the manufacturing process			
a. for the drug substance, intermediate or starting material	None	Refer to Quality Guidance Document[5]	Supplement
	1-8	2-6, 8-9, 11	Annual Notification

Conditions

1. No change in the identicality of the drug substance in accordance with Health Canada's interpretation of identical medicinal ingredient.
2. No change in the physical state (e.g. crystalline, amorphous, solid, semi-solid, liquid or gas) of the drug substance.
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 TSE Certificate of Suitability (CEP) issued by the EDQM or the source of the material new supplier has been previously authorised for viral safety data or TSE risk assessment.
5. No Level I change in the drug substance specifications.
6. No change in the route of synthesis including starting materials, solvents, reagents, intermediates, and purification/isolation steps . The impurity profile of the drug substance remains the same (no new impurity

above 0.10%, no change in the approved total impurity limits, and residual solvents within ICH limits) OR the change of the manufacturing process is supported by a valid Certificate of Suitability (CEP) issued by the EDQM.

7. The change does not affect the sterilization procedures of a sterile drug substance.
8. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1, 5) Where materials of human or animal origin are used in the process, the change of source is supported by a valid TSE Certificate of Suitability (CEP) issued by the EDQM or the source of the material from the new supplier has been previously authorized by TPD for viral safety data or TSE risk assessment .
2. (S) Updated or new ASMF (with a Letter of Access provided in Module 1) or relevant information on the starting material, intermediate or drug substance OR a copy of the Certificate of Suitability (CEP) issued by the EDQM which is current and valid CEP (i.e., not been suspended or withdrawn). If the CEP is in lieu of an ASMF, the declaration of access box shows the drug product manufacturer's name.
3. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
4. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed starting material, intermediate or drug substance.
5. (S.2.3) For starting materials, intermediates or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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) should be provided where available.
6. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.
8. (S.3.1) Evidence for elucidation of structure, where applicable.
9. (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 one (1) batch of the currently approved and proposed processes.
10. (S.7.3) Results of two (2) batches with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.
11. (P.8.2) Where the route of synthesis of the drug substance has been substantially changed or for drug products where stability issues are known (e.g. due to poorly stable drug substances) or where the changes may affect manufacturing or performance of the drug product, an 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.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
5. Change in the batch size for the drug substance or for a continuous process	1-3	1-3	Annual Notification
Conditions			
1. No Level I changes in the drug substance specifications. 2. The change does not affect the sterilization procedures of a sterile drug substance. 3. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).			
Supporting Data			
1. (S.2.2) A brief narrative description of the proposed manufacturing process(es). 2. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization. 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 one batch.			

3.2.S.3 Characterisation

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

3.2.S.4 Control of the drug substance

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
6. Change in the standard claimed for the drug substance (e.g., from a House Standard to a Schedule B pharmacopoeial standard or from one Schedule B standard to a different Schedule B standard)	1-3	1-5	Annual Notification
7. Change in the specification for the drug substance to comply with an updated Schedule B pharmacopoeial monograph or change to House Standard	1-2	1-5	Annual Notification

Conditions

1. The change is made exclusively to comply with the pharmacopoeia.
2. No Level I changes to the specifications with respect to functional properties of the drug substance (e.g., particle size distribution, polymorphic form) and to tests that impact safety (e.g. sterility, bacterial endotoxins).
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria for tests that do not appear in a pharmacopoeial monograph.

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 one batch if new tests and/or analytical methods are implemented.
4. (S.4.5) Justification of the proposed drug substance specification (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities).
5. Equivalency study results between the House and Compendial method, when a Schedule B standard exists and a House analytical method is used.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
8. Change in the specification for the drug substance involving test and acceptance criteria:			
a. for sterile drug substances, replacing the sterility test with alternate microbiological methods or process parametric release	None	1-7	Supplement
b. deletion of a test	1-5	2, 7-8	Annual Notification
c. replacement of a test	1-6	2-5, 7-8	Annual Notification
d. addition of a test	None	2-5, 7-8	Annual Notification
e. relaxation of an acceptance criterion	1-4, 6	2, 7-8	Annual Notification
f. tightening of an acceptance criterion	None	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. No change in the polymorphic form and impurity profile that impacts safety or efficacy of the drug product.
3. The change does not concern sterility testing.
4. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).
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 (e.g. removal of an organic volatile solvent test after at least 10 commercial scale batches tested and meet acceptance criteria, or provide valid scientific justification).
6. The relaxed criterion is in accordance with compendial and/or ICH criterion.

Supporting Data

1. (S.2.5) QC approved process validation and/or evaluation studies or the proposed validation protocol of the proposed drug substance.
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 for one batch, or batch analysis report and summary of results, of a sufficient number of batches (minimum of ten batches) to support the process parametric release. 7. (S.4.5) Justification of the proposed drug substance specification (e.g., test parameters, acceptance criteria, or analytical procedures). 8. (P.2) Where appropriate (e.g., for a change in particle size limit for a poorly soluble drug substance), comparative, multi-point dissolution profiles in the release medium for one batch of the drug product using material from the approved and change drug substance specifications.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
9. Change in the specification for the drug substance involving analytical procedures:			
a. deletion of an analytical procedure	1	1	Annual Notification
b. replacement of, alternate, or additional analytical procedure	1	1-5	Annual Notification
c. change from a House analytical procedure to a Schedule B analytical procedure or a change from an approved compendial analytical procedure to an harmonized compendial procedure	None	1, 3-4	Annual Notification
Conditions			
1. The change does not concern a non-compendial (Schedule B) sterility testing 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 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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
10. Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1-3	Supplement
	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 (e.g., including results of transportation or interaction studies, if appropriate). 2. The change does not impact sterilization parameters of a sterile drug substance.			
Supporting Data			
1. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process. 2. (S.6) Information on the proposed container closure system (e.g., description, specifications). 3. (S.7.3) Results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the drug substance in the proposed container closure system.			

3.2.S.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
11. Change in the re-test period (or shelf-life) for the drug substance	None	1-2	Annual Notification
Conditions			
None			
Supporting Data			
1. (S.7.2) Updated post-approval stability protocol and stability commitment. 2. (S.7.3) Results of stability testing generated on at least two pilot and/or commercial scale batches with stability data to support the proposed re-test period or shelf-life.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
12. Change in the labelled storage conditions for the drug substance, involving: addition/deletion of a cautionary statement or relaxation/tightening of a temperature criterion (e.g., 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 not less than two (2) lots (pilot or commercial scale).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
13. Change to the post-approval stability protocol or stability commitment	None	1-2	Annual Notification
Conditions			
None			
Supporting Data			
1. (S.7.1) Justification of the change to the post-approval stability protocol or stability commitment. 2. (S.7.2) QC approved updated post-approval stability protocol and stability commitment.			

3.2.P Drug product

3.2.P.1 Description and Composition of the Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
14. Addition of a dosage form or strength	None	1-16	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, e.g.:
   - when the changes in excipients for a new strength of an immediate release solid oral dosage form containing a single drug substance, expressed as percentage (w/w) of total formulation, are greater than the ranges outlined in Appendix 6: supporting clinical or comparative bioavailability data and in vitro data to be included in CTD modules 1,5);
   - when the changes in excipients for new strength of an immediate release solid oral dosage form containing a single drug substance, expressed as percentage (w/w) of total formulation, are less than or equal to the ranges outlined in Appendix 6: supporting in vitro data to be included in CTD modules 1,5).
2. (1.2.5) GMP and Establishment License (EL) Information [e.g. Confirmation of a satisfactory GMP rating by the Health Product Compliance Directorate of the Regulatory Operations and Regions Branch (RORB).
3. (1.2.6) Letters of Access if Master Files are submitted for new excipients.
4. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels.
5. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved].
6. (P.1) Description and composition of the dosage form.
7. (P.2) Where applicable, information on Pharmaceutical Development including discussion on the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing (e.g., 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.
8. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
9. (P 3.5) QC approved Process validation protocol of the proposed drug product. In addition, for a sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
10. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
11. (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 one (1) pilot scale batch per strength).

12. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
13. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches), results of a minimum of six (6) months of accelerated (or intermediate as appropriate) and six (6) months of long term testing of the proposed drug product; (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
14. (P.8.2) Updated post-approval stability protocols and stability commitments 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).
15. (R.1) Executed Production Documents for one batch of each new dosage form or strength.
16. Additional documentation may be required in certain situations, (e.g., complexity of the dosage form, ICH guidance, new scientific evidence, clinical requirements).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
15. Change in the composition of a solution dosage form	None	1-13	Supplement
	1-8	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 (For the purposes of this document, essentially the same would be interpreted as the amount (or concentration) of each excipient in the test product to be within ±10% of the amount (or concentration) of each excipient in the reference product, as defined in the Health Canada guidance document Pharmaceutical Quality of Aqueous Solutions).
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 to affect the solubility of the drug substance.
4. The proposed excipient(s) does/do not function as a preservative.
5. No change in the specifications of the drug product other than changes to comply with a Schedule B monograph.
6. No change to the physical characteristics of the drug product (e.g., viscosity, pH, osmolality).
7. The change does not concern a sterile drug product.
8. The change concerns a drug product that contains drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1,5) Supporting clinical or comparative bioavailability data or a request for a waiver of in vivo studies, e.g.:
   - when the changes in excipients are not considered to be qualitatively the same and quantitatively essentially the same: supporting clinical or comparative bioavailability data and in vitro data on the physicochemical properties;
   - when the changes in excipients are considered to be qualitatively the same and quantitatively essentially the same: supporting in vitro data on the physicochemical properties.
2. (1.2.6) Letters of Access if Master Files, are submitted for new excipients.
3. (1.3.1) Product Monograph (Title page, ''Dosage Forms, Composition, and Packaging'' section).
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing on the physicochemical properties for the approved and proposed products, 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) QC approved Process validation protocol of the proposed drug product. In addition, for a sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
9. (P.4) Control of Excipients, if new excipients are proposed (e.g., 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 one pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches), e.g.:
    - when the changes in excipients are not considered to be qualitatively the same and quantitatively essentially the same: results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product;
    - when the changes in excipients are considered to be qualitatively the same and quantitatively essentially the same: stability data at the time of filing would not be necessary (see P.8.2 below) (bracketing and matrixing 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 one batch representative of each strength of the proposed product.

<table>
<tr><th>Description of Change</th><th>Conditions to be Fulfilled</th><th>Supporting Data</th><th>Reporting Category</th></tr>
<tr><td rowspan="2">16. Change in the composition of an immediate release dosage form including film-coating, colours, flavours and printing inks. Film coating could be for enhancing appearance, masking taste and/or ensuring stability)</td><td>None</td><td>1-14</td><td>Supplement</td></tr>
<tr><td>1-8</td><td>2-7, 9-14</td><td>Annual Notification</td></tr>
<tr><td colspan="4">Conditions</td></tr>
<tr><td colspan="4">1. The changes in excipients of the approved and proposed drug products are considered to be qualitatively the same OR the qualitative change in the formulation only includes substitution of a different colour or in the flavour where the flavour is not necessary for taste-masking purposes.
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 6.
3. The change does not affect performance characteristics of the drug product (e.g. release rate).
4. The proposed excipient(s) does/do not function to affect the absorption of the drug substance.
5. The proposed excipient(s) does/do not function to affect the solubility of the drug substance.
6. The proposed excipient(s) does/do not function as a preservative.
7. No change in the specifications of the drug product other than appearance and changes to comply with a Schedule B monograph
8. The change concerns a drug product that contains drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).</td></tr>
<tr><td colspan="4">Supporting Data</td></tr>
<tr><td colspan="4">1. (1,5) Supporting clinical or comparative bioavailability data or a request for a waiver of in vivo studies (to be included in CTD modules 1,5), e.g.:
- when the changes in excipients, expressed as percentage (w/w) of total formulation, are greater than the ranges outlined in Appendix 6: supporting clinical or comparative bioavailability data and in vitro data;
- when the changes in excipients, expressed as percentage (w/w) of total formulation, are less than or equal to the ranges outlined in Appendix 6: supporting in vitro data.
2. (1.2.6) Letters of Access if Master Files are submitted for new excipients.
3. (1.3.1) Product Monograph (Title page, ''Dosage Forms, Composition, and Packaging'' section).
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved].
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing where applicable [e.g., depending on the solubility and permeability of the drug (refer to Appendix 5), multi-point dissolution profiles in either the release medium or in multiple media covering the physiological pH range] for the approved and proposed products,</td></tr>
</table>

discussion of any in vitro and/or in vivo studies, results of preservative effectiveness testing (if applicable). Comparative in vitro dissolution tests are normally not expected for changes in colours, flavours and printing inks.

7. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation.
8. (P 3.5) QC approved Process validation protocol of the proposed drug product. In addition, for a sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
9. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
10. (P.5) Specification(s) and Batch Analyses (certificate of analyses for a minimum of one pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches) results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product; (bracketing and matrixing 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 one batch representative of each strength of the proposed product.
14. The new flavour or colour is not prohibited by the Canadian regulations and complete safety data is available on file. The new excipient does not affect the performance characteristics of the drug product or the release or bioavailability of the drug substance. Stability data for the new formulation shows no change in the stability profile. Changes to the drug product specifications are those necessitated only by the change to the colour or the flavour.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
17. Change in the composition (qualitative or quantitative) in the release controlling agent of a modified release dosage form (for changes in other excipients in a modified release dosage form, refer to change example #16)	None	1-13	Supplement
	1-2 (quantitative changes only)	2-8, 10-13	Annual Notification

Conditions

1. The change is only quantitative and is within parameters established by an in vitro in vivo correlation previously approved by Health Canada in the original (S)NDS/(S)ANDS.
2. No change in the specifications of the drug product other than appearance and 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).
2. (1.2.6) Letters of Access if Master Files are submitted for new excipients.
3. (1.3.1) Product Monograph (Title page, ''Dosage Forms, Composition, and Packaging'' section).
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing [e.g., depending on the mechanism for drug release (extended or delayed), drug release profiles in multi-media 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).
7. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
8. (P 3.5) QC approved Process validation protocol of the proposed drug product. In addition, for s sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
9. (P.4) Control of Excipients, **if new excipients are proposed** (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
10. (P.5) Specification(s) and Batch Analyses (certificate of analyses for a minimum of one pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches), e.g.:
    - results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product; (bracketing and matrixing 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 one batch of each strength.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
18. Change to product markings, involving a change in embossing, debossing, or engraving (except scorelines/break lines) (e.g., plain tablet to engraved, engraved to plain, change in engraving) or a change in imprinting (e.g., plain tablet/capsule to imprinted tablet/capsule)	1-2	1-3	Annual Notification
Conditions			
1. The change does not affect the performance characteristics (e.g., release rate) of the drug product. 2. The change does not impact Safety, Efficacy (e.g., removal of identification of tablet strength may cause confusion in patients with respect to identification of strength).			
Supporting Data			
1. (1.3.1) Product Monograph (Title page, ''Dosage Forms, Composition, and Packaging'' sections). 2. (P.5) Specification(s) and Batch Analyses (certificate of analyses for a minimum of one pilot scale 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).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
19. Change in scoring configuration, involving:			
a. addition or deletion of a score line to a generic product that is not consistent with a similar score line in the innovator product (Canadian Reference Product).	1-3	1-7	Supplement
b. addition of a scoreline	1-4	1-6	Annual Notification
c. deletion of a scoreline	1-4	1, 4-6	Annual Notification

Conditions

1. The change does not affect the performance characteristics (e.g., 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. (1.3.1) Product Monograph (Title page, ''Dosage Forms, Composition, and Packaging'' sections).
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 Analyses (certificate of analyses for a minimum of one pilot scale 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 one batch representative of each strength of the proposed product.
7. Recommendations and justification as outlined in Health Canada’s Notice: Tablet Scoring of Subsequent-entry Pharmaceutical Products.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
20. Change in shape or dimensions of tablets, capsules, suppositories or pessaries	1-3	1-7	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 affect the performance characteristics (e.g., release rate) of a drug product.			
Supporting Data			
1. (1.3.1) Product Monograph (Title page, ''Dosage Forms, Composition, and Packaging'' sections). 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). 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 one batch representative of each strength of the proposed product. 7. Recommendations and justification as outlined in Health Canada's Notice: Tablet Scoring of Subsequent-entry Pharmaceutical Products.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
21. Change in diluent, involving:			
a. replacement or addition of a diluent for a lyophilized powder or concentrated solution	None	1-12	Supplement
b. deletion of a diluent	None	2	Annual Notification
Conditions			
None			
Supporting Data			

1. (1.2.6) Letters of Access if Master Files are submitted for new excipients.
2. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels.
3. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]
4. (P.1) Description and composition of the diluent if it is included with the product.
5. (P.2) Discussion of the components of the drug product, as appropriate (e.g., choice of excipients, compatibility of the drug product with the diluent with respect to appearance, pH, assay, degradation products, extractables/leachables profile and particulate matter).
6. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation and testing standards for the diluent if it is included with the product.
7. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
8. (P.5) Batch Analyses (certificate of analyses for a minimum of one pilot scale batch of the diluent if it is included with the product.)
9. (P.7) Discussion (including description, materials of construction of the container closure system, compatibility studies for the diluent if it is included with the product).
10. (P.8.1) Stability Summary and Conclusions: results for two pilot scale batches of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the diluent if it is included with the product.

11 (P.8.2) Updated post-approval stability protocol and stability commitment for the diluent if it is included with the product.

12. (R.1) Executed Production Documents for one batch of the diluent, if it is included with the product.

3.2.P.2 Pharmaceutical development

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
22. Change in the approved design space, involving:			
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	Annual Notification
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).			

3.2.P.3 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
23. Replacement or addition of a drug product manufacturer / manufacturing site, involving:			
a. production of a modified release or a sterile drug product; or production of an immediate release product that does not meet the conditions for Annual Notification	None	1-6,8-10	Supplement
b. production of an immediate release product (e.g., tablet, capsule, liquids, semi-solids)	1-4	2-5,8-11	Annual Notification
c. primary packaging	1-3	2-3,5-6,9	Annual Notification
d. testing (e.g., release, stability)	3	2-3,5,7-8	Annual Notification
e. storage and distribution	3	2-3	Annual Notification

Conditions

1. No Level 1 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 1 change in the container closure system.
3. The proposed facility has a current satisfactory GMP rating as determined by Health Product Compliance Directorate of the Regulatory Operations and Regions Branch (RORB) or is included in the EL.
4. Three consecutive production scale batches have been successfully validated at the currently approved site as well as the proposed site as per QC approved validation protocol and Technical transfer and/or process validation reports for three production scale batches at the proposed site are available [Concurrent validation of three production scale batches would be acceptable for orphan drugs and low volume drug products (e.g. only two batches manufactured per year)].

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 vivo/in vitro correlation has been established).
2. (1.2.5) GMP and Establishment License (EL) Information (e.g. Confirmation of a satisfactory GMP rating by the Health Product Compliance Directorate of the Regulatory Operations and Regions Branch (RORB)).
3. (P) Confirmation that information on the drug product has not changed as a result of the submission (e.g., other that change in site).
4. (P.2) Comparative in vitro testing (e.g., multi-point and multi-media dissolution profiles 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 5 for additional detail.

5. (P.3.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing and/or storage and distribution.
6. (P.3.5) QC approved Process validation protocol of the proposed drug product. In addition, for a sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
7. (P.5.3) Copies or summaries of validation/ method transfer reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site.
8. (P.5.4) Certificate of analyses for one 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 at the new site 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 one representative batch of each strength of the proposed product.
11. (P 3.5) Process validation data on three consecutive commercial scale batches and confirmation that the results are in accordance with the QC approved validation protocol. [Concurrent validation of three commercial scale batches would be acceptable for orphan drugs and low volume drug products (e.g. only two batches manufactured per year)].

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
24. Change in the batch size for the drug product, involving:			
a. increase in batch size beyond a factor of ten (10) times for a Modified Release product	None	1-7	Supplement
b. increase in batch size up to and including a factor of ten (10) times for a Modified Release product	4	2-3,5-8	Annual Notification
c. increase in batch size of an immediate release product (e.g., tablet, capsule, liquid, sterile product, semi-solid)	1-5	2-3,5-8	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, (e.g., 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. Three consecutive production scale batches have been successfully validated as per QC approved validation protocol [Concurrent validation of three production scale batches would be acceptable for orphan drugs and low volume drug products (e.g. only two batches manufactured per year)].
5. The change does not affect the sterilization parameters of a sterile drug product.

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 vivo/in vitro correlation has been established).
2. (P.2) Comparative in vitro testing (e.g., 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) QC approved process validation protocol of the proposed drug product. Confirmation that the reference batch size has been previously validated as per approved process validation protocol. In addition, for a sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
5. (P.5.4) Description of the batches and summary of results for at least one 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 one batch representative of each strength of the proposed product.

8. (P 3.5) Process validation data on three consecutive commercial scale batches and confirmation that the results are in accordance with the QC approved validation protocol [Concurrent validation of three commercial scale batches would be acceptable for orphan drugs and low volume drug products (e.g. only two batches manufactured per year)].

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
25. Change in the drug product manufacturing process	None	1-9	Supplement
	1-8	2-10	Annual Notification

Conditions

1. The change does not require supporting in vivo data or does not require the filing of a request for a waiver of in vivo studies.
2. The manufacturing processes for the approved and proposed products use the same principles (e.g., a change from wet to dry granulation, from direct compression to wet/dry granulation or vice versa would be considered a change in manufacturing principle).
3. Changes to equipment, operating procedures, and process controls, are minor/non-critical. The equipment used in critical-processes 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 scale-up/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. Three consecutive commercial scale batches have been successfully validated as per QC approved validation protocol; condition could be waived with justification for minor/non-critical changes as outlined in condition #3. [Concurrent validation of three commercial scale batches would be acceptable for orphan drugs and low volume drug products (e.g. only two batches manufactured per year)].
7. The change is minor/non-critical and does not affect the performance characteristics (e.g., release rate) of a modified release drug product.
8. The change is minor/non-critical and does not affect the sterilization parameters of a sterile drug product.

Supporting Data

1. (1,5) Supporting clinical or comparative bioavailability data, where applicable, e.g.:
   - for a change using different manufacturing principles (e.g., a change from wet to dry granulation, from direct compression to wet/dry granulation or vice versa would be considered a change in manufacturing principle.)
   - for modified release dosage forms supporting clinical or comparative bioavailability data may be waived if an acceptable in vivo/in vitro correlation has been established).
   - for immediate release dosage forms, supporting clinical or comparative bioavailability data may be waived if an acceptable dissolution data (multi-point and multi-media) are provided to support the change.
2. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]

3. (P.2) Discussion of the development of the manufacturing process, where applicable, comparative in vitro testing (e.g., multi-point dissolution profiles for solid dosage units, comparative diffusion test results for semi-solids) for the approved and proposed products, discussion of any in vitro and/or in vivo studies, where applicable.
4. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates,
5. (P 3.5) QC approved Process validation protocol of the proposed drug product. In addition, for a sterile drug product, evidence of process validation and/or evaluation studies for sterilization procedures.
6. (P.5) Specification(s) (if specification(s) have changed), Batch Analyses (certificate of analyses for one commercial scale batch per strength).
7. (P.8.1) Stability Summary and Conclusions, e.g.:
    - for a major change to the manufacturing process (e.g., change in equipment class or manufacturing principles): results for two pilot scale batches of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product;
    - for a minor change to the manufacturing process (e.g., change in mixer stirring speed): stability data at the time of filing would not be necessary (see P.8.2 below) (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
8. (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).
9. (R.1.2) Executed Production Documents for one batch representative of each strength of the proposed product.
10. (P 3.5) Process validation data on three consecutive commercial scale batches and confirmation that the results are in accordance with the QC approved validation protocol; supporting data could be waived with justification for minor/non-critical changes as outlined in condition #3. [Concurrent validation of three commercial scale batches would be acceptable for orphan drugs and low volume drug products (e.g. only two batches manufactured per year)].

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
26. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates			
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 (e.g., colour), and does not pertain to a critical quality attribute of the product (e.g., 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) QC approved process validation and/or evaluation studies or the proposed validation protocol of the proposed drug product, where appropriate.
3. (P.5.4) Description of the batches, and summary of results, for at least one commercial scale batch.
4. (R.1.2) Executed Production Documents for one batch representative of each strength of the proposed product or Master Production Documents.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
27. Change in the approved protocol for process validation and/or evaluation studies	1-2	1	Annual Notification
Conditions			
1. The change does not concern the critical process parameters and controls of a drug product. 2. The change does not affect the sterilization procedures of a sterile drug product.			
Supporting Data			
1. (P.3.5) QC approved Process validation and/or evaluation studies or the revised validation protocol of the proposed drug product.			

3.2.P.4 Control of excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
28. Change in the source of an excipient from a vegetable source, synthetic source, or non-TSE (e.g., animal) to a TSE risk (e.g., animal) source, or from a TSE risk (e.g., animal) to a different TSE risk (e.g., animal source)	None	2-4	Supplement
	1	2-4	Annual Notification
29. Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	None	1,3	Annual Notification
Conditions			
1. The change of source is supported by a valid TSE Certificate of Suitability (CEP) issued by the 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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
30. Change in the standard claimed for the drug product (e.g., from a House Standard to a Schedule B pharmacopoeial standard) or change in the specification for the drug product to comply with an updated Schedule B pharmacopoeial monograph	1-2	1-6	Annual Notification
Conditions			
1. The change is made exclusively to comply with the pharmacopoeia. 2. No change to the specification that results in a potential impact on the performance of the drug product.			
Supporting Data			
1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] 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.5.3) Where a House analytical method is used and a Schedule B standard exists, 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, for at least one batches (minimum pilot scale) of the drug product tested according to the proposed specification. 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).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
31. Change in the specification for the drug product tests and acceptance criteria, involving:			
a. for sterile products, replacing the sterility test with process parametric release	None	1-2,5,7-8	Supplement
b. deletion of a test	1,5-7	2,8	Annual Notification
c. replacement or addition of a test	1-4,6-7	2-6,8	Annual Notification
d. relaxation of an acceptance criterion	1,4,6-8	2,5-6,8	Annual Notification
e. tightening of an acceptance criterion	None	2,8	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 (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 change in the assay limits and no change in the impurity profile that impacts safety of the drug product.
5. The deleted test has been demonstrated to be either redundant with respect to the remaining tests and/or does not impact the safety or overall quality of the product [e.g. removal of an organic volatile solvent test after at least ten (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 including drug release (dissolution) specification for modified release products.
7. The change does not concern sterility testing.
8. The relaxed criterion is in accordance with Schedule B compendial monograph.

Supporting Data

1. (P.3.5) Process validation results.
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 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 one (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 (e.g., demonstration of the suitability to control the drug product, including degradation products).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
32. Change in the specification for the drug product, for analytical procedures involving:			
a. deletion of an analytical procedure	5-6	1,6	Annual Notification
b. replacement, alternate, or additional analytical procedure	1-5	1-6	Annual Notification
c. change from a House analytical procedure to a Schedule B analytical procedure or a change from an approved compendial analytical procedure to an harmonized compendial procedure	1,3	1-6	Annual Notification

Conditions

1. No change in the approved acceptance criteria other than those permitted by the Schedule B monograph.
2. The method of analysis is based on the same analytical technique or principle and no new impurities are detected.
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 or does not impact the dissolution test condition (e.g., apparatus, speed, medium) for a modified release product.
6. The deleted analytical procedure has been demonstrated to be redundant with respect to the remaining analytical procedures for the same test and does not impact the safety or overall quality of the 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, and summary of results, for at least one (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 (e.g., demonstration of the suitability to control the drug product, including degradation products), if applicable.

3.2.P.7 Container closure system

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
33. Replacement or addition of a primary container closure system, for:			
a. sterile drug products	None	1-6	Supplement
b. other products	1-2	1-2,4-6	Annual Notification
Conditions			
1. No change in the type of container closure (e.g. from HDPE to PET). 2. The change does not concern a container closure that functions to meter the drug product (e.g., inhalation product).			
Supporting Data			
1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels. 2. (P.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing, permeation testing, light transmission). 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, process validation and/or evaluation studies. Evidence of process validation for sterilization processes for the container/closure. 4. (P.7) Information on the proposed container closure system (e.g., 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 two (2) pilot scale, of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing and, where applicable, results of photostability studies; (bracketing and matrixing for multiple strengths and packaging components could be applied, 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).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
34. Change in the package size, involving:			
a. change in the fill weight / fill volume	1-3	1-6	Annual Notification
b. change in the number of units (e.g., tablets, capsules) per package	1,3	1-6	Annual Notification

Conditions

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

Supporting Data

1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels.
2. (P.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing, permeation testing, light transmission). 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, process validation and/or evaluation studies. Evidence of process validation for sterilization processes for the container/closure.
4. (P.7) Information on the proposed container closure system (e.g., 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 two (2) pilot scale, of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing and, where applicable, results of photostability studies (bracketing and matrixing for multiple strengths and packaging components could be applied, 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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
35. Change in qualitative and/or quantitative composition of any primary or functional secondary container closure component	1-2	1-6	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. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels.
2. (P.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing, permeation testing, light transmission). 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) Where appropriate, process validation and/or evaluation studies.
4. (P.7) Information on the proposed container closure system (e.g., 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 two (2) pilot scale batches, three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing and, where applicable, results of photostability studies (bracketing and matrixing for multiple strengths and packaging components could be applied, 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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
36. Change in the specification for a primary or functional secondary container closure component where there is no other change in the container closure system	None	1-2	Annual Notification
Conditions			
None			
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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
37. Change in the shelf-life for the drug product, involving:			
a. extension	1-4	1-5	Annual Notification
b. reduction	1,3,5	1-6	Annual Notification

Conditions

1. No change to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2. Where the approved shelf-life is less than 24 months and data for potency, purity and performance for the proposed extension (not exceeding 24 months) does not exhibit significant trends for at least two (2) pilot scale batches.

   or

   where the approved shelf-life is at least 24 months, full long term stability data *is* available covering the proposed shelf-life and *is* based on stability data generated on at least three commercial scale batches.
3. Stability data was generated in accordance with the approved stability protocol.
4. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.
5. The reduction in shelf-life is due to stability concern and sponsor's assessment has determined that there is no impact on patient safety with the revised shelf-life or the reduction in shelf-life was not due to stability concern (e.g., business decision to streamline shelf in different regions).

Supporting Data

1. (P.8.1) Summary of stability testing and results (e.g., 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 in fulfilment of the aforementioned condition 2 (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6. Investigation report in fulfilment of condition #5.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
38.Change in the labelled conditions for drug product, or reconstituted/diluted product involving: - storage conditions [relaxation/tightening of storage condition (e.g., temperature)] - cautionary statement (addition/deletion)			
a. for sterile products	None	1-2	Supplement
b. for other products	None	1-2	Annual Notification
Conditions			
None			
Supporting Data			
1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels. 2. (P.8.3) If applicable, stability and/or compatibility testing results to support the change to the storage conditions.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
39. Change to the post-approval stability protocol or stability commitment	None	1-4	Annual Notification
Conditions			
None			
Supporting Data			
1. (P.8.1) Proposed storage conditions and shelf-life. 2. (P.8.2) Updated QC approved post-approval stability protocol and stability commitment. 3. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment. 4. (P.8.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment.			

Appendix 2: Quality Post-NOC Changes (veterinary drugs)

The Veterinary Drugs Directorate Appendix 2 to the Post-Notice of Compliance (NOC) Changes Quality Guidance Document is intended to clarify the chemistry and manufacturing changes relevant to the approved veterinary drugs. This Appendix 2 was developed by Health Canada in consultation with their stakeholders.

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

(a) 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. Similarly, if the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of an NDS or an ANDS;

(b) 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, these documents should be available in an official language (English or French), or a translation from the original language.

(c) The reporting category (e.g., Supplement, Notifiable Change or Annual Notification).

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.

Scope

The VDD Appendix 2 should facilitate sponsors' submissions with respect to the chemistry and manufacturing requirements of Division 8 of the Food and Drug Regulations.

The VDD Appendix 2 should neither be regarded as the only interpretation of the Guidance, nor can it cover every conceivable case for changes to veterinary drugs. Alternative means of complying with Appendix 2: Quality Post-NOC Changes (Veterinary Drugs) could be considered using appropriate scientific justification. When in doubt, sponsors are encouraged to contact the Veterinary Drugs Directorate (VDD) for further guidance.

Appendix 2: Quality Post-NOC Changes (Veterinary Drugs) supersede relevant sections of the Guidance for Industry: Preparation of Veterinary New Drugs Submissions.

Appendix 2: Quality Post-NOC Changes (Veterinary Drugs) is applicable to all veterinary drugs that have a Notice of Compliance (NOC). It is not applicable to veterinary biologics (e.g., biological vaccines) regulated by the Canadian Food Inspection Agency (CFIA). For veterinary biologics, please refer to applicable CFIA guidelines and policies.

When biotechnological tools (e.g., rDNA technology, gene targeting, DNA cloning) are used at any stage during synthesis of drug substance(s), or when biological processes (e.g.,

fermentation) are used during manufacturing of a veterinary drug product, the sponsor is encouraged to consult the VDD for specifics of conditions, data requirements and submission classifications. In these cases, the VDD will consult Appendix 3: Quality Post-NOC Changes (Biologics), pertaining to products regulated by the Biologics and Genetics Therapeutics Directorate (BGTD).

While ICH Q8, ICH Q9, and ICH Q10 apply to medicinal products for human use only, the related concepts are also expected to be useful in the context of veterinary drug products. It is therefore proposed that the design space concept is made applicable to both human and veterinary drugs and that sponsors of veterinary drugs submissions refer to these relevant ICH guidelines.

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

- The term Master File (MF) used in Appendix 2 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 2.1.1), no filing of Active Substance Master File (ASMF) is required.
- With respect to the drug substance information to be included in the submission, as a minimum the sponsor should submit the information 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.

Certain post NOC Quality changes could result in the formation of new degradant(s) or detection of previously unknown degradant(s) that require identification and/or qualification. If a sponsor chooses to implement these Quality changes, and an initial assessment indicates that the change(s) may have an impact on the withdrawal period of a veterinary drug used in food producing animals, the VDD recommends that these changes be submitted as Supplements, with appropriate human safety data, regardless of the recommended reporting category for the change outlined in Appendix 2: Quality Post-NOC Changes (Veterinary Drugs). During the review of the Supplement submission, VDD will assess the impact of any change in the withdrawal period and human safety of the drug product

A veterinary drug may have the identical composition, manufacturing processes, and analytical tests as a corresponding human drug product. If a Post-NOC Quality change has been submitted and approved for the human version of a veterinary drug product, the sponsor should submit, in addition to the requirements in the Guidance, a copy of the approval issued by the TPD or the BGTD and a certification that the animal and human drug products are identical except for the labelling, (i.e., "For Veterinary Use Only").

All Supplements to New Drug Submissions (SNDS) and Notifiable Changes (NC) should be submitted along with the VDD-CPID or an update of the existing VDD-CPID, to account for the proposed change(s) in chemistry and manufacturing information of the approved drug product. Sponsors are encouraged to submit the VDD-QOS document along with their Supplement and

Notifiable Change submissions. If a Supplement or a Notifiable Change submission contains more than one change, the sponsor should demonstrate that the proposed changes are consequential and should describe the association between the proposed changes.

3.2.S Drug Substance

3.2.S.1 General Information

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Change in the name of the drug substance	1	1-2	Annual Notification
Conditions			
1. Confirmation that the information on the drug substance has not changed as a result of the change [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]			
Supporting Data			
1. Package Insert and Inner and Outer Labels. 2. (S.1.1) Information on the proposed nomenclature of the drug substance [e.g., chemical name(s), compendial name [(Schedule B of the Food and Drug Regulations)] and evidence that the proposed name for the drug substance is recognized [e.g., Recommended International Non-Proprietary Name (INN), United States Adopted Names (USAN), British Approved Names (BAN)].			

3.2.S.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Replacement or addition of a manufacturing site and/or manufacturer, involving:			
a. production of the starting material, intermediate, or drug substance	None	1-10	Supplement
	2-5	2-10	Notifiable Change
	1-5	2-10	Annual Notification
b. testing (e.g., release, stability)	None	2,6,8-10	Notifiable Change
	6	2,6,8-10	Annual Notification
3. deletion of a manufacturing site or manufacturer for the starting material, intermediate, or drug substance	None	None	Annual Notification

Conditions

1. No Level I or Level II changes in the drug substance specifications (refer to Appendix 2, Change #9).
2. No change in the manufacturing process and/or route of synthesis (e.g. starting materials, intermediates and in-process controls remain the same), physical characteristics, and impurity profile of the drug substance (i.e., no new potentially genotoxic impurity or new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within VICH limits).
3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment of viral safety data or TSE risk assessment is required.
4. The change does not concern a sterile drug substance.
5. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).
6. The analytical method(s) for the new testing site is/are identical to the analytical method(s) in the compendial drug substance monograph (Schedule B of the Food and Drug Regulations).

Supporting Data

1. (1, 5) Viral safety data (ref. Condition 3) or supporting or comparative bioavailability data (ref. Condition 5) (whichever is applicable).
2. (1.2.5) Evidence of Canadian GMP compliance of the site involved in manufacturing, packaging, and/or testing of the drug substance. Health Product Compliance Directorate of the Regulatory Operations and Regions Branch (RORB)).
3. For sterile drug substances, evidence of validation of the sterilization process.
4. (S) Where applicable, updated or new MF (with a Letter of Access), the drug substance information relevant to the change or where applicable, a copy of the Certificate of Suitability (CEP) granted by the EDQM with the associated attestations.

5. (S.2) Confirmation that the synthetic route, process controls, control of materials, and specifications of the intermediate or drug substance (as appropriate) in the manufacturing process of the proposed drug substance are the same as those previously approved or revised information if any of the attributes have changed.
6. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing, packaging, and testing.
7. (S.2.3) For drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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) should be provided where available.
8. (S.4.3) Copies or summaries of validation reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site.
9. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for one batch of the currently approved and proposed drug substance release testing sites.
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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
4. Change in the manufacturing process for the drug substance or intermediate	1	1-11	Supplement
	1-4,7-8	2-9,11	Notifiable Change
	1-8	2-6,8-9,11	Annual Notification

Conditions

1. No change in the identicality of the drug substance (as defined in the Health Canada policy Interpretation of "Identical Medicinal Ingredient").
2. No change in the physical state (e.g. crystalline, amorphous, solid, semi-solid, liquid or gas) of the drug substance.
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 manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No Level I or Level II changes in the drug substance specifications.
6. No change in the route of synthesis (i.e., 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 ICH limits).
7. The change does not concern a sterile drug substance.
8. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1, 5) Viral safety data (ref. Condition 4) or supporting clinical or comparative bioavailability data (ref. Conditions 3, 8) (whichever is applicable).
2. (S) Updated or new Master File (MF) (with a Letter of Access) or relevant drug substance information. Where available, a copy of the Certificate of Suitability (CEP) issued by the EDQM with associated attestations.
3. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
4. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance, as applicable. 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.
5. (S.2.3) For drug substances or intermediates manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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) should be provided where available.

6. (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.
7. (S.2.5) For sterile drug substances, evidence of validation of the sterilization process.
8. (S.3.1) Evidence for elucidation of structure, where applicable.
9. (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 one (1) batch of the currently approved and proposed processes.
10. (S.7.3) Results of two (2) batches with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.
11. (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.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
5. Change in the batch size for the drug substance	7-8	1-3	Notifiable Change
	1-8	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 (e.g., 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 does not affect the sterilization procedures of a sterile drug substance.
7. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).
8. 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 one batch.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
6. Change in the controls for the materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) or the controls performed at critical steps in the process	None	1-4	Notifiable Change
	1-5	1-4	Annual Notification

Conditions

1. No Level I or Level II changes in the drug substance specifications (refer to Appendix 2, Change #9).
2. No change in the impurity profile of the drug substance (i.e., no new impurity above 0.1%, no change in the approved total impurity limit and residual solvents within VICH limits).
3. The change in control(s) does not constitute a relaxation from the approved controls and is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
4. The change does not affect the sterilization procedures of a sterile drug substance.
5. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (S.2.3) Information on the quality and controls of the materials (e.g., 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 one batch of each of the drug substance manufactured by the current and proposed methods.

3.2.S.3 Characterisation

There are not any 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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
7. Change in the standard claimed for the drug substance (e.g., 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
8. Change in the specification for the drug substance to comply with an updated Schedule B pharmacopoeial monograph	1,2	1-4	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 [i.e., functional properties of the drug substance (e.g., 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 one batch if new tests and/or analytical methods are implemented. 4. (S.4.5) Justification of the proposed drug substance specification (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
9. Change in the specification for the drug substance involving test and acceptance criteria:			
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
	1,2,5	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 substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

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 ten batches) to support the process parametric release. 7. (S.4.5) Justification of the proposed drug substance specification (e.g., test parameters, acceptance criteria, or analytical procedures). 8. (P.2) Where appropriate (e.g., for a change in particle size limit for a poorly soluble drug substance), comparative, multi-point dissolution profiles in the release medium for one batch of the drug product using material from the approved and change drug substance specifications.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
10. Change in the specification for the drug substance involving analytical procedures:			
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 or a change from an approved compendial analytical procedure to an harmonized compendial procedure	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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
11. 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 (e.g., including results of transportation or interaction studies, if appropriate). 2. The change does not concern 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 (e.g., description, materials of construction, specifications). 3. (S.7.3) Results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the drug substance in the proposed container closure system.			

3.2.S.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
12. Change in the re-test period (or shelf-life) for the drug substance, involving:			
a. Extension	None	1-4	Notifiable Change
	1-6	1-4	Annual Notification
b. Reduction	None	1-4	Notifiable Change
	1,3-4	1-4	Annual Notification
Conditions			
1. No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance. 2. The approved re-test period (or shelf-life) is at least 24 months. 3. 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 three commercial scale batches. 4. Stability data was generated in accordance with the approved stability protocol. 5. Significant changes as defined in VICH GL3 guidelines were not observed in the stability data. 6. The drug substance has not been subject to a previous reduction in re-test period (or shelf-life).			
Supporting Data			
1. (S.7.1) Summary of stability testing and results (e.g., 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 two pilot and/or commercial scale batches with stability data to support the proposed re-test period or shelf-life.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
13. Change in the labelled storage conditions for the drug substance, involving: addition/deletion of a cautionary statement or relaxation/tightening of a temperature criterion (e.g., 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 not less than two (2) lots (pilot or commercial scale).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
14. Change to the post-approval stability protocol or stability commitment	None	1,2	Annual Notification
Conditions			
None			
Supporting Data			
1. (S.7.1) Justification of the change to the post-approval stability protocol or stability commitment. 2. (S.7.2) QC approved updated post-approval stability protocol and stability commitment.			

3.2.P Drug product

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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
15. Addition of a dosage form or strength	None	1-15	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, e.g.: - when the changes in excipients for a new strength of an immediate release solid oral dosage form containing a single drug substance, expressed as percentage (w/w) of total formulation, are greater than the ranges outlined in Appendix 6. - when the changes in excipients for new strength of an immediate release solid oral dosage form containing a single drug substance, expressed as percentage (w/w) of total formulation, are less than or equal to the ranges outlined in Appendix 6. 2. (1.2.5) GMP and Establishment License (EL) Information (i.e., Confirmation of a satisfactory Canadian GMP rating by the Health Product Compliance Directorate of the Regulatory Operations and Regions Branch RORB)). 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. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.] 6. (P.1) Description and composition of the dosage form. 7. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative *in vitro* testing (e.g., 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. 8. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates. 9. (P 3.5) Process validation data on three 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. 10. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations). 11. (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 one (1) pilot scale batch per strength).			

12. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
13. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches), results of a minimum of six (6) months of accelerated (or intermediate as appropriate) and six (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.
14. (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).
15. (R.1) Executed Production Documents for at least one (1) pilot scale batch of each new dosage form or strength.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
16. Change in the composition of a solution dosage form	None	1-13	Supplement
	1-4,8	2-13	Notifiable Change
	1-8	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 Solutions).
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 to affect the solubility of the drug substance.
4. The proposed excipient(s) does/do not function as a preservative or preservative enhancer.
5. No change in the specifications of the proposed excipient(s) or the drug product.
6. No change to the physical characteristics of the drug product (e.g., viscosity, pH, osmolality).
7. The change does not concern a sterile drug product.
8. The change concerns a drug product that contains drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1,5) Supporting clinical or comparative bioavailability data or a request for a waiver of in vivo studies, e.g.:
   - when the changes in excipients are not considered to be qualitatively the same and quantitatively essentially the same: supporting clinical or comparative bioavailability data and in vitro data on the physicochemical properties;
   - when the changes in excipients are considered to be qualitatively the same and quantitatively essentially the same: supporting in vitro data on the physicochemical properties.
2. (1.2.6) Letters of Access if Master Files (MFs), are submitted for new excipients.
3. Package Insert and Inner and Outer Labels.
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing on the physicochemical properties for the approved and proposed products, 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 three 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.
9. (P.4) Control of Excipients, if new excipients are proposed (e.g., 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 one pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches), e.g.:
    - when the changes in excipients are not considered to be qualitatively the same and quantitatively essentially the same: results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product;
    - when the changes in excipients are considered to be qualitatively the same and quantitatively essentially the same: stability data at the time of filing would not be necessary (see P.8.2 below).
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 one pilot scale batch of each strength of the proposed product.
14. The new flavour or colour is not prohibited by the Canadian regulations and complete safety data is available on file. The new excipient does not affect the performance characteristics of the drug product or the release or bioavailability of the drug substance. Stability data for the new formulation shows no change in the stability profile. Changes to the drug product specifications are those necessitated only by the change to the colour or the flavour.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
17. Change in the composition of an immediate release dosage form (other than a medicated premix)	None	1-13	Supplement
	1,3-5,8	2-13	Notifiable Change
	1-8	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 6.
3. The change does not require supporting in vivo data and does not affect the performance characteristics of the drug product (e.g. release rate).
4. The proposed excipient(s) does/do not function to affect the absorption of the drug substance.
5. The proposed excipient(s) does/do not function to affect the solubility of the drug substance.
6. The proposed excipient(s) does/do not function as a preservative or preservative enhancer.
7. No Level I or Level II changes in the specifications of the proposed excipient(s) or the drug product.
8. The change concerns a drug product that contains drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1,5) Supporting clinical or comparative bioavailability data or a request for a waiver of in vivo studies, e.g.:
   - when the changes in excipients, expressed as percentage (w/w) of total formulation, are greater than the ranges outlined in Appendix 6: supporting clinical or comparative bioavailability data and in vitro data;
   - when the changes in excipients, expressed as percentage (w/w) of total formulation, are less than or equal to the ranges outlined in Appendix 6: supporting in vitro data.
2. (1.2.6) Letters of Access if Master Files (MFs) are submitted for new excipients.
3. Package Insert and Inner and Outer Labels.
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing (e.g., depending on the solubility and permeability of the drug (refer to Appendix 5), multi-point dissolution profiles in either the release medium or in multiple media covering the physiological pH range) for the approved and proposed products, 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 three 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.
9. (P.4) Control of Excipients, if new excipients are proposed [e.g., 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 one pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches): results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (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 one batch representative of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
18. Change in the composition of a medicated premix dosage form	None	1-12	Supplement
	1-3,6	2-12	Notifiable Change
	1-6	2-12	Annual Notification

Conditions

1. Any qualitative and /or quantitative change in the composition does not require supporting in vivo data.
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 to affect the solubility of the drug substance.
4. The proposed excipient(s) does/do not function as a preservative or preservative enhancer.
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 that contains drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1,5) Supporting clinical or comparative bioavailability data, where applicable, or a request for a waiver of in vivo studies.
2. (1.2.6) Letters of Access if Master Files (MFs) are submitted for new excipients.
3. Package insert (title page, ''Dosage Forms, Composition, and Packaging'' section).
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.)]
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients).
7. (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.
8. (P.4) Control of Excipients, if new excipients are proposed (e.g., 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 one pilot scale batch).
10. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches) – results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product. Bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified.

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 one batch representative of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
19. 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 (e.g., 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. 4. (R.1) Executed Production Documents for one batch representative of each strength of the proposed product.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
20. Addition, deletion or replacement of carrier used in a medicated premix	1-3	1-4	Annual Notification

Conditions

1. Confirmation that there is no change in the potency, strength, particle size, and efficacy of the medicated premix.
2. The proposed carrier is listed as an approved feed ingredient as defined in the Feed Regulations.
3. 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 carrier (e.g., demonstration of the suitability of the new carrier to control the drug premix, including batch to batch consistency). Justification that there is no "statistically significant" deviation from complete mixing.
2. (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.
3. (R.1) Executed Production Documents for one batch representative of each strength of the proposed product.
4. Demonstration of homogeneity, non-segregation, and stability properties of the proposed medicated premix.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
21. Change in the release controlling agent of a modified release solid oral dosage form (for changes in other excipients, refer to Appendix 2 change #17	None	1-13	Supplement
	1-2	1-13	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).
2. (1.2.6) Letters of Access if Master Files (MFs) are submitted for new excipients.
3. Package Insert and Inner and Outer Labels.
4. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]
5. (P.1) Description and composition of the dosage form.
6. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing [e.g., 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)].
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 three 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.
9. (P.4) Control of Excipients, if new excipients are proposed (e.g., 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 one pilot scale batch per strength).
11. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches), e.g.:
    - results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing 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 one batch of each strength.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
22. Change to product markings, involving a change in embossing, debossing, or engraving (except scorelines/break lines) (e.g., plain tablet to engraved, engraved to plain, change in engraving) or a change in imprinting (e.g., 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 (e.g., 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 (e.g. Certificate of Analysis for one 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).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
23. Change in scoring configuration, involving:			
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 (e.g., 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 (e.g. Certificate of Analysis for one 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 one batch representative of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
24. 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 (e.g. release rate) of the drug product.

Supporting Data

1. Package Insert and Inner and Outer Labels.
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 (e.g. Certificate of Analysis for one 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 one batch representative of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
25. Change in diluent, involving:			
a. replacement or addition of a diluent for a lyophilized powder or concentrated solution	None	1-12	Supplement
	1	2,3,5,9	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. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.)]
4. (P.1) Description and composition of the diluent.
5. (P.2) Discussion of the components of the drug product, as appropriate (e.g., choice of excipients, compatibility of the drug product with the diluent).
6. (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.
7. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
8. (P.5) Batch Analyses (e.g. Certificate of Analysis for a minimum of one pilot scale batch of the diluent, if it is included with the product.
9. (P.7) Discussion (including description, materials of construction on the container closure system, compatibility studies with the diluent).
10. (P.8.1) Stability Summary and Conclusions: results for two pilot scale batches of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the diluent.
11 (P.8.2) Updated post-approval stability protocol and stability commitment for the diluent if it is included with the product.
12. (R.1) Executed Production Documents for one batch of the diluent if it is included with the product.

3.2.P.2 Pharmaceutical development

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
26. Change in the approved design space, involving:			
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).			

3.2.P.3 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
27. Replacement or addition of a drug product manufacturer / manufacturing site, involving:			
a. production of a modified release or sterile product	None	1-10	Supplement
b. production of an immediate release product (e.g., tablet, capsule, liquids, semi-solids)	None	2-10	Notifiable Change
	1-4	2-10	Annual Notification
c. primary packaging	2-3	2,5	Annual Notification
d. testing (e.g., release, stability)	None	2,5,7,8,9	Notifiable Change
	5	2,5,7,8,9	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, RORB, or is already included in the Establishment License.
4. Three 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 of three production scale batches would be acceptable for low volume drug products (e.g. only two batches manufactured per year)].
5. The analytical method(s) for the new testing site is/are identical to the analytical method(s) in the compendial drug product monograph (Schedule B of the Food and Drug Regulations).

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 vivo/in vitro correlation has been established).
2. (1.2.5) GMP and Establishment License (EL) Information (i.e., Confirmation of a satisfactory Canadian GMP rating by the Health Product Compliance Directorate of RORB).
3. (P) Confirmation that information on the drug product has not changed as a result of the submission (e.g., other than change in site).
4. (P.2) Comparative in vitro testing (e.g., 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 5 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 three 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.
7. (P.5.3) Copies or summaries of method validation data / method transfer reports, which demonstrate equivalency of analytical procedures used by the currently approved and proposed drug product release testing sites.
8. (P.5.4) Certificate of analyses for at least one 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 one commercial scale batch of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
28. Change in the batch size for the drug product, involving:			
a. increase in batch size beyond a factor of (10) for a modified release drug product	None	1-7	Supplement
b. increase in batch size beyond a factor of ten (10) times for an immediate release drug product	1-5	2-7	Notifiable Change
c. increase in batch size, up to and including a factor of ten (10) times	1-5	2-7	Annual Notification
d. a downscaling in the batch size	1-5	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, (e.g., 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. Three consecutive production scale batches have been successfully validated as per QC approved process validation protocol [Concurrent validation of three production scale batches would be acceptable for low volume drug products (e.g. only two 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 (the supporting clinical or comparative bioavailability data may be waived if an acceptable in vivo/in vitro correlation has been established).
2. (P.2) Comparative in vitro testing (e.g., 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 three consecutive production scale batches of the proposed drug product and /or QC approved process validation protocol. 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 one 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 one commercial scale batch of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
29. Change in the drug product manufacturing process	None	1-9	Supplement
	1-8	2-9	Annual Notification

Conditions

1. The change does not require supporting in vivo data or does not require the filing of a request for a waiver of in vivo studies.
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. Three 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 of three commercial batches would be acceptable for low volume drug products (e.g. only two 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, where applicable, or a request for a waiver of in vivo studies, e.g.:
   - for a change using different manufacturing principles (e.g., from a wet to dry granulation): supporting clinical or comparative bioavailability data
   - for a change using the same manufacturing principles: supporting in vitro data
2. (S) Confirmation that the information on the drug substance has not changed [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.)]
3. (P.2) Discussion of the development of the manufacturing process, where applicable, comparative in vitro testing (e.g., multi-point dissolution profiles in the release medium for solid dosage units, comparative diffusion test results for semi-solids) for the approved and proposed products, discussion of any in vitro and/or in vivo studies, where applicable.
4. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
5. (P.3.5) Process validation data on three 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.
6. (P.5) Specification(s) (if specification(s) have changed), Batch Analyses (certificate of analyses for at least one commercial scale batch per strength). (P.8.1).
7. Stability Summary and Conclusions, e.g.:

- for a major change to the manufacturing process (e.g., change in equipment class or manufacturing principles): results for two pilot scale batches of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product;
- for a minor change to the manufacturing process [e.g., change in mixer stirring speed): stability data at the time of filing would not be necessary (see P.8.2 below).]

8. (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).
9. (R.1.2) Executed Production Documents for at least one commercial scale batch of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
30. Change in the manufacturing process of a Veterinary medicated premix (e.g., from regular powder to granulated form and/or vice versa)	None	1-9	Supplement
	1	1,3-9	Notifiable Change
	1-7	1,3-9	Annual Notification

Conditions

1. The change does not affect performance characteristics (e.g. bioavailability) of the medicated premix.
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 powder blend to granular premix, or vice versa, would be considered a change in manufacturing principle.
3. The change is not the result of unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
4. The same operating procedures and process controls are used for the approved and proposed products. The equipment used to produce the proposed product may vary in capacity, but are of the same class and operating principles.
5. No Level I or Level II changes to the drug product specifications (refer to Appendix 2, Change #37).
6. No change in the shelf-life, the stability protocol, stability tests, and stability commitment of the medicated premix.
7. Three consecutive commercial scale batches have been successfully validated as per QC-approved process validation protocol; condition could be waived with justification for minor/non-critical changes as outlined in Condition #2. Concurrent validation of three commercial scale batches would be acceptable for low volume drug products (e.g. only two batches manufactured per year).

Supporting Data

1. Package Insert (title page, ''Dosage Forms, Composition, and Packaging'' section).
2. (1,5) Supporting clinical or comparative bioavailability data
3. (P.2) Discussion of the development of the new manufacturing process and differences in manufacturing process(es) between the approved and proposed products and the potential impact on product performance
4. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates.
5. (P.3.5) Process validation data on three consecutive commercial batches and /or QC approved process validation protocol
6. (P.5) Specification(s), Analytical Procedures and their validation (if new analytical methods are used), Batch Analyses (certificate of analyses for at least one commercial scale batch).
7. (P.8.1) Stability Summary and Conclusions (minimum of two pilot scale batches for a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug product).

8. (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 could be applied, if scientifically justified).
9. (R.1) Executed Production Documents for at least one commercial scale batch of each strength of the proposed product.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
31. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates			
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 (e.g., colour), and does not pertain to a critical quality attribute of the product (e.g., 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.
3. (P.5.4) Description of the batches, and certificate of analyses for at least one commercial scale batch.
4. (R.1.2) Executed Production Documents for at least one batch of each strength of the proposed product or Master Production Documents.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
32. 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			

3.2.P.4 Control of excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
33. Change in the source of an excipient from a vegetable, synthetic source, or non-TSE (e.g., animal) to a TSE risk (e.g., animal) source, or from a TSE risk (e.g., animal) source to a different TSE risk (e.g., animal)	None	2-4	Notifiable Change
34. Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	None	1,3	Annual Notification
Conditions			
None			
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 [For a veterinary drug used in a food producing animal, as outlined in Appendix 4 of the Form HC-SC 3011].			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
35. Change in the analytical test method of an excipient in a medicated premix to comply with an updated version of a Schedule B pharmacopoeial monograph	1	1,2	Annual Notification
Conditions			
1. No deletion or relaxation of any of the other tests, analytical procedures, or acceptance criteria of the approved specification of the excipient and the medicated premix.			
Supporting Data			
1. (P.5.1) Updated, QC approved, medicated premix specification. 2. (P.5.3) Where an updated version of a Schedule B analytical procedure is used, if applicable, results of an equivalency study (e.g. system suitability test) between the current and updated compendial methods.			

3.2.P.5 Control of drug product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
36. Change in the standard claimed for the drug product (e.g., from a Professed to Schedule B pharmacopoeial standard) or change in the specification for the drug product to comply with an updated Schedule B pharmacopoeial monograph	1,2	1-5	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 one batches (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).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
37. Change in the specification for the drug product tests and acceptance criteria, involving:			
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	1,2,4-7	2,8-9	Annual Notification
c. replacement or addition of a test	1-4,6-8	2-6,8-9	Annual Notification
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 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 and does not impact the safety or overall quality of the product [e.g. removal of an organic volatile solvent test after at least ten (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.
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 one (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 (e.g., demonstration of the suitability to control the drug product, including degradation products).
9. For drug products that contain a drug substance that is not a discrete chemical entity (i.e., this does not include polymeric complexes), demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
38. Change in the specification for the drug product, for analytical procedures, involving:			
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 or a change from an approved compendial analytical procedure to an harmonized compendial procedure	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.
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 (e.g. 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 (e.g. 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 one (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 (e.g., demonstration of the suitability to control the drug product, including degradation products), if applicable.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
39. 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 (e.g. solubility, release rate, dissolution).
5. The change does not concern sterility testing.
6. The change does not affect the withdrawal period 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 two batches (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 (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).
8. For drug products that contain a drug substance that is not a discrete chemical entity (i.e., this does not include polymeric complexes), demonstration that consistency of quality and of the production process is maintained.
9. Confirmation that the withdrawal period has not been affected as a result of the change.

3.2.P.7 Container closure system

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
40. Replacement or addition of a primary container closure system	None	1-6	Notifiable Change
	1-4	1,2,4-5	Annual Notification
41. Change in the package size, involving:			
a. change in the fill weight / fill volume	None	1-5	Notifiable Change
	1-3	1,2,4,6	Annual Notification
b. a change in the number of units (e.g., tablets, ampoules) per package	None	1-5	Notifiable Change
	1-3	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.
2. (P.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing, permeation testing, biological reactivity tests, light transmission), USP General Chapters <661.1>, <661.2>, <1663>, <1664>, <87>, and <88>, as applicable. 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, where applicable.
4. (P.7) Information on the proposed container closure system (e.g., 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 two (2) pilot scale, of three (3) months of accelerated (or intermediate as appropriate) and three (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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
42. Change in qualitative and/or quantitative composition of any primary or functional secondary container closure component	None	1-6	Notifiable Change
	1,2	1-4,6	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.
2. (P.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing, permeation testing, biological reactivity tests, light transmission). USP General Chapters <661.1>, <661.2>, <1663>, <1664>, <87>, and <88>, as applicable. 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, process validation and/or evaluation studies.
4. (P.7) Information on the proposed container closure system (e.g., 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 two (2) pilot scale batches, three (3) months of accelerated (or intermediate as appropriate) and three (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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
43. 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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
44. Change in the shelf-life for the drug product, involving:			
a. Extension	None	1-5	Notifiable Change
	1-6	1,2,5	Annual Notification
b. Reduction	None	1-5	Notifiable Change
	1,6-7	1-5	Annual Notification

Conditions

1. No change to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2. The approved shelf-life is at least 24 months.
3. Full long term stability data *is* available covering the proposed shelf-life and *is* based on stability data generated on at least three commercial scale batches.
4. Stability data was generated in accordance with the approved stability protocol.
5. Significant changes (as defined in VICH GL3 guideline were not observed in the stability data.
6. The drug product has not been subject to a previous reduction in shelf-life.
7. The reduction in shelf-life is a result of a business decision to streamline shelf-life in different regions.

Supporting Data

1. (P.8.1) Summary of stability testing and results (e.g., 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 (i.e., full long term stability data covering the proposed shelf-life generated on at least three 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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
45. Change in the labelled storage conditions for the drug product or the diluted or reconstituted product, involving:			
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.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
46. Change to the post-approval stability protocol or stability commitment	None	1-4	Annual Notification
Conditions			
None			
Supporting Data			
1. (P.8.1) Proposed storage conditions and shelf-life. 2. (P.8.2) Updated QC approved post-approval stability protocol and stability commitment. 3. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment. 4. (P.8.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
47. Change in the stability protocol or the shelf-life for a medicated premix, involving:			
a. extension of the shelf-life	1-6	1-3,5	Annual Notification
b. reduction of the shelf-life	1-7	1-5	Annual Notification
c. addition of a time point at any time, or deletion of time points beyond the approved expiration period	1	1-4	Annual Notification
d. changes to comply with a relevant VICH guidance (e.g. deletion of a time point from previously approved stability protocol, or change in storage conditions)	1,5-6	1-5	Annual Notification

Conditions

1. No change to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2. The approved shelf-life is at least 24 months.
3. Full long term stability data is available covering the proposed shelf-life and is based on stability data generated on at least three commercial scale batches.
4. Stability data was generated in accordance with the approved stability protocol.
5. 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”.
6. The medicated premix has not been subject to a previous reduction of an expiration date.
7. The reduction in shelf-life is due to a business decision to streamline shelf-life in different regions.

Supporting Data

1. (P.8.1) Summary of stability testing and results (e.g., 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 (i.e., full long term stability data covering the proposed shelf-life generated on at least three commercial scale batches, bracketing and matrixing could be applied, if justified).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
48. Change to the post-approval stability protocol or stability commitment of a sterile veterinary drug used as euthanasia drug or an ear implant for bovine and ovine species	1,2	1-5	Annual Notification

Conditions

1. The proposed analytical method is at least equivalent or is superior to detect the drug substance or, impurities, or degradation products as specified in the drug product shelf-life specifications
2. There is no change to the shelf-life specifications and the storage conditions.

Supporting Data

1. (P.8.1) Proposed storage conditions and shelf-life.
2. (P.8.2) Updated post-approval stability protocol and stability commitment.
3. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment.
4. (P.8.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment.
5. Copies or summaries of validation reports for the proposed analytical procedures, and comparative results demonstrating that the approved and proposed analytical procedures are equivalent.

3.2.R.2 Devices

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
49. Change of an approved device used for administration of a veterinary drug			
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	1-3,6-7	Notifiable Change
	1-6	1,3,6-7	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	1,3,6-7	Annual Notification
c. change in an approved multi-dose administration device for an injectable veterinary drug product	4	1-7	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. (1.3) Package Insert and Inner and Outer Labels.
2. Data demonstrating the suitability and compatibility of the materials of construction of the device system (e.g., extractable/leachable testing, permeation testing, biological reactivity tests light transmission, as applicable).
3. Information on the proposed measuring device system (e.g., 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 (e.g., 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. Amended relevant sections of VDD-CPID, or equivalent (including description, detailed drawing and composition of the device material and supplier where appropriate).
7. Reference to certificate of analysis, or other manufacturer standards for the device, where applicable, demonstrating the delivered dose (accuracy, precision) of the proposed device.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
50. Significant change to a device used in administration of an extended release veterinary drug (e.g. addition, deletion, replacement of, or change in materials of construction of an extended release device (e.g. for intra ruminal boluses used for continued release) of a veterinary drug product).	None	1-8	Supplement
	3-5	1,3-8	Notifiable Change
	1-6	1,3-8	Annual Notification

Conditions

1. No change in the type of or materials of construction (e.g. 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 (e.g. encapsulated gelatin)

Supporting Data

1. (1.3) Package Insert and Inner and Outer Labels.
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 (e.g., 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 (e.g., 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. Amended relevant sections of VDD-CPID, , or equivalent (including description, detailed drawing and composition of the device material and supplier where appropriate).
7. 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.
8. TSE Certificate of Suitability (CEP) issued by the EDQM, if available, or satisfactory TSE risk assessment on material of construction of the device as outlined in Appendix 4 of the HC-SC 3011.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
51. Minor changes to a device used in administration an extended release veterinary drug			
a. tightening of specification limits of an administration device for a veterinary drug (e.g. changes in balling gun used for intra-ruminal boluses to control drug product rate of release).	None	1-4	Notifiable Change
	2-3	1,4-5	Annual Notification
b. minor change to an approved test procedure	1-3	3-5	Annual Notification
c. addition of a new test parameter	2	1,4	Annual Notification
Conditions			
1. The change is not a consequence of any commitment placed in the submission review process. 2. The change should not be the result of unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits.			
Supporting Data			
1. Package Insert and Inner and Outer Labels. 2. Data demonstrating the suitability of the materials of construction of the measuring device system (e.g., 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 (e.g., 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.			

Appendix 3: Quality Post-NOC Changes (biologics)

The change examples presented below are intended to assist with the classification of changes made to the Quality information of Schedule D (biologic) drugs. The information summarized in the tables provides recommendations for:

(a) The conditions to be fulfilled for a given change to be classified as either a Level I - Supplement, a Level II - Notifiable Change, or a Level III - Annual Notification. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Level II - Notifiable Change are not fulfilled, the change is considered a Level I - Supplement. Similarly, if any of the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of an NDS;

(b) The supporting data for a given change is to be submitted to Health Canada and/or maintained by the sponsor. Where applicable, the corresponding modules of the Common Technical Document (CTD) for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided.

(c) The reporting category (e.g., Supplement, Notifiable Change or Annual Notification).

For convenience, the change examples are organized according to the format defined by the Common Technical Document (CTD), refer to the Guidance for industry for the preparation of the quality information for drug submissions in CTD format: Biotechnological/Biological (Biotech) products; Blood products; Conventional biotherapeutic products; and the Guidance Document on the Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application.

When submitting a QOS, the relevant QOS for Biologics should be used as described in the above mentioned guidance documents with the changes clearly indicated.

When applicable, an annotated and non-annotated (clean) copy of the Certified Product Information Document for Schedule D drugs (Biologics) (CPID-B) should be provided with the Level I and Level II changes.

3.2.S Drug substance

3.2.S.1 General information

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Change in the name of the drug substance	1	1-2	Annual Notification
Conditions			
1. Confirmation that information on the drug substance has not changed as a result of the submission [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's /sponsor's name, submission type, control number, date approved)].			
Supporting Data			
1. (1.3) Product Monograph [e.g., Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels. 2. (S.1.1) Information on the proposed nomenclature of the drug substance [chemical name(s), compendial name] and evidence that the proposed name for the drug substance is recognized (e.g., proof of acceptance by WHO, recommended INN, USAN, BAN).			

3.2.S.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Change to a drug substance manufacturing facility, involving:			
a. replacement or addition of a manufacturing facility for the bulk drug substance, or any intermediate of the drug substance	None	1-7,9-14,16	Supplement
	1-5	3,7,9-13,19	Notifiable Change
b. introduction of microbial hosts into a multi-product mammalian cell culture suite or vice versa	None	14-15	Supplement
c. conversion of production and related area(s) from campaign to concurrent for a multi-product facility	5-6	17-18	Notifiable Change
d. conversion of a drug substance manufacturing facility from single-product to multi-product	5	14,16	Notifiable Change
e. addition of product(s) to an approved multi-product manufacturing facility	4-5,7	14,17	Annual Notification
f. introduction of a different host/media-type into an approved multi-product facility	7	8,16	Annual Notification
g. deletion of a manufacturing facility or manufacturer for a bulk intermediate, or drug substance	None	None	Annual Notification

Conditions

1. The proposed manufacturing facility/suite is a Health Canada approved biological drug substance manufacturing site for the same sponsor (the control # of the prior approved application should be provided).
2. No changes have been made to the validated manufacturing process and controls, and identical or equivalent equipment are used (see Glossary for the definition of equivalent equipment).
3. The new facility/suite is under the same QA/QC oversight.
4. No changes have been made to the approved and validated cleaning and change-over procedures.
5. The proposed change does not involve additional containment requirements.
6. The manufacturing process is a closed process for shared areas.
7. No changes to the cleaning protocol are necessary to support the introduction of new products (no changes in acceptance criteria, and no new materials have been introduced that need to be evaluated for clearance in a cleaning step).

Supporting Data

1. (1.2.5) GMP and EL information.
2. (S) Updated or new DMF (with a Letter of Access provided in Module 1) or relevant drug substance information.

3. (S.2.1) Name, address, and responsibility of the proposed production facility or facility involved in manufacturing and testing.
4. (S.2.3) For drug substances obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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). An EDQM TSE Certificate of Suitability, if available, is acceptable for raw materials, auxiliary materials, and reagents only.
5. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed drug substance.
6. (S.2.5) Summary of the process validation and/or evaluation studies, including information demonstrating qualification of the equipment (e.g., operational qualification, performance qualification). The complete report with all raw data could be requested during review.
7. (S.2.6) Comparability of the approved and proposed drug substance with respect to physico-chemical characterization, biological activity, and impurity profile. [N.B. Occasionally, the sponsor may undertake bridging non-clinical or clinical studies (e.g. bioequivalence) to support the quality data].
8. (S.4) Information on the in-process control testing to demonstrate lack of carry-over or cross-contamination.
9. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed drug substance (certificates of analysis to be provided in section 3.2.R.3).
10. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug substance, or longer if less than three (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.
11. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale drug product batches manufactured using the proposed drug substance (certificates of analysis to be provided in section 3.2.R.3).
12. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance into the stability program.
13. (A.1) Information on the proposed production facility involved in the manufacture of the drug substance, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate.
14. (A.1) Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If no revisions, a signed attestation from the manufacturer that no changes were made to the change-over procedures.
15. (A.1) Results of the environmental monitoring studies in critical classified areas.
16. (A.1) Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.
17. (A.1) Data demonstrating lack of carry-over or cross-contamination.
18. Description of the segregation procedures to avoid cross-contamination.
19. Rationale for considering the proposed equipment as equivalent, if applicable.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
3. Modification to a facility involved in the manufacture of a drug substance, such as:			
a. for an active ingredient manufactured in an open system, any changes which has the potential to increase the environmental risk to the product	None	1-2,5	Notifiable Change
b. relocation of equipment to another room in the same facility, qualification of a new room or change in classification of an existing room	1-3	3-5	Annual Notification
c. modification to a manufacturing area or modification to an existing service/system (e.g., change to WFI systems or HVAC systems, moving a wall)	1-2	3-5	Annual Notification
d. change in the location of steps in the production process within the same facility	1	1,4-5	Annual Notification
Conditions			
1. The change has no impact on the risk of contamination or cross-contamination. 2. The modification has no product impact. 3. Re-qualification of the equipment follows the original qualification protocol, if applicable.			
Supporting Data			
1. (S.2.4) Information on the in-process control testing. 2. (S.2.5) Process validation and/or evaluation studies (e.g., equipment qualification). The proposed validation protocol is acceptable, but data could be requested. 3. (S.2.5) Information demonstrating re-qualification of the equipment or re-qualification of the change (e.g., operational qualification, performance qualification), as appropriate. 4. (A.1) Information on the modified production facility/area involved in manufacturing, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems). 5. (A.1) Results of the environmental monitoring studies in critical classified areas.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
4. Change to the drug substance fermentation process, involving:			
a. a critical change (e.g., incorporation of disposable bioreactor technology)	None	1-3,7-8, 10,12-13	Supplement
b. a change with moderate potential to adversely impact quality of the product (e.g., extension of the in vitro cell age beyond validated parameters)	2,4	2-3,7,9,11	Notifiable Change
c. a non-critical change (i.e. expected to have no impact on the quality or the impurity profile of the drug substance) , such as: • change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale; or • duplication of a fermentation train; or • addition of identical or similar/comparable bioreactors	1-6,8-9	2-3,7,9	Annual Notification
5. Change to the drug substance purification process, involving:			
a. a critical change (e.g., change that impact negatively the viral clearance capacity of the process or the impurity profile of the drug substance)	None	1-2,5,7-8,10,12-14	Supplement
b. a change with moderate potential to adversely impact quality of the product (e.g., change in the chemical separation method, for example ion-exchange HPLC to reverse phase HPLC)	2,4	1-2,7-8,11,13	Notifiable Change
c. a non-critical change (i.e., expected to have no impact on the viral clearance capacity of the process or the impurity profile of the drug substance)	1-5	1-2,7,9	Annual Notification
6. Change in scale of the manufacturing process:			
a. at the fermentation stage	10-11	3,7-8, 10,12-13,15	Notifiable Change
b. at the purification stage	1,3,5,7	7-8, 10,12-13	Notifiable Change
7. Introduction of reprocessing steps	12	5, 9,11,13	Annual Notification

8. Change in the parameters of an approved holding step or addition of a new holding step	None	5-6	Notifiable Change

Conditions

1. No change in the principle of the sterilization procedures of the drug substance.
2. The change does not impact the viral clearance data or the chemical nature of an inactivating agent for a vaccine.
3. No change in the drug substance specifications outside of the approved ranges.
4. No change in the impurity profile of the drug substance outside of the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The change in scale is linear.
8. The new fermentation train is identical to the approved fermentation train(s), if applicable.
9. No change in the approved in vitro cell age.
10. No change in the proportionality of the raw materials (i.e., the change in scale is linear).
11. The change in scale involves the use of the same bioreactor (i.e., does not involve the use of a different size bioreactor or a change to the expansion chain).
12. The proposed reprocessing step is a refiltration step and involves only one refiltration.

Supporting Data

1. (S.2.2) Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
2. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance.
3. (S.2.3) If the change results in an increase in the number of population doublings, information on the characterization and testing of the post-production cell bank for recombinant product, or of the drug substance for non-recombinant product.
4. (S.2.3) For drug substances obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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). An EDQM TSE Certificate of Suitability, if available, is acceptable for raw materials, auxiliary materials, and reagents only.
5. (S.2.5) Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization, new reprocessing step, new or revised holding step).
6. (S.2.5) Demonstration that the revised or new holding step has no negative impact on the quality of the drug substance (data from one (1) commercial scale batch should be provided).
7. (S.2.6) Comparability of the approved and proposed product with respect to physico-chemical characterization, biological activity, and impurity profile.

8. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed drug substance (certificates of analysis to be provided in section 3.2.R.3).
9. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed drug substance (certificate of analysis to be provided in section 3.2.R.3).
10. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug substance, or longer if less than three (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.
11. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on one (1) commercial scale batch of the proposed drug substance, or longer if less than three (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.
12. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale drug product batches manufactured using the proposed drug substance (certificates of analysis to be provided in section 3.2.R.3).
13. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance into the stability program.
14. (A.2) Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk), or an EDQM TSE Certificate of Suitability, if available.
15. Rationale for regarding the bioreactors as similar/comparable, if applicable.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
9. Change in the auxiliary materials/reagents of biological origin (e.g., foetal calf serum, insulin), involving:			
a. Change in **supplier**	None	2,6,8-9	Notifiable Change
	1	2,6	Annual Notification
b. Change in **source**	None	2,7-9	Notifiable Change
	1	2,7	Annual Notification
10. Change in specification for the materials, involving:			
a. raw materials, starting materials	3,4,6-8	1,3-5	Annual Notification
b. solvents, reagents, catalysts	2-4	1,3-5	Annual Notification
11. Change in raw materials testing site	5	10	Annual Notification

Conditions

1. The change is for a compendial auxiliary materials/reagents of biological origin (excluding human plasma-derived materials).
2. The Grade of the materials is the same or is of higher quality.
3. No change in drug substance specifications outside of the approved ranges.
4. No change in the impurity profile of the drug substance outside of the approved limits.
5. No change in specifications of the raw material outside of the approved ranges.
6. The change has no significant effect on the overall quality of the drug substance and/or drug product and there are no changes to the cell banks.
7. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
8. The test does not concern a critical attribute (e.g. content, impurity, any critical physical characteristics or microbial purity).

Supporting Data

1. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance.
2. (S.2.3) For drug substances obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material

does not pose a potential BSE/TSE risk (e.g., 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). An EDQM TSE Certificate of Suitability, if available, is acceptable for raw materials, auxiliary materials, and reagents only.

3. (S.4.1) Updated, QC approved copy of the proposed drug substance specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval), if changed.
4. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
5. (S.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
6. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed drug substance (certificate of analysis to be provided in section 3.2.R.3).
7. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed drug substance (certificates of analysis to be provided in section 3.2.R.3).
8. (A.2) Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk), or an EDQM TSE Certificate of Suitability, if available.
9. Information demonstrating comparability of the auxiliary materials/reagents or starting materials of both sources.
10. Evidence that the new company/facility is GMP compliant.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
12. Changes to the cell banks, involving:			
a. generation of new Master Cell Bank (MCB) from the same expression construct with same or closely related cell line; or generation of a new MCB from a different expression construct with the same coding sequence and the same cell line; or adaptation of a MCB into a new fermentation medium	None	1-2,5,8-11	Supplement
b. generation of a new MCB for a recombinant product or a viral vaccine	1	1-2,5,8-10	Notifiable Change
c. generation of a new Working Cell Bank (WCB) for a bacterial or a viral vaccine	None	1-2	Notifiable Change
	2-4	1-2	Notifiable[6] Change
d. generation of a new Working Cell Bank (WCB) for a recombinant product (excluding vaccine)	2-4	1-2,7	Annual Notification
e. extension of shelf-life of the MCB or WCB	5	1-2	Annual Notification
13. Changes to the seed banks, involving:			
a. a new Master Seed Bank (MSB); or Working Seed Bank (WSB) extended beyond an approved passage level	None	5-6,8-10,12	Supplement
b. generation of a new WSB	2-3	5-6,8-10	Notifiable Change
	2-4	5-6	Notifiable[7] Change
14. Change in cell bank/seed bank manufacturing site	None	1-2,13	Notifiable Change
15. Change in cell bank/seed bank testing site	6	13	Annual Notification

16. Change in cell bank/seed bank qualification protocol	None	3-4	Notifiable Change
	7	4	Annual Notification

Conditions

1. The new MCB is generated from a pre-approved Master or Working Cell Bank.
2. The new cell/seed bank is generated from a pre-approved MCB/MSB.
3. The new cell/seed bank is at the pre-approved passage level.
4. The new cell/seed bank is released according to a pre-approved protocol.
5. The testing to support the extension of shelf-life is performed according to the pre-approved protocol.
6. No changes have been made to the tests/acceptance criteria used for the release of the cell/seed bank.
7. The protocol is considered more stringent (i.e., addition of new tests or tightening of acceptance criteria).

Supporting Data

1. (S.2.3) Qualification of the cell bank as per ICH Q5A and Q5D.
2. (S.2.3) Information on the characterization and testing of the post-production cell bank for recombinant product, or of the product for non-recombinant product.
3. (S.2.3) Justification of the change to cell bank/seed bank qualification protocol.
4. (S.2.3) Updated cell bank/seed bank qualification protocol
5. (S.3.1) Comparability of the approved and proposed product with respect to physico-chemical characterization, biological activity, and impurity profile. [N.B. Occasionally, the sponsor may undertake bridging non-clinical or clinical studies, (e.g. bioequivalence, to support the quality data)].
6. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for the new seed lot (certificate of analysis to be provided in section 3.2.R.3).
7. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least one (1) commercial scale batch or one (1) batch manufactured from an appropriate scale-down model of the drug substance derived from the new cell bank (certificates of analysis to be provided in section 3.2.R.3).
8. (S.4.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the drug substance derived from the new cell/seed bank (certificates of analysis to be provided in section 3.2.R.3).
9. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug substance, or longer if less than three (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.
10. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance into the long term stability program.
11. Supporting non-clinical and clinical data or a request for a waiver of in vivo studies.

12. Supporting clinical data.
13. Evidence that the new company/facility is GMP compliant.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
17. Change in product-contact equipment/material used in the drug substance manufacturing process, such as:			
a. equipment having different operating principles/properties from those originally approved	1-3	1-3	Annual Notification
b. introduction of new product-contact equipment used in a critical step (e.g., change in equipment model for a continuous centrifuge, water bath for viral inactivation)	1-3	1-3	Annual Notification
c. replacement of equipment with an equivalent equipment	None	3-4	Annual Notification
d. replacement of the membrane (filter) used during the UF/DF step	4	1,3	Annual Notification
e. product-contact equipment change from dedicated to shared	5-6	1,5	Annual Notification

Conditions

1. The change does not affect equipment used in the fermentation process.
2. The manufacturing process is not impacted by the change in product-contact equipment.
3. The change has no product impact.
4. The change is considered “like for like” (e.g., change in supplier of the same filter).
5. The site is approved as multi-product facility by Health Canada.
6. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.

Supporting Data

1. (S.2.4) Information on the in-process control testing.
2. (S.2.5) Process validation and/or evaluation studies, including equipment qualification, as appropriate. The proposed validation protocol is acceptable, but data could be requested.
3. (S.2.5) Information demonstrating re-qualification of the equipment/material (e.g., operational qualification, performance qualification).
4. (S.2.5) Demonstration that performance of the proposed equipment is equivalent to the approved equipment (i.e., data from one batch).
5. (A.1) Information describing the change-over procedures for the shared product-contact equipment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
18. Change in the controls (in-process tests and/or acceptance criteria) applied during the drug substance manufacturing process or on intermediates, such as[8]:			
a. deletion of an in-process test	4-6	3	Annual Notification
b. replacement or addition of an in-process test	1-4,7	1-2,4	Annual Notification
c. relaxation of an acceptance criterion	None	1,3-4	Notifiable Change
d. tightening of an acceptance criterion	None	1, 3-4	Notifiable Change
	2	1	Annual Notification
19. Change in in-process controls testing site	8	5	Annual Notification

Conditions

1. The change is not necessitated by recurring events 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 principle of the sterilization procedures of the drug substance.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The deleted test is not for a viral clearance/removal step.
7. The replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. No Level II changes are made to the approved in-process tests and/or acceptance criteria.

Supporting Data

1. (S.2.4) Description of the proposed process controls or acceptance criteria.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.4) Data to show that the relaxation has not a negative impact on the quality of the batch. Results for at least one (1) commercial scale batch are required.
4. Rationale for the change supported by data.
5. Evidence that the new company/facility is GMP compliant.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
20. Change in the approved design space, involving:			
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	1	1	Annual Notification
Conditions			
1. The reduction in design space is not necessitated by recurring problems having arisen during manufacture.			
Supporting Data			
1. (S.2.6) Manufacturing development data to support the establishment or changes to the design space (including changes to process parametric release for sterile products).			

3.2.S.3 Characterisation

There are not any 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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
21. Changes affecting the quality control (QC) testing of the drug substance (release and stability), involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company, to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable Change
	1	1-2	Annual Notification
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	2	1-2	Annual Notification
Conditions			
1. The transfer involves the relocation of the equipment and laboratory staff to the new laboratory or building. 2. The transferred QC test is not a potency assay or a bioassay.			
Supporting Data			
1. (S.2.5) Information demonstrating technology transfer qualification for the non-pharmacopoeial assays or verification for the pharmacopoeial assays. 2. Evidence that the new company/building is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
22. Change in the standard/monograph (i.e., specifications) claimed for the drug substance, involving:			
a. a change from a Schedule B pharmacopoeial standard/monograph to a House standard	None	1-5	Notifiable Change
b. a change from a House/Professed standard to a Schedule B pharmacopoeial standard/ monograph or from one Schedule B standard/ monograph to a different Schedule B standard/monograph	1-4	1-3	Annual Notification
23. Change in the specifications for the drug substance to comply with an updated Schedule B pharmacopoeial standard/monograph	1-2	1-3	Annual Notification
Conditions			
1. The change is made exclusively to comply with a Schedule B pharmacopoeial monograph. 2. No change in drug substance specifications outside of the approved ranges. 3. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph. 4. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.			
Supporting Data			
1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels. 2. (S.4.1) Updated, QC approved copy of the proposed drug substance specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval). 3. (S.4.3) Where a House/Professed analytical procedure is used and a Schedule B standard/monograph is claimed, results of an equivalency study between the House/Professed and compendial methods. 4. (S.4.3) Copies or summaries of validation reports, if new analytical procedures are used. 5. (S.4.5) Justification of specifications with data.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
24. Changes in the control strategy of the drug substance, involving:			
a. Change from end-product testing to upstream controls for some test(s) (e.g., Real-Time Release Testing, Process Analytical Technology)	None	1-5	Supplement
b. Addition of a new Critical Quality Attribute (CQA) in the control strategy	None	1-5	Notifiable Change
c. Deletion of a Critical Quality Attribute (CQA) from the control strategy	None	1,5	Notifiable Change
Conditions			
None			
Supporting Data			
1. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance. 2. (S.4.1) Updated, QC approved copy of the proposed drug substance specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval), if changed. 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. Justification and supporting data for each proposed change to the control strategy.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
25. Change in the drug substance release or shelf-life specifications, involving:			
a. deletion of a test	None	1,6	Notifiable Change
	11	1,6	Annual Notification
b. addition of a test	1-2	1-3,6	Annual Notification
c. replacement of an analytical procedure	10	1-3,5-6	Annual Notification
d. minor changes to an approved analytical procedure	3-7	1,5-6	Annual Notification
e. a change from a House/Professed analytical procedure to a Schedule B analytical procedure or change from an approved compendial analytical procedure to an harmonized compendial procedure	3,7	1-3	Annual Notification
f. relaxation of an acceptance criterion	None	1,6	Notifiable Change
g. tightening of an acceptance criterion	8-9	1	Annual Notification

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same and is based on the same analytical technique or principle (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
6. The modified analytical procedure maintains or improves performance parameters of the method.
7. The change does not concern potency testing.
8. The change is within the range of approved acceptance criteria.
9. Acceptance criterion for any Class 3 residual solvent is within the ICH limits.
10. The change is from a pharmacopoeial assay to another pharmacopoeial assay.
11. The deleted test is the Abnormal Toxicity Test/General Safety Test.

Supporting Data

1. (S.4.1) Updated, QC approved copy of the proposed drug substance specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (S.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (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/Professed and compendial methods.
5. (S.4.3) Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
6. (S.4.5) Justification of the proposed drug substance specifications (e.g., tests, acceptance criteria, or analytical procedures).

3.2.S.5 Reference standards or materials used in the release of the drug substance

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
26. Change the reference standards from pharmacopoeial to House	None	1-2	Notifiable Change
27. Change the reference standards from House/Professed to pharmacopoeial	1-2	1-2	Annual Notification
28. Qualification of a new lot of reference standard against the approved reference standard (except for a bacterial or viral vaccine, bacterial toxin or blood product)	1	2	Annual Notification
29. Qualification of a new lot of reference standard against the approved reference standard for a bacterial or viral vaccine, bacterial toxin or blood product, involving:			
a. a reference standard used in a qualitative test	1	2	Annual Notification
b. a reference standard used in a physicochemical test	1,3-4	2	Annual Notification
c. a reference standard used in a semi-quantitative or quantitative biological assay.	1,3-4	2	Annual Notification
30. Change to reference standard qualification protocol (except for a bacterial or viral vaccine, bacterial toxin or blood product)	None	3-4	Notifiable Change
	5	4	Annual Notification
31. Change to reference standard qualification protocol for a bacterial or viral vaccine, bacterial toxin or blood product, involving:			
a. a reference standard used in a qualitative test	None	3-4	Annual Notification
b. a reference standard used in a physicochemical test	5	3-4	Annual Notification
c. a reference standard used in a semi-quantitative or quantitative biological assay.	3-5	3-4	Annual Notification
32. Extension of the reference standard shelf-life or retest period	2,6	5	Annual Notification

Conditions
1. Qualification of the reference standard is performed according to the Health Canada approved protocol (i.e., no deviation from the approved protocol). 2. The reference standard is not for a key quality control or in process control assay for a bacterial or a viral vaccine, for bacterial toxins or for a product in lot release group 2. 3. The reference standard is not used to calculate the potency of the drug substance or intermediate. 4. The reference standard is not used to generate the calibration curve in test for a critical quality attribute or critical process parameter. 5. The protocol is considered more stringent (i.e., addition of new tests or tightening of acceptance criteria). If deletion of tests is proposed, the tests proposed to be deleted were not implemented to monitor the quality of the reference standard (e.g., was implemented for research or validation work). 6. The extension of the shelf-life or re-test period is made in accordance with the Health Canada approved protocol.
Supporting Data
1. (1.3) Revised Product monograph to reflect the change in reference standard. 2. (S.5) Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis). 3. (S.5) Justification of the change to reference standard qualification protocol. 4. (S.5) Updated reference standard qualification protocol. 5. (S.7.1) Summary of stability testing and results to support the extension of reference standard shelf-life.

3.2.S.6 Container closure system

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
33. Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1-2,4	Notifiable Change
	1-2	1,3	Annual Notification

Conditions

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (including results of transportation or compatibility studies, if appropriate).
2. The change does not concern a sterile drug substance.

Supporting Data

1. (S.6) Information on the proposed container closure system (e.g., description, specifications).
2. (S.6) Demonstration of compatibility with the drug substance.
3. (S.6) Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (e.g., results of transportation or interaction studies, extractable/leachable studies).
4. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug substance, or longer if less than three (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. Results from one (1) batch may be sufficient based on rationale.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
34. Change in the supplier for a primary container closure, involving:			
a. replacement or addition of a supplier	None	1-3	Notifiable Change
	1-2	None	Annual Notification
b. deletion of a supplier	None	None	Annual Notification
Conditions			
1. No change in the type of container closure, materials of construction or in the sterilization process for a sterile container closure component. 2. No change in the specifications of the container closure component outside of the approved ranges.			
Supporting Data			
1. (S.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing). 2. (S.6) Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications). 3. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug substance, or longer if less than three (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.			

3.2.S.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
35. Change in the shelf-life for the drug substance or for a stored intermediate of the drug substance, involving:			
a. extension	None	1-4,6	Notifiable Change
	1-5	1-2,5	Annual Notification
b. reduction	None	1-5	Notifiable Change
	6	2-4	Annual Notification

Conditions

1. No changes to the container closure system in direct contact with the drug substance with the potential of impact on the drug substance; or to the recommended storage conditions of the drug substance.
2. The approved shelf-life is at least 24 months.
3. Full long term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three (3) commercial scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.
6. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns (i.e., problems arising during manufacturing or stability concerns should be reported for evaluation).

Supporting Data

1. (S.7.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. (S.7.1) Proposed storage conditions and shelf-life, as appropriate.
3. (S.7.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
4. (S.7.2) Justification of the change to the post-approval stability protocol or stability commitment.
5. (S.7.3) Results of stability testing on both upright and inverted samples, except for lyophilized products (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance.
6. (S.7.3) Interim stability testing results and a commitment to notify Health Canada of any failures in the ongoing long term stability studies. Extrapolation of shelf-life should be made in accordance with ICH Q1E guideline. For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance (i.e., batch analysis on three (3) commercial scale batches).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
36. Change in the post-approval stability protocol of the drug substance, involving:			
a. major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature	None	3-6	Notifiable Change
	1	1-2,4-5	Annual Notification
b. addition of time point(s) into the post-approval stability protocol	None	4-5	Annual Notification
c. addition of test(s) into the post-approval stability protocol	2	4-5	Annual Notification
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4-5	Annual Notification
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4-5	Annual Notification
Conditions			
1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 2. The addition of test(s) is not due to stability concerns or to the identification of new impurities. 3. Deletion of time point(s) is made according to ICH Q5C.			
Supporting Data			
1. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used. 2. (S.4.3) Copies or summaries of validation reports, if new analytical procedures are used. 3. (S.7.1) Proposed storage conditions and or shelf-life, as appropriate. 4. (S.7.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment. 5. (S.7.2) Justification of the change to the post-approval stability protocol or stability commitment. 6. (S.7.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
37. Change in the labelled storage conditions for the drug substance, involving:			
a. addition or change of storage condition for the drug substance (e.g., relaxation or tightening of a temperature criterion)	None	1-5	Notifiable Change
	1-2	1-4	Annual Notification
b. addition of a cautionary statement	None	1-2,4-5	Notifiable Change
	1	1-2,4-5	Annual Notification
c. deletion of a cautionary statement	None	1-2,4,6	Annual Notification
Conditions			
1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 2. The change consists in the tightening of a temperature criterion within the approved ranges.			
Supporting Data			
1. (1.3) Revised Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels, as applicable. 2. (S.7.1) Proposed storage conditions and shelf-life. 3. (S.7.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment. 4. (S.7.2) Justification of the change in the labelled storage conditions/cautionary statement. 5. (S.7.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on one (1) commercial scale batch). 6. (S.7.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).			

3.2.P Drug product

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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
38. Change in the description or composition of the drug product, involving:			
a. addition of a dosage form or change in the formulation (e.g., lyophilized powder to liquid, change in the amount of excipient, new diluent for lyophilized product)	None	1-11	Supplement
b. change in fill volume (same concentration, different volume)	None	2-4,6,8-11	Supplement
c. change in the concentration of the active ingredient (e.g., 20 units/mL vs 10 units/mL)	None	2-4,6,8,10,12	Supplement
d. addition of a new presentation (e.g., addition of syringes to vials)	None	2-3,6,8-10,12	Supplement
Conditions			
None			
Supporting Data			
1. (1.2.6) Letters of Access [e.g., Drug Master Files (DMFs)], if new excipients are included. 2. (1.3) Product Monograph [e.g., Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels. 3. (S) Confirmation that information on the drug substance has not changed as a result of the submission [e.g., cross reference(s) should be provided to the previously approved drug submission, quoting the date approved and Control Number(s)] or revised information on the drug substance, if any of the attributes have changed. 4. (P.1) Description and composition of the dosage form. 5. (P.2) Discussion of the components of the drug product, as appropriate [e.g., choice of excipients, compatibility of drug substance and excipients, the leachates, compatibility with new container closure system (as appropriate)]. 6. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies. 7. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations). 8. (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 analysis for three (3) consecutive commercial scale batches to be provided in section 3.2.R.3). For multiple strength products, container sizes and/or fill volumes, three (3) commercial scale batches at each end are expected. However, other strategies may be acceptable if scientifically justified (refer to ICH Q1D).			

9. (P.7) Information on the container closure system, if any of the components have changed (e.g. description, materials of construction, summary of specifications).
10. (P.8.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug product, or longer if less than three (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 (consult with Health Canada for changes b and c). Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
11. Supporting clinical data or a request for a waiver of in vivo studies based on scientific evidences.
12. Supporting clinical data (usually comparative PK/PD) or a request for a waiver of in vivo studies based on scientific evidences.

3.2.P.1 Description and composition of the drug product: Change to an adjuvant

Change in type/structure of a chemical adjuvant or in the type of a biological adjuvant may necessitate the filing of a NDS. Sponsors are encouraged to contact Health Canada for further guidance.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
39. Change involving a chemical/synthetic adjuvant:			
a. change in supplier of a chemical/synthetic adjuvant	None	4-6,10	Notifiable Change
	1-2	5	Annual Notification
b. change in manufacture of a chemical/synthetic adjuvant	None	4-6,10	Notifiable Change
	1-2	5	Annual Notification
c. change in release specifications of a chemical/synthetic adjuvant (including the tests and/or the analytical procedures)	None	6-7,10	Notifiable Change
	1,3	7-9	Annual Notification
40. Change involving a biological adjuvant:[9]			
a. change in supplier of a biological adjuvant	None	1-7,10-11	Supplement
b. change in manufacture of a biological adjuvant	None	1-7,10	Supplement
	4	1-5,7	Notifiable Change
c. change in release specifications of a biological adjuvant (including the tests and/or the analytical procedures)	None	6-10	Notifiable Change
	1,3	7-9	Annual Notification
Conditions			
1. No change in the release specifications of the adjuvant outside of the approved ranges. 2. The adjuvant is an aluminium salt. 3. The change in specifications consists in the addition of a new test or in a minor change to an analytical procedure. 4. No change in the supplier of the adjuvant.			

Supporting Data

1. (S.2.3) Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk).
2. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.
4. (S.2.5) Process validation and/or evaluation studies (e.g., for manufacturing of the adjuvant).
5. (S.3.1) Description of the general properties, characteristic features and characterization data of the adjuvant, as appropriate.
6. (S.7.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed adjuvant, or longer if less than three (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.
7. (P.5.1) Updated, QC approved copy of the proposed specifications for the adjuvant (or where applicable, the final version of the specifications to be signed by QC after HC approval).
8. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
9. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
10. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the drug product with the approved and proposed adjuvant, as applicable. Certificates of analysis to be provided in section 3.2.R.3.
11. Supporting non-clinical and clinical data, if applicable.

3.2.P.1 Description and Composition of the Drug Product: Change to a diluent [10]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
41. Change to diluent, involving:			
a. replacement of or addition to the source of a diluent	None	1-8	Notifiable Change
	1-3	1-4	Annual Notification
b. change in facility used to manufacture a diluent (same company)	1-2	3-4,6-8	Annual Notification
c. addition of a diluent filling line	1-2,4	1-4,6	Annual Notification
d. addition of a diluent into a Health Canada approved filling line	1-2	1-4,6	Annual Notification
e. deletion of a diluent	None	None	Annual Notification

Conditions

1. The diluent is water for injection (WFI) or a salt solution [i.e., does not include an ingredient with a functional activity, (e.g., a preservative)].
2. After reconstitution, there is no change in the drug product specifications outside of the approved ranges.
3. The proposed diluent is commercially available in Canada.
4. The addition of the diluent filling line is in a Health Canada approved filling facility.

Supporting Data

1. (P.3.3) Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
2. (P.5.1) Updated, QC approved copy of the proposed specifications for the diluent (or where applicable, the final version of the specifications to be signed by QC after HC approval).
3. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed diluent (certificates of analysis to be provided in section 3.2.R.3, as applicable).
4. (P.8.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed diluent, or longer if less than three (3) time points are available (including the zero time point).
5. (P.8.3) Updated stability data on the product reconstituted with the new diluent.
6. (A.1) Cleaning procedures (including data in a summary validation report) demonstrating lack of carry-over or cross-contamination.

7. (A.1) Information on the proposed production facility involved in manufacturing the diluent, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems).
8. (1.2.5) GMP and EL information.

3.2.P.2 Pharmaceutical development

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
42. Change in the approved design space, involving:			
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	1	1	Annual Notification
Conditions			
1. The reduction in design space is not necessitated by recurring problems having arisen during manufacture.			
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).			

3.2.P.3 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
43. Change involving a drug product manufacturer/manufacturing facility, such as:			
a. replacement or addition of a manufacturing facility for the drug product (includes primary packaging facility)	None	1-6,8-9,11-14	Supplement
	1-5	1-4,6,8-9,11-14	Notifiable Change
b. replacement or addition of a formulation/ filling suite to an approved formulation/ filling facility	None	3,5-6,8-9,11-14	Supplement
	1,8	3-4,6,8,10,12, 14-15	Notifiable Change
c. replacement or addition of a secondary packaging facility; a labelling/storage facility; or a distribution facility	2-3	1-2,4	Annual Notification
d. modification to a manufacturing area or modification to an existing service/system (e.g., change to WFI systems or HVAC systems, moving a wall)	6-7	7,12,14	Annual Notification
e. qualification of a new room or change in classification of an existing room	6-7	7,12,14	Annual Notification
f. deletion of a drug product manufacturing facility	None	None	Annual Notification

Conditions

1. The proposed facility is a Health Canada approved formulation/filling facility for the same sponsor (the control # of the prior approved application should be provided).
2. No change in the composition, manufacturing process and drug product specifications.
3. No change in the container/closure system.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the one of those already approved at the site and uses the same filling process/equipment.
6. The change has no impact on the risk of contamination or cross-contamination.
7. The modification has no product impact.
8. The new formulation/filling suite is equivalent to the approved formulation/filling suite.

Supporting Data

1. (1.2.5) GMP and EL information.
2. (P) Updated or new DMF (with a Letter of Access provided in Module 1) or relevant drug product information.

3. (P) Confirmation that information on the drug product has not changed as a result of the submission (e.g., other than change in facility) or revised information on the drug product, if any of the attributes have changed.
4. (P.3.1) Name, address, and responsibility of the proposed production facility involved in manufacturing and testing.
5. (P.3.3) Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed drug product.
6. (P.3.5) Process validation and/or evaluation studies (e.g., equipment qualification, media fills, as appropriate). The proposed validation protocol is acceptable, but data could be requested.
7. (P.3.5) Information demonstrating re-qualification of the equipment or re-qualification of the change (e.g., operational qualification, performance qualification), as appropriate.
8. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed drug product (certificates of analysis to be provided in section 3.2.R.3). For multiple strength products, container sizes and/or fill volumes, three (3) commercial scale batches at each end are expected. However, other strategies may be acceptable if scientifically justified (refer to ICH Q1D).
9. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
10. (P.8.2) Commitment to place the first commercial scale batch of the drug product manufactured using the proposed formulation/filling suite into the stability program, and to notify Health Canada of any failures in the ongoing long term stability studies.
11. (P.8.3) Stability test results from:

    a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and

    b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the drug product manufactured using the proposed manufacturing facility, or longer if less than three (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 ICH Q1D).
12. (A.1) Information on the proposed production facility involved in the manufacture of the drug product, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate.
13. (A.1) Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as applicable. If no revisions, a signed attestation that no changes were made to the change-over procedures.
14. (A.1) Results of the environmental monitoring studies in classified areas.
15. Rationale for considering the proposed formulation/filling suite as equivalent.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
44. Effect on the existing drug products in a drug product manufacturing facility involving introduction of a new product or change in concurrence:			
a. conversion of a drug product manufacturing facility from single-product to multi-product	None	1-3	Notifiable Change
b. conversion of formulation and filling area(s) from campaign to concurrent for multiple product manufacturing areas	1	1-2	Notifiable Change
c. introduction of new product into an approved multi-product formulation/filling suite	2-4	1-3	Annual Notification
Conditions			
1. The manufacturing process is a closed process for shared areas. 2. The newly introduced product does not introduce significantly different risk issues (i.e., cytotoxic drugs to cytokine manufacturing area). 3. The newly introduced product is not of significantly different strength (i.e., mg vs µg). 4. The maximum allowable carry-over is not affected by the introduction of the new product.			
Supporting Data			
1. (A.1) Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products) demonstrating lack of carry-over or cross-contamination. 2. (A.1) Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as appropriate. If no revisions, a signed attestation that no changes were made to the change-over procedures. 3. (A.1) Information on the product(s) which share the same equipment (e.g., therapeutic classification).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
45. Change in the drug product manufacturing process, such as:			
a. scale-up of the manufacturing process at the formulation/filling stage	1-4	1,3,5-6,8,12	Notifiable Change
b. addition or replacement of equipment (e.g., formulation tank, filter housing, filling line and head, and lyophilizer) within the existing filling areas	None	1-4,7,10	Notifiable Change
	5	3-4	Annual Notification
c. addition or replacement of equipment (e.g., lyophilizer) in a new area (e.g., adjacent room)	None	1-4,7,9-10	Notifiable Change
d. product-contact equipment change from dedicated to shared (e.g., formulation tank, filter housing, filling line and head, lyophilizer)	6-7	2,11	Annual Notification
e. addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	1-4	1-3,5,7,12	Annual Notification
f. change in process flow or procedures	None	1-3,5-6,8	Notifiable Change

Conditions

1. The proposed scale uses similar/comparable equipment to that approved (N.B. change in equipment size is not considered as using similar/comparable equipment).
2. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized).
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the drug product.
5. For product-contact equipment, the change is considered 'like for like' (i.e., in term of product-contact material/equipment size).
6. The site is approved as multi-product facility by Health Canada.
7. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.

Supporting Data

1. (P.3.3) Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed drug product.
2. (P.3.4) Information on the in-process control testing, as applicable.

3. (P.3.5) Process validation and/or evaluation studies (e.g., equipment qualification, media fills, as appropriate). The proposed validation protocol is acceptable, but data could be requested.
4. (P.3.5) Information demonstrating qualification of the equipment (operational qualification, performance qualification), or qualification of the change, as applicable.
5. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed drug product (certificates of analysis to be provided in section 3.2.R.3). For multiple strength products, container sizes and/or fill volumes, three (3) commercial scale batches at each end are expected. However, other strategies may be acceptable if scientifically justified (refer to ICH Q1D).
6. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
7. (P.8.2) Commitment to place the first commercial scale batch of the drug product manufactured using the proposed formulation/filling suite into the stability program, and to notify Health Canada of any failures in the ongoing stability studies.
8. (P.8.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug product, or longer if less than three (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 ICH Q1D).
9. (A.1) Information on the updated facility, including updated flow diagrams and identification of the products using the new equipment/area.
10. (A.1) Cleaning procedures (including data in a summary validation report) demonstrating lack of carry-over or cross-contamination.
11. (A.1) Information describing the change-over procedures for the shared product-contact equipment.
12. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
46. Change in the controls (in-process tests and/or acceptance criteria) applied during the drug product manufacturing process or on intermediates, such as[11]:			
a. deletion of an in-process test	4-6	3	Annual Notification
b. replacement or addition of an in-process test	1-4,7	1-2,4	Annual Notification
c. relaxation of an acceptance criterion	None	1,3-4	Notifiable Change
d. tightening of an acceptance criterion	None	1,3-4	Notifiable Change
	2	1	Annual Notification
47. Change in in-process controls testing site	8	5	Annual Notification

Conditions

1. The change is not necessitated by recurring events 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 principle of the sterilization procedures of the drug product.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The deleted test is not for a viral clearance/removal step.
7. The replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. No Level II changes are made to the approved in-process tests and/or acceptance criteria.

Supporting Data

1. (P.3.3) Description of the proposed process controls or acceptance criteria.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.4) Data to show that the relaxation has not a negative impact on the quality of the batch. Results for at least one (1) commercial scale batch are required.
4. Rationale for the change supported by data.
5. Evidence that the new company/facility is GMP compliant.

3.2.P.4 Control of excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
48. Change in the standard/monograph (i.e., specifications) claimed for the excipient	None	1-4	Notifiable Change
	1-5	1-4	Annual Notification
49. Change in the specification for the excipient to comply with an updated Schedule B pharmacopoeial standard/monograph	2-3	1-2,4	Annual Notification

Conditions

1. The change is from a House/Professed standard to a Schedule B pharmacopoeial standard/monograph.
2. The change is made exclusively to comply with a Schedule B pharmacopoeial standard/monograph.
3. No change to the specifications for the functional properties of the excipient outside of the approved ranges nor that results in a potential impact on the performance of the drug product.
4. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
5. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting Data

1. (P.4.1) Updated excipient specifications.
2. (P.4.3) Where a House analytical procedure is used and a Schedule B standard/monograph is claimed, results of an equivalency study between the House and compendial methods.
3. (P.4.4) Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).
4. Declaration that consistency of quality and of the production process of the excipient is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
50. Change in the specifications used to release the excipient, involving:			
a. deletion of a test	5	1,3-4	Annual Notification
b. addition of a test	4	1-4	Annual Notification
c. replacement of an analytical procedure	1-3	1-2	Annual Notification
d. minor changes to an approved analytical procedure	None	1-2	Annual Notification
e. a change from a House/Professed analytical procedure to a Schedule B analytical procedure	None	1-2	Annual Notification
f. to reflect a pharmacopoeial monograph update	None	1	Annual Notification
g. relaxation of an acceptance criterion	4,6	1,3-4	Annual Notification
h. tightening of an acceptance criterion	3-4	1	Annual Notification

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the excipient.
4. Acceptance criterion for any Class 3 residual solvent is within the ICH limits.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
6. The change to the specifications does not affect the functional properties of the excipient nor result in a potential impact on the performance of the drug product.

Supporting Data

1. (P.4.1) Updated excipient specifications.
2. (P.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. (P.4.4) Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product). 4. Declaration that consistency of quality and of the production process of the excipient is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
51. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk	None	2-8	Supplement
52. Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	2	1,3,5-7	Notifiable Change
53. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source (e.g., different country of origin, different animal species)	2,6-7	2-6,8	Annual Notification
54. Change in manufacture of a biological excipient	None	3-8	Supplement
	2	3,5-8	Notifiable Change
	1-2	3,5	Annual Notification
55. Change in supplier for a human plasma-derived excipient (e.g., human serum albumin)	None	4-9	Supplement
	3-4	5-7,10	Notifiable Change
56. Change in supplier of an excipient of non-biological origin or of biological origin (excluding human plasma-derived excipient)	None	3,5-8	Notifiable Change
	1,5	3	Annual Notification
57. Change in excipient testing site	1	11	Annual Notification

Conditions

1. No change in the specifications of the excipient or drug product outside of the approved ranges.
2. The change does not concern a human plasma-derived excipient.
3. The excipient from the new supplier is a Health Canada approved excipient.
4. No chemistry and manufacturing changes were made by the supplier of the new excipient since its last approval in Canada.
5. The excipient does not influence the structure/conformation of the active ingredient (e.g., Protamine involved in the crystallization of the insulin).
6. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material.
7. The new excipient does not require the assessment of viral safety data.

Supporting Data
1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin. 2. Details of the source or the excipient (e.g., animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure. 3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient. 4. (P.3.3) Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient. 5. (P.4.5) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient (certificates of analysis to be provided in section 3.2.R.3). 6. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) batches of the drug product with the proposed excipient (certificates of analysis to be provided in section 3.2.R.3). 7. (P.8.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) batches of the drug product with the proposed excipient, or longer if less than three (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. 8. (A.2) Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk). 9. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient. 10. Letter from the supplier certifying that no changes were made to the excipient since its last approval in Canada (DIN provided). 11. Evidence that the new company/facility is GMP compliant.

3.2.P.5 Control of drug product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
58. Changes affecting the quality control (QC) testing of the drug product (release and stability), involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company, to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable Change
	1	1-2	Annual Notification
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	2	1-2	Annual Notification
Conditions			
1. The transfer involves the relocation of the equipment and laboratory staff to the new laboratory or building. 2. The transferred QC test is not a potency assay or a bioassay.			
Supporting Data			
1. (P.3.5) Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay. 2. Evidence that the new company/building is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
59. Change in the standard/monograph (i.e., specifications) claimed for the drug product, involving:			
a. a change from a Schedule B pharmacopoeial standard/monograph to a House standard	None	1-5	Notifiable Change
b. a change from a House/Professed standard to Schedule B pharmacopoeial standard/ monograph or from one Schedule B standard/ monograph to a different Schedule B standard/monograph	1-4	1-3	Annual Notification
60. Change in the specifications for the drug product to comply with an updated Schedule B pharmacopoeial standard/monograph	1-2	1-3	Annual Notification

Conditions

1. The change is made exclusively to comply with a Schedule B pharmacopoeial standard/monograph.
2. The change to the specifications does not result in a potential impact on the performance of the drug product (i.e., the new standard is not less stringent than the approved standard/specifications).
3. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
4. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting Data

1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels.
2. (P.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.5.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
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. Justification of specifications with data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
61. Changes in the control strategy of the drug product, involving:			
a. Change from end-product testing to upstream controls for some test(s) (e.g., Real-Time Release Testing, Process Analytical Technology)	None	1-5	Supplement
b. Addition of a new Critical Quality Attribute (CQA) in the control strategy	None	1-5	Notifiable Change
c. Deletion of a Critical Quality Attribute (CQA) from the control strategy	None	1,5	Notifiable Change
Conditions			
None			
Supporting Data			
1. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed product. 2. (S.4.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval), if changed. 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. Justification and supporting data for each proposed change to the control strategy.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
62. Change in the drug product release or shelf-life specifications, involving:			
a. for sterile products, replacing the sterility test with process parametric release	None	1-2,6,8-9	Supplement
b. deletion of a test	None	2,8-9	Notifiable Change
	10	2, 8	Annual Notification
c. addition of a test	1-2	2-4,8	Annual Notification
d. change in animal species/strains for a test (e.g., new species/ strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)	None	5,10	Notifiable Change
e. replacement of an analytical procedure	9	2-4,7	Annual Notification
f. minor changes to an approved analytical procedure	3-6	3-4,7	Annual Notification
g. change from a House/Professed analytical procedure to a Schedule B analytical procedure or change from an approved compendial analytical procedure to an harmonized compendial procedure	3,6	2-4	Annual Notification
h. relaxation of an acceptance criterion	None	2,8-9	Notifiable Change
i. tightening of an acceptance criterion	7-8	2	Annual Notification

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or improves performance parameters of the method.
6. The change does not concern potency testing.

7. The change is within the range of approved acceptance criteria. 8. Acceptance criterion for any Class 3 residual solvent is within the ICH limits. 9. The change is from a pharmacopoeial assay to another pharmacopoeial assay. 10. The deleted test is the Abnormal Toxicity Test/General Safety Test.
Supporting Data
1. (P.3.5) Process validation and/or evaluation studies or validation protocol of the proposed drug product. 2. (P.5.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval). 3. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used. 4. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used. 5. (P.5.3) Data demonstrating that the change in animals gives comparable results with those obtained using the approved animals. 6. (P.5.4) Description of the batches and summary of results as quantitative data, of a sufficient number of batches to support the process parametric release (certificates of analysis to be provided in section 3.2.R.3). 7. (P.5.6) Justification for the change to the analytical procedure (e.g., demonstration of the suitability of the analytical procedure to monitor the drug product, including the degradation products). 8. (P.5.6) Justification of the proposed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products). 9. Declaration/evidences that consistency of quality and of the production process is maintained. 10. Copies of relevant certificate of fitness for use (e.g., veterinary certificate).

3.2.P.6 Reference standards or materials used in the release of the drug product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
63. Change the reference standards from pharmacopoeial to House	None	1-2	Notifiable Change
64. Change the reference standards from House/Professed to pharmacopoeial	1-2	1-2	Annual Notification
65. Qualification of a new lot of reference standard against the approved reference standard (except for a bacterial or viral vaccine, bacterial toxin or blood product)	1	2	Annual Notification
66. Qualification of a new lot of reference standard against the approved reference standard for a bacterial or viral vaccine, bacterial toxin or blood product, involving:			
a. a reference standard used in a qualitative test	1	2	Annual Notification
b. a reference standard used in a physicochemical test	1,3-4	2	Annual Notification
c. a reference standard used in a semi-quantitative or quantitative biological assay.	1,3-4	2	Annual Notification
67. Change to reference standard qualification protocol (except for a bacterial or viral vaccine, bacterial toxin or blood product)	None	3-4	Notifiable Change
	5	4	Annual Notification
68. Change to reference standard qualification protocol for a bacterial or viral vaccine, bacterial toxin or blood product, involving:			
a. a reference standard used in a qualitative test	None	3-4	Annual Notification
b. a reference standard used in a physicochemical test	5	3-4	Annual Notification
c. a reference standard used in a semi-quantitative or quantitative biological assay.	3-5	3-4	Annual Notification
69. Extension of the reference standard shelf-life or re-test period	2,6	5	Annual Notification
Conditions			
1. Qualification of the reference standard is performed according to the Health Canada approved protocol (i.e., no deviation from the approved protocol).			

2. The reference standard is not for a key quality control or in process control assay for a bacterial or a viral vaccine, for bacterial toxins or for a product in lot release group 2. 3. The reference standard is not used to calculate the potency of the drug substance or intermediate. 4. The reference standard is not used to generate the calibration curve in test for a critical quality attribute or critical process parameter. 5. The protocol is considered more stringent (i.e., addition of new tests or tightening of acceptance criteria). If deletion of tests is proposed, the tests proposed to be deleted were not implemented to monitor the quality of the reference standard (e.g., was implemented for research or validation work). 6. The extension of the shelf-life or re-test period is made in accordance with the Health Canada approved protocol.
Supporting Data
1. (1.3) Revised Product monograph to reflect the change in reference standard. 2. (P.6) Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis). 3. (P.6) Justification of the change to reference standard qualification protocol. 4. (P.6) Updated reference standard qualification protocol. 5. (P.8.1) Summary of stability testing and results to support the extension of reference standard shelf-life.

3.2.P.7 Container closure system

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
70. Modification of a primary container closure system (e.g., new coating, adhesive, stopper, type of glass) Note: The addition of a new container closure system (e.g., addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation (see **change 38.d**).	None	1-7	Notifiable Change
	1-3	1,3	Annual Notification
71. Addition of a secondary container closure system	None	1-3,7	Supplement
	4	1,3	Annual Notification
72. Change from a reusable container to a disposable container with no changes in product-contact material (e.g., change from reusable pen to disposable pen)	None	1,3,7	Notifiable Change
73. Change from approved single-dose container to multi-dose container	None	1-7	Notifiable Change
74. Deletion of a container closure system	None	1	Annual Notification

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change is made only to improve quality of the container and does not modify the product-contact material (e.g., increase thickness of the glass vial without changing interior dimension).
4. The new container closure system is not a functional container closure system (e.g., pre-filled auto injector).

Supporting Data

1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels, as appropriate.
2. (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.
3. (P.7) Information on the proposed container closure system, as appropriate (e.g., description, materials of construction of primary/secondary packaging components, performance specifications).
4. (P.7) Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.
5. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
6. (P.8.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product;

and b) three (3) months of real time/real temperature testing on three (3) drug product batches stored in the proposed container, or longer if less than three (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 ICH Q1D).

7. (A.1) Information demonstrating suitability of the proposed container/closure system with respect to its relevant properties (e.g., results from last media fills, results of transportation and/or interaction studies demonstrating preservation of protein integrity and maintenance of the sterility for sterile products, maintenance of the sterility in multi-dose container).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
75. Change in the supplier for a primary container closure component, involving:			
a. replacement or addition of a supplier	None	1-3	Notifiable Change
	1-2	None	Annual Notification
b. deletion of a supplier	None	None	Annual Notification

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or in the sterilization process for a sterile container closure component.
2. No change in the specifications of the container closure component outside of the approved ranges.

Supporting Data

1. (P.2) Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing).
2. (P.7) Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications).
3. (P.8.3) Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on one (1) drug product batch stored in the proposed container, or longer if less than three (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 ICH Q1D).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
76. Change in the specifications used to release a primary or functional secondary container closure component, involving:			
a. deletion of a test	1-2	1-2	Annual Notification
b. addition of a test	3	1-2	Annual Notification
c. replacement of an analytical procedure	6-7	1-3	Annual Notification
d. minor changes to an analytical procedure	4-7	1-3	Annual Notification
e. relaxation of an acceptance criterion	None	1-2	Notifiable Change
f. tightening of an acceptance criterion	8	1	Annual Notification

Conditions

1. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specifications does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the drug product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. No change in the acceptance criteria outside of the approved ranges.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the container closure component.

Supporting Data

1. (P.7) Updated, QC approved copy of the proposed specifications for the primary or functional secondary container closure component (or where applicable, the final version of the specifications to be signed by QC after HC approval).
2. (P.7) Rationale for the change in specifications for a primary container closure component.
3. (P.7) Description of the analytical procedure and, if applicable, validation data.

3.2.P.8 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
77. Change in the shelf-life for the drug product, involving:			
a. extension	None	1-4,6	Notifiable Change
	1-5	1-2,5	Annual Notification
b. reduction	None	1-5	Notifiable Change
	6	2-4	Annual Notification

Conditions

1. No changes to the container closure system in direct contact with the drug product with the potential of impact on the drug product; or to the recommended storage conditions of the drug product.
2. The approved shelf-life is at least 24 months.
3. Full long term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three (3) commercial scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.
6. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns (i.e., problems arising during manufacturing or stability concerns should be reported for evaluation).

Supporting Data

1. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. (P.8.1) Proposed storage conditions and shelf-life, as appropriate.
3. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) 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 on both upright and inverted samples, except for lyophilized products (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).
6. (P.8.3) Interim stability testing results and a commitment to notify Health Canada of any failures in the ongoing long term stability studies. Extrapolation of shelf-life should be made in accordance with ICH Q1E guideline.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
78. Change in the post-approval stability protocol of the drug product, involving:			
a. major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature	None	3-6	Notifiable Change
	1	1-2,4-5	Annual Notification
b. addition of time point(s) into the post-approval stability protocol	None	4-5	Annual Notification
c. addition of test(s) into the post-approval stability protocol	2	4-5	Annual Notification
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4-5	Annual Notification
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4-5	Annual Notification
f. replacement of the sterility testing by the container/closure system integrity testing	None	1-2,4-5	Notifiable Change
	4	4-5	Annual Notification

Conditions

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
3. The deletion of time points is made according to ICH Q5C.
4. The method used to demonstrate the container/closure system integrity has already been approved as part of a previous application (e.g., NDS, S/NDS, NC).

Supporting Data

1. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
2. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.8.1) Proposed storage conditions and or shelf-life, as appropriate.
4. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
5. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment.
6. (P.8.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
79. Change in the labelled storage conditions for the drug product or the diluted or reconstituted product, involving:			
a. addition or change of storage condition for the drug product (e.g., relaxation or tightening of a temperature criterion)	None	1-5	Notifiable Change
	1-2	1-4	Annual Notification
b. addition of a cautionary statement (e.g., "Do not freeze")	1	1-2,4-5	Annual Notification
c. deletion of a cautionary statement (e.g., "Do not freeze")	None	1-2,4,6	Annual Notification

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change consists in the tightening of a temperature criterion within the approved ranges.

Supporting Data

1. (1.3) Revised Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels, as applicable.
2. (P.8.1) Proposed storage conditions and shelf-life.
3. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
4. (P.8.2) Justification of the change in the labelled storage conditions/cautionary statement.
5. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on one (1) commercial scale batch).
6. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).

Appendix 4: Quality Post-NOC Changes (Schedule C Drugs)

Radiopharmaceuticals, kits and generators are listed in Schedule C to the Food and Drugs Act and regulated under the Food and Drug Regulations. Radiopharmaceuticals are pre-radiolabeled drug products ready for patient administration. Kits contain a drug substance of either chemical or biologic origin which is reconstituted with the recommended radioisotope immediately prior to patient administration. Generators contain a parent radionuclide undergoing decay to a daughter radionuclide (e.g., Mo-99 to Tc-99m) which is then eluted from the generator for use either in the reconstitution of kits or for direct administration to the patient. Each of these products contains radionuclides that exhibit spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons (such as positron, beta negative, alpha emitters or gamma ray).

In the guidance below, a radiolabeled product resulting from reconstitution of a kit is referred to as a "reconstituted final drug product" to distinguish it from a pre-radiolabeled drug product (radiopharmaceutical). These two types of radiopharmaceutical products are handled together whereas generators are handled separately. The examples are grouped, in order, as follows:

3.2.S DRUG SUBSTANCE (Kits/radiopharmaceuticals containing drug substance of chemical origin).

3.2.S DRUG SUBSTANCE (Kits/radiopharmaceuticals containing drug substance of biological origin).

3.2.P DRUG PRODUCT (Kits/radiopharmaceuticals containing drug substance of chemical or biological origin).

3.2.P DRUG PRODUCT (Generators).

The information summarized in the tables provides recommendations for:

(a) The conditions to be fulfilled for a given change to be classified as either Level I, II, or III change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Level II - Notifiable Change are not fulfilled, the change is considered a Level I - Supplement. Similarly, if any of the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of an NDS;

(b) The supporting data for a given change, either to be submitted to Health Canada and/or maintained by the sponsor. Where applicable, the corresponding modules of the Common Technical Document (CTD) for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided. (N.B. Guidance for using CTD document for Schedule C drugs is under development. Therefore, the numbering is not directly relevant to the use of the QIS-R).

(c) The reporting category (e.g., Supplement, Notifiable Change or Annual Notification).

3.2.S Drug substance (Kits/radiopharmaceuticals containing drug substance of chemical origin)

3.2.S.1 General information

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Change in the name of the drug substance	1	1-2	Annual Notification
Conditions			
1. Confirmation that the information on the drug substance has not changed as a result of the change [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]			
Supporting Data			
1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] or Package Insert for veterinary drugs, and Inner and Outer Labels. 2. (S.1.1) Information on the proposed nomenclature of the drug substance [e.g., chemical name(s), compendial name] and evidence that the proposed name for the drug substance is recognized (e.g., Recommended INN, USAN, BAN).			

3.2.S.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Replacement or addition of a manufacturing site and/or manufacturer, involving:			
a. production of the starting material, intermediate, or drug substance	None	1-9	Supplement
	3,5	2-9	Notifiable Change
	1-5	3-7	Annual Notification
3. Deletion of a manufacturing site or manufacturer for the starting material, intermediate, or drug substance	None	None	Annual Notification

Conditions

1. No Level I or Level II changes in the drug substance specifications.
2. No change in the route of synthesis, physical characteristics, and impurity profile of the drug substance [that is (i.e.,) no new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within ICH limits].
3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment of viral safety data or TSE risk assessment is required.
4. The change does not concern a sterile drug substance.
5. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1, 5) Viral safety data (ref. Condition 3) or supporting or comparative bioavailability data (ref. Condition 5) (whichever is applicable to be included in CTD modules 1 and 5).
2. (1.2.5) GMP and EL information.
3. (S) Updated or new DMF (with a Letter of Access provided in Module 1), any relevant drug substance information should be provided where available.
4. (S.2) Confirmation that the synthetic route, process controls, control of materials, and specifications of the intermediate or drug substance (as appropriate) in the manufacturing process of the proposed drug substance are the same as those previously approved or revised information if any of the attributes have changed.
5. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and testing.
6. (S.2.3) For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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) should be provided where available.

7. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for one batch of the currently approved and proposed drug substance manufacturing sites. If a batch size range is proposed, then a batch from the lowest and highest scale should be provided.
8. (S.7.3) Stability data from one (1) batch with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.
9. (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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
4. Change in the manufacturing process for the drug substance or intermediate	1	1-11	Supplement
	1-4,8	2-9,11	Notifiable Change
	1-8	2-6,8-9,11	Annual Notification

Conditions

1. No change in the identicality of the drug substance (as defined in the Health Canada policy Interpretation of "Identical Medicinal Ingredient").
2. No change in the physical state (e.g. crystalline, amorphous, solid, semi-solid, liquid or gas) of the drug substance.
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 manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No Level I or Level II changes in the drug substance specifications.
6. No change in the route of synthesis (i.e., 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 ICH limits).
7. The change does not concern a sterile drug substance.
8. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (1.5) Viral safety data (ref. Condition 4) or supporting clinical or comparative bioavailability data (ref. Conditions 3,8) (whichever is applicable to be included in CTD modules 1&5).
2. (S) Updated or new DMF (with a Letter of Access provided in Module 1) or relevant drug substance information.
3. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es), including comparison with the approved process.
4. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance.
5. (S.2.3) For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., 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) should be provided where available.
6. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance, including comparison with the approved controls.
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.

8. (S.3.1) Evidence for elucidation of structure, where applicable.
9. (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 one (1) batch of the currently approved and proposed processes.
10. (S.7.3) Results of two (2) batches with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.
11. (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.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
5. Change in the batch size for the drug substance	None	1-4	Notifiable Change
	1-8	1-4	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 (e.g., 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. The change does not affect the sterilization procedures of a sterile drug substance.
6. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).
7. The change does not concern a sterile drug substance.
8. There is no change in the stability profile of the drug substance manufactured using the new batch size.

Supporting Data

1. (S.2.2) A brief narrative description of the proposed manufacturing process(es).
2. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.
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 one batch compared to the previous batch size.
4. (S.7.3) Stability data from one (1) batch with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
6. Change in the controls for the materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) or the controls performed at critical steps in the process	None	1 or 2-4	Notifiable Change
	1-5	1 or 2,4	Annual Notification

Conditions

1. No Level I or Level II changes in the drug substance specifications.
2. No change in the impurity profile of the drug substance (i.e., no new impurity above 0.1%, no change in the approved total impurity limit and residual solvents within ICH limits).
3. The change in control(s) does not constitute a relaxation from the approved controls and is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
4. The change does not affect the sterilization procedures of a sterile drug substance.
5. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data

1. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance.
2. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
3. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.
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 one batch of each of the drug substance manufactured by the current and proposed methods.

3.2.S.3 Characterisation

There are not any 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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
7. Changes affecting the quality control (QC) testing of the drug substance (release and stability), involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company, to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable Change
	1	1-2	Annual Notification
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	2	1-2	Annual Notification
Conditions			
1. The transfer involves the relocation of the equipment and laboratory staff to the new laboratory or building. 2. The transferred QC test is not a potency assay.			
Supporting Data			
1. (S.2.5) Information demonstrating technology transfer qualification for the non-pharmacopoeial assays or verification for the pharmacopoeial assays. 2. Evidence that the new company/building is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
8. Change in the standard claimed for the drug substance (e.g., from a Professed to Schedule B pharmacopoeial standard or from one Schedule B standard to a different Schedule B standard)	1-3	1-4	Annual Notification
9. Change in the specification for the drug substance to comply with an updated Schedule B pharmacopoeial monograph	1-2	1-4	Annual Notification

Conditions

1. The change is made exclusively to comply with a Schedule B pharmacopoeia.
2. No Level I or Level II changes to the specifications with respect to the functional properties of the drug substance (e.g., particle size distribution, polymorphic form) and to the tests that impact safety (e.g., sterility, bacterial endotoxins).
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria for tests that do not appear in a pharmacopoeial monograph.

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 one batch if new tests and/or analytical methods are implemented.
4. (S.4.5) Justification of the proposed drug substance specification (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
10. Change in the drug substance release or shelf-life specifications involving test and acceptance criteria:			
a. for sterile drug substances, replacing the sterility test with process parametric release	None	1-7	Supplement
b. deletion of a test	None	2,7	Notifiable Change
	1-2,5	2,7	Annual Notification
c. replacement of a test	1-7	2-5,7	Annual Notification
d. addition of a test	1,3-4,6-7	2-5,7	Annual Notification
e. relaxation of an acceptance criterion	None	2,7	Notifiable Change
	1,4,6-7	2,7	Annual Notification
f. tightening of an acceptance criterion	2	2,7	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 ICH 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 (e.g., removal of an organic volatile solvent test after at least 10 commercial scale batches tested and meet acceptance criteria, or provide valid scientific justification).
6. The change does not concern sterility testing.
7. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting Data
1. (S.2.5) QC approved Process validation and/or evaluation studies or the proposed validation protocol of the proposed drug substance. 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 ten batches) to support the process parametric release. 7. (S.4.5) Justification of the proposed drug substance specification (e.g., test parameters, acceptance criteria, or analytical procedures).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
11. Change in the drug substance release and shelf-life specifications involving analytical procedures:			
a. deletion of an analytical procedure	None	1	Notifiable Change
	5	1	Annual Notification
b. replacement of, alternate, or additional analytical procedure	None	1-4	Notifiable Change
	1-4	1-4	Annual Notification
c. change from a House analytical procedure to a Schedule B analytical procedure or a change from an approved compendial analytical procedure to an harmonized compendial procedure	None	1,4	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 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.

3.2.S.6 Container closure system

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
12. 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	Annual Notification
Conditions			
1. The proposed container closure system is at least equivalent to the approved container closure with respect to its relevant properties (e.g., including results of transportation or compatibility studies, if appropriate). 2. The change does not concern a sterile drug substance.			
Supporting Data			
1. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process. 2. (S.6) Information on the proposed container closure system (e.g., description, specifications). 3. (S.7.3) Results of a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the drug substance in the proposed container closure system.			

3.2.S.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
13. Change in the re-test period (or shelf-life) for the drug substance, involving:			
a. Extension	None	1-4	Notifiable Change
	1-2,4-6	1-4	Annual Notification
b. Reduction	None	1-4	Notifiable Change
	1,3,5	1-4	Annual Notification
Conditions			
1. No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance. 2. The approved re-test period (or shelf-life) is at least 24 months. 3. 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 three commercial scale batches.			

4. Full long term stability data is available covering the proposed re-test period (or shelf-life) or is based on stability data generated on at least three commercial scale batches. If the proposed re-test period (or shelf-life) is beyond the available long term data, the extrapolation is in accordance with ICH's Q1E guideline. 5. Stability data was generated in accordance with the approved stability protocol. 6. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.
Supporting Data
1. (S.7.1) Summary of stability testing and results (e.g., 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 two pilot and/or commercial scale batches with stability data to support the proposed re-test period or shelf-life, inverted and upright except for lyophilized powder.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
14. Change in the labelled storage conditions for the drug substance, involving: addition/deletion of a cautionary statement or relaxation/tightening of a temperature criterion (e.g., 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 not less than two (2) lots (pilot or commercial scale).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
15. Change to the post-approval stability protocol or stability commitment	None	1-2	Annual Notification
Conditions			
None			
Supporting Data			
1. (S.7.2) QC approved updated post-approval stability protocol and stability commitment. 2. (S.7.2) Justification of the change to the post-approval stability protocol or stability commitment.			

3.2.S Drug substance (Kits/Radiopharmaceuticals containing drug substance of biological origin)

Refer to Appendix 3: Quality Post-NOC Changes (Biologics) Section 3.2.S

3.2.P Drug product (Kits/Radiopharmaceuticals containing drug substance of either chemical or biological origin)

3.2.P.1 Description and Composition of the Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Addition or modification of radioactive strength	None	1-13	Supplement
	1-5	1,3-6,12-13	Notifiable Change

Conditions

1. No change in the origin or supplier of radioisotope for radiopharmaceutical.
2. No change in the formulation with the exception of increased radioactivity.
3. No change to shelf-life of kit, reconstituted final product or radiopharmaceutical.
4. No change in reconstitution and/or quality control methodology.
5. No change in radiochemical purity and/or impurity specifications outside of the approved ranges for reconstituted final product or radiopharmaceutical.

Supporting Data

1. Supporting batch analyses data to demonstrate the chemical equivalence with approved product for all parameters except total radioactivity, radioactive concentration and specific activity.
2. (1.2.6) Letters of Access [(e.g., Drug Master Files (DMFs)] or detailed information, if new excipients are included such as preservatives, radioprotective agents or reducing agents.
3. (1.3) Product Monograph (title page, ''Dosage Forms, Composition, and Packaging'' section).
4. (1.3) Inner and Outer Labels.
5. (S) Confirmation that the information on the drug substance has not changed as a result of the change.
6. (P.1) For radiopharmaceuticals, description of the new radioactive strength.
7. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients).
8. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies.
9. (P.4) Control of Excipients, if new excipients are proposed (e.g., 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 one (1) production scale batch to be provided in section 3.2.R.3).
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, [e.g. for reconstituted final product, or radiopharmaceutical, test results including storage conditions for at least three (3) final product lots in upright and inverted vial orientations, including a minimum of three (3) time points (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 ICH Q1D).
13. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance into the long term stability program.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Change in the formulation of a kit or radiopharmaceutical	None	1-12	Supplement
	1-8	2,11	Notifiable Change

Conditions

1. No qualitative change in the formulation.
2. The proposed excipient(s) does/do not affect the physicochemical properties of the drug substance.
3. The proposed excipient(s) does/do not affect the solubility of the drug substance.
4. The proposed excipient(s) does/do not function as a preservative or preservative enhancer or as radioprotective or reducing agent.
5. No change in the specifications of the drug product outside of the approved ranges.
6. No change to the physical and radiochemical characteristics of the drug product (e.g., pH, chemical and radiochemical purity/impurity, specific activity, osmolality).
7. The change does not concern sterility or apyrogenicity of the drug product.
8. The change does not affect the shelf-life of the kit, reconstituted final product or radiopharmaceutical.

Supporting Data

1. Supporting in vivo clinical and/or bioequivalence/chemical equivalence data or a request for a waiver of in vivo studies.
2. (1.2.6) Letters of Access [e.g., Drug Master Files (DMFs)] detailed information, if new excipients are included such as preservatives, radioprotective agents or reducing agents.
3. (1.3) Product Monograph (title page, ''Dosage Forms, Composition, and Packaging'' section).
4. (S) Confirmation that the information on the drug substance has not changed as a result of the change.
5. (P.1) Description of each ingredient in the new formulation of the kit or radiopharmaceutical.
6. (P.2) Discussion of function of each component of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in-vitro testing for the approved and changed products, discussion of any in vitro and/or in vivo studies, results of preservative effectiveness testing (if applicable).
7. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
8. (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 one (1) commercial scale batch).
9. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
10. (P.8.1) Stability Summary and Conclusions, e.g. for reconstituted final product, or radiopharmaceutical, test results including storage conditions for at least three (3) final product lots in upright and inverted vial orientations, including a minimum of three (3) time points. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
11. (P.8.2) Updated, QC approved post-approval stability protocol and stability commitment.

12. (P.8.3) Results of a minimum of three (3) months of accelerated and three (3) months of long term testing of the proposed formulation of kit or longer if less than three (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.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
3. Change of a radioisotope either for reconstitution of a kit or preparation of a radiopharmaceutical, involving:			
a. addition or replacement of a radioisotope	None	1-12	Supplement
b. deletion of a radioisotope	1-5	2,4,6-7,9-11	Notifiable Change

Conditions

1. The change does not affect the stability or radiochemical characteristics (e.g., shelf-life, radiochemical purity and/or impurity) of the reconstituted final drug product or radiopharmaceutical product.
2. Changes to the drug product specifications are those necessitated only by the change to the radioisotope.
3. No change in the excipient(s) of the drug product.
4. No change in the mode of decay of the radioisotope.
5. No change in the shelf-life of the final product (reconstituted final product or radiopharmaceutical).

Supporting Data

1. (1.2.6) Letters of Access [e.g., Master Files (MFs)] or detailed information, if new excipients are included such as preservatives, radioprotective agents or reducing agents.
2. (1.3) Product Monograph (title page, and other relevant sections affecting the change including ''Dosage Forms, Composition, and Packaging'' section).
3. (P.1) Description of the radioisotope including data for radionuclidic and metallic impurities, name of supplier, country of origin and other relevant data for the radioisotope including decay chart.
4. (P.2) Scientific rationale for addition or replacement or deletion of a radioisotope for reconstitution of a kit or for production of a radiopharmaceutical.
5. (P.2) Scientific rationale for change in decay mode of a radioisotope (e.g., positron instead of gamma or vice versa).
6. (P.3) Batch Formula for radiopharmaceutical.
7. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
8. (P.5) Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (specificity of the analytical method and/or validation of new analytical methods), Batch Analyses (certificate of analyses for one (1) commercial scale batch to be provided in section 3.2.R.3).
9. (P.5) Reconstitution and quality control procedure, if new procedure is introduced; otherwise, confirmation that these procedures have not been changed.
10. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
11. (P.8.1) Stability Summary and Conclusions, [e.g. for reconstituted final product, or radiopharmaceutical, test results including storage conditions for at least three (3) final product lots in upright and inverted vial orientations, including a minimum of three (3) time points or longer if less than three (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 ICH Q1D).

12. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

3.2.P.2 Pharmaceutical development

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
4. Change in the approved design space, involving:			
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	1	1	Annual Notification
Conditions			
1. The reduction in design space is not necessitated by recurring problems having arisen during manufacture.			
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).			

3.2.P.3 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
5. Replacement or addition of a drug product manufacturer / manufacturing site, involving:			
a. production of a kit or radiopharmaceutical	None	1-8	Supplement
b. primary packaging (other than vial and stopper such as radiopharmaceutical in syringe)	1-3	2-3,5-6,8	Notifiable Change
c. secondary packaging which impacts temperature control during shipping	1-3	2-3,5	Notifiable Change
d. labelling	1-3	2-3,5	Notifiable Change
e. storage and distribution	1-3	2-3,5	Annual Notification
6. Deletion of any drug product manufacturer / manufacturing site	None	None	Annual Notification

Conditions

1. No change in the Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, or Drug Product Specifications outside of the approved ranges.
2. No significant change in the container closure system (e.g., vial size, type; septum formulation; supplier).
3. No change in the product shelf-life for the kit, reconstituted final product or radiopharmaceutical.

Supporting Data

1. Supporting in vivo clinical and/or bioequivalence data.
2. (1.2.5) GMP and EL information.
3. (P) Confirmation that information on the drug product has not changed as a result of the submission (e.g., other than change in site) or revised information on the drug product, if any of the attributes have changed.
4. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed drug products. For kits, test should also include reconstituted final product analyses for various test parameters such as: appearance, pH, chemical and radiochemical purity/impurity, sterility and apyrogenicity.
5. (P.3) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and testing.
6. (P.3.5) Process validation and/or evaluation studies. The proposed validation protocol may be sufficient, but data could be requested.
7. (P.5.4) Batch Analyses (certificate of analyses for one (1) commercial scale batch to be provided in section 3.2.R.3).
8. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
7. Change in the batch size for the drug product, involving:			
a. Up scaling or down scaling in the batch size	1-4	1-5	Notifiable Change

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, [e.g., use of different sized equipment (i.e., the same formulation, controls, standard operating procedures (SOPs) are utilized)].
2. The change should not be a result of recurring events arising during manufacture or because of stability concerns.
3. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the kit, reconstituted final product or radiopharmaceutical.
4. The change does not affect the shelf-life of Kit, reconstituted final product or radiopharmaceutical.

Supporting Data

1. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed drug products. For kits test should also include reconstituted final product analyses for various test parameters such as appearance, pH, chemical and radiochemical purity/impurity and sterility and apyrogenicity.
2. (P.3) Batch formula of the proposed drug product.
3. (P.3.5) Process validation and/or evaluation studies. The proposed validation protocol may be sufficient, but data could be requested.
4. (P.5.4) Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least one (1) commercial scale batch of the proposed drug product compared to previous scale.
5. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
8. Change in the drug product manufacturing process	None	1-7	Supplement
	1-5	1-7	Notifiable Change

Conditions

1. No Level I changes made to the drug product manufacturing process.
2. The change is not the result of recurring events arising during manufacture or because of stability concerns.
3. The change does not involve the packaging or labelling where the primary packaging provides a syringe for patient administration purposes.
4. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the kit, reconstituted final product or radiopharmaceutical.
5. The change does not affect the shelf-life of kit, reconstituted final product or radiopharmaceutical.

Supporting Data

1. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed drug products. For kits test should also include reconstituted final product analyses for various test parameters such as appearance, pH, chemical and radiochemical purity/impurity and sterility and apyrogenicity.
2. (S) Confirmation that the information on the drug substance has not changed as a result of the change.
3. (P.2) Discussion of the development of the manufacturing process for the approved and proposed drug products, discussion of any in vitro and/or in vivo studies.
4. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies.
5. (P.5) Specification(s) (if specification(s) have changed), Batch Analyses (certificate of analyses for one (1) commercial scale batch to be provided in section 3.2.R.3).
6. (P.8.1) Stability Summary and Conclusions.
7. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
9. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
a. deletion of an in-process test	4-5	3	Annual Notification
b. replacement or addition of an in-process test	1-4,6	1-2,4	Annual Notification
c. relaxation of an acceptance criterion	None	1,3-4	Notifiable Change
d. tightening of an acceptance criterion	None	1,3-4	Notifiable Change
	2	1	Annual Notification

Conditions

1. The change is not necessitated by recurring events 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 principle of the sterilization procedures and no impact on the apyrogenicity of the kit, reconstituted final product or radiopharmaceutical.
5. The deleted test has been demonstrated to be redundant with respect to the remaining analytical tests.
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.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.4) Data to show that the relaxation or deletion has not a negative impact on the quality of the batch. Results for at least one (1) commercial scale batch are required.
4. Rationale for the change supported by data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
10. Major change to the following process validation protocols used during the manufacture of the kit, reconstituted final product or radiopharmaceutical: introduction of product into an approved multi-product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)	None	1-2	Notifiable Change
Conditions			
None			
Supporting Data			
1. (P.3.5) Proposed validation protocol. Process validation and/or evaluation studies could be requested. 2. Rationale for the change in the validation protocol.			

3.2.P.4 Control of excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
11. Change in the standard/monograph (i.e., specifications) claimed for the excipient	None	1-4	Notifiable Change
	1-5	1-4	Annual Notification
12. Change in the specification for the excipient to comply with an updated Schedule B pharmacopoeial standard/monograph	2-3	1-2,4	Annual Notification

Conditions

1. The change is from a House/Professed standard to a Schedule B pharmacopoeial standard/monograph.
2. The change is made exclusively to comply with a Schedule B pharmacopoeial standard/monograph.
3. No change to the specifications for the functional properties of the excipient outside of the approved ranges nor that results in a potential impact on the performance of the drug product.
4. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
5. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting Data

1. (P.4.1) Updated excipient specifications.
2. (P.4.3) Where a House analytical procedure is used and a Schedule B standard/monograph is claimed, results of an equivalency study between the House and compendial methods.
3. (P.4.4) Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).
4. Declaration that consistency of quality and of the production process of the excipient is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
13. Change in the specifications used to release the excipient, involving:			
a. deletion of a test	3	1,3-4	Annual Notification
b. addition of a test	2,5	1-4	Annual Notification
c. replacement of an analytical procedure	5,8-9	1-2	Annual Notification
d. minor changes to an approved analytical procedure	5-7,10	1-2	Annual Notification
e. a change from a House/Professed analytical procedure to a Schedule B analytical procedure	5-6,10	1-2	Annual Notification
f. to reflect a pharmacopoeial monograph update	5	1	Annual Notification
g. relaxation of an acceptance criterion	2,4	1,3-4	Annual Notification
h. tightening of an acceptance criterion	1-2	1	Annual Notification

Conditions

1. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the excipient.
2. Acceptance criterion for any Class 3 residual solvent is within the ICH limits.
3. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
4. The change to the specifications does not affect the functional properties of the excipient nor result in a potential impact on the performance of the drug product.
5. The change does not concern sterility testing.
6. No change in the approved acceptance criteria outside of the approved ranges.
7. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
8. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
9. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
10. The change does not concern a kit or radiopharmaceutical that contains a drug substance that is not a discrete chemical entity (e.g., polymeric complexes).

Supporting Data
1. (P.4.1) Updated excipient specifications. 2. (P.4.3) Where a House/Professed analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House/Professed and compendial methods. 3. (P.4.4) Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product). 4. For a kit or radiopharmaceutical containing a drug substance that is not a discrete chemical entity (e.g., polymeric complexes), declaration that consistency of quality and of the production process of the excipient is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
14. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a a TSE or viral risk (e.g., animal) source	None	2-8	Supplement
15. Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	3	1,3,5-7	Notifiable Change
16. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source (e.g., different country of origin, different animal species)	3,7-8	2-6,8	Annual Notification
17. Change in manufacture of a biological excipient	None	3-8	Supplement
	3	3,5-8	Notifiable Change
	1-4	3,5	Annual Notification
18. Change in supplier for a human plasma-derived excipient (e.g., human serum albumin)	None	4-9	Supplement
	5-6	5-7,10	Notifiable Change
19. Change in supplier of an excipient of non-biological origin or of biological origin (excluding human plasma-derived excipient)	1,4	3	Annual Notification

Conditions

1. No change in the specifications of the excipient or drug product outside of the approved ranges.
2. No negative impact on the chemical and radiochemical purity/impurity or stability of the drug product.
3. The change does not concern a human plasma-derived excipient.
4. Properties of the proposed excipient are not different from those of the approved excipient.
5. The excipient from the new supplier is a Health Canada approved excipient.
6. No chemistry and manufacturing changes were made by the supplier of the new excipient since its last approval in Canada.
7. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material.
8. The new excipient does not require the assessment of viral safety data.

Supporting Data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.

2. Details of the source or the excipient (e.g., animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient.
4. (P.3.3) Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient.
5. (P.4.5) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient (certificates of analysis to be provided in section 3.2.R.3).
6. (P.5.4) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) batches of the drug product with the proposed excipient (certificates of analysis to be provided in section 3.2.R.3).
7. (P.8.3) Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) batches of the drug product with the proposed excipient, or longer if less than three (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.
8. (A.2) Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk).
9. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
10. Letter from the supplier certifying that no changes were made to the excipient since its last approval in Canada (DIN provided).

3.2.P.5 Control of drug product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
20. Changes affecting the quality control (QC) testing of the drug product, involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable Change
	1	1-2	Annual Notification
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	2	1-2	Annual Notification
Conditions			
1. The transfer involves the relocation of the equipment and laboratory staff to the new laboratory or building. 2. The transferred QC test is not a potency assay.			
Supporting Data			
1. (P.3.5) Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay. 2. Evidence that the new company/building is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
21. Change in the standard/monograph (i.e., specifications) claimed for the drug product, involving:			
a. a change from a Schedule B pharmacopoeial standard/monograph to a House standard	None	1-5	Notifiable Change
b. a change from a House/Professed standard to Schedule B pharmacopoeial standard/ monograph or from one Schedule B standard/ monograph to a different Schedule B standard/monograph)	1-4	1-3	Annual Notification
22. Change in the specifications for the drug product to comply with an updated Schedule B pharmacopoeial standard/monograph	1-2	1-3	Annual Notification

Conditions

1. The change is made exclusively to comply with a Schedule B pharmacopoeial standard/monograph.
2. The change to the specifications does not result in a potential impact on the performance of the drug product.
3. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
4. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting Data

1. (1.3) Product Monograph [e.g., Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels.
2. (P.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.5.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
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. Justification of specifications with data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
23. Change in the drug product release and shelf-life specifications, involving:			
a. for sterile products, replacing the sterility test with process parametric release	None	1-2,5,7-8	Supplement
b. deletion of a test	None	2,7-8	Notifiable Change
c. addition of a test	1-2	2-4,7	Annual Notification
d. replacement of an analytical procedure	None	2-4,6	Notifiable Change
e. minor changes to an approved analytical procedure	3-6	3-4,6	Annual Notification
f. change from a House/Professed analytical procedure to a Schedule B analytical procedure or change from an approved compendial analytical procedure to an harmonized compendial procedure	3,6	2-4	Annual Notification
g. relaxation of an acceptance criterion	None	2,7-8	Notifiable Change
h. tightening of an acceptance criterion	7-8	2	Annual Notification

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern sterility testing.
7. The change is within the range of approved acceptance criteria.
8. Acceptance criterion for any Class 3 residual solvent is within the ICH limits.

Supporting Data

1. (P.3.5) Process validation and/or evaluation studies or validation protocol of the proposed drug product.
2. (P.5.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
3. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

4. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
5. (P.5.4) Description of the batches and summary of results as quantitative data, of a sufficient number of batches to support the process parametric release (certificates of analysis to be provided in section 3.2.R.3).
6. (P.5.6) Justification for the change to the analytical procedure (e.g., demonstration of the suitability of the analytical procedure to monitor the drug product, including the degradation products).
7. (P.5.6) Justification of the proposed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).
8. Declaration that consistency of quality and of the production process is maintained.

3.2.P.6 Reference standards or materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
24. Change the reference standards from pharmacopoeial to House	None	1-2	Notifiable Change
25. Change the reference standards from House/Professed to pharmacopoeial	1	1-2	Annual Notification
26. Qualification of a new lot of reference standard against the approved reference standard	1	2	Annual Notification
27. Extension of reference standard shelf-life	2	3	Annual Notification
Conditions			
1. Qualification of the reference standard is performed according to the approved protocol (i.e., no deviation from the approved protocol). 2. The extension of the shelf-life or re-test period is made in accordance with the Health Canada approved protocol.			
Supporting Data			
1. (1.3) Revised Product monograph to reflect the change in reference standard. 2. (P.6) Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis). 3. (P.8.1) Summary of stability testing and results to support the extension of reference standard shelf-life.			

3.2.P.7 Container closure system

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
28. Change in the primary container closure system, involving:			
a. replacement or addition of a container closure system	None	1-5	Notifiable Change
	1,3-6	1,3-5	Annual Notification
b. deletion of a container closure system	None	1	Annual Notification
29. Change in the package size, involving:			
a. change in the fill weight / fill volume/total radioactivity	None	1-2,4-5	Notifiable Change
b. a change in the number of units (e.g., vials) per package	None	1-2,4-5	Notifiable Change
	1-6	1,3	Annual Notification

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change does not concern a container closure that functions to meter the drug product.
4. No change in the principle of the sterilization procedures of the drug product.
5. The change does not negatively impact the stability of the drug product.
6. The change is within the range of approved package sizes.

Supporting Data

1. (1.3) Product Monograph [e.g., Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels.
2. (P.3.5) Process validation and/or evaluation studies.
3. (P.7) Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications, including results of transportation studies, if appropriate).
4. (P.8.1) Stability Summary and Conclusions.
5. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
30. Change in the materials of construction of any primary or functional secondary container closure component	None	1-7	Supplement
	1-4	1-5	Notifiable Change

Conditions

1. The change does not affect negatively the shelf-life of the drug product.
2. The change does not affect negatively the chemical or radiochemical purity of a reconstituted final drug product or radiopharmaceutical.
3. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the drug product.
4. The change does not increase the amount of adsorption of radioactivity or reconstituted solution.

Supporting Data

1. (1.3) Product Monograph [e.g., Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels.
2. (P.3.5) Process validation and/or evaluation studies.
3. (P.7) Information on the changed container closure system (e.g., description, materials of construction of primary packaging components, specifications, including results of transportation or interaction studies, if appropriate).
4. (P.7) Data demonstrating product compatibility with the vial/stopper material when in close contact.
5. (P.7) Applicable data demonstrating acceptability of the packaging for the purpose intended (e.g., extractable/leachable testing, permeation testing, light transmission). For changes to functional packaging, data to demonstrate that the functioning of the new packaging is equivalent to that previously approved.
6. (P.8.1) Stability Summary and Conclusions.
7. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
31. Change in the supplier for a primary container closure component, involving			
a. replacement or addition of a supplier	None	1-6	Notifiable Change
	1-6	1	Annual Notification
b. deletion of a supplier	None	None	Annual Notification

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or specifications outside of the approved ranges.
2. The change does not concern a sterile container closure component.
3. The change does not affect negatively the shelf-life of the drug product.
4. The change does not affect negatively the chemical or radiochemical purity of a reconstituted final drug product or radiopharmaceutical.
5. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the drug product.
6. The change does not increase the adsorption of radioactivity or reconstituted solution.

Supporting Data

1. (P.3.5) Process validation and/or evaluation studies.
2. (P.7) Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications, including results of transportation or interaction studies, if appropriate).
3. (P.7) Data demonstrating product compatibility with the vial/stopper material when in close contact.
4. (P.8.1) Stability Summary and Conclusions.
5. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
6. Declaration that consistency of quality is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
32. Change in the specifications used to release a primary or functional secondary container closure component, involving:			
a. deletion of a test	1-2	1-2	Annual Notification
b. addition of a test	3	1-2	Annual Notification
c. replacement of an analytical procedure	6-8	1-3	Annual Notification
d. minor changes to an analytical procedure	4-8	1-3	Annual Notification
e. relaxation of an acceptance criterion	None	1-2	Notifiable Change
f. tightening of an acceptance criterion	9	1	Annual Notification

Conditions

1. The deleted test parameter has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specifications does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the drug product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. No change in the acceptance criteria outside of the approved ranges.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change does not concern sterility testing.
9. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the container closure component.

Supporting Data

1. (P.7) Updated, QC approved copy of the proposed specifications for the primary container closure (or where applicable, the final version of the specifications to be signed by QC after HC approval).
2. (P.7) Rationale for the change in specifications for a primary container closure component.
3. (P.7) Description of the analytical procedure and, if applicable, validation data.

3.2.P.8 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
33. Change in the shelf-life for the drug product such as kit, reconstituted final product or radiopharmaceutical, involving:			
a. extension	None	1-2,6-7	Notifiable Change
	1-5,7-9	1-2,5,7	Annual Notification
b. reduction	None	1-5,7	Notifiable Change
	6	2-4	Annual Notification

Conditions

1. No significant changes to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2. The approved shelf-life is at least 24 months for the kit and eight (8) hours for the reconstituted final product or three (3) days for the radiopharmaceutical.
3. Full long term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three (3) commercial scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.
6. The reduction of the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns (i.e., problems arising during manufacturing or stability concerns should be reported for evaluation).
7. Stability data for reconstituted product was generated with the approved quantity of radioisotope in approved volume of final product.
8. Stability data for the radiopharmaceutical was generated post calibration with the quantity of radioisotope in approved volume of final product.
9. The change does not affect the specific activity, injection volume, chemical or radiochemical purity/impurity of the reconstituted final drug product or radiopharmaceutical.

Supporting Data

1. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. (P.8.1) Proposed storage conditions and shelf-life, as appropriate.
3. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) 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 on both upright and inverted samples, except for lyophilized products (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).
6. (P.8.3) Interim stability testing results and a commitment to notify Health Canada of any failures in the ongoing long term stability studies. Extrapolation of shelf-life should be made in accordance with ICH Q1E guideline.
7. (P.8.3) For reconstituted final product or radiopharmaceutical, test data up to the proposed expiry for three (3) commercial scale batches in vial orientation of upright and inverted.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
34. Change in the post-approval stability protocol of the drug product, involving:			
a. major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature	None	3-6	Notifiable Change
	1	1-2,4-5	Annual Notification
b. addition of time point(s) into the post-approval stability protocol	None	4-5	Annual Notification
c. addition of test(s) into the post-approval stability protocol	2	4-5	Annual Notification
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4-5	Annual Notification
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3-4	4-5	Annual Notification

Conditions

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
3. In the case of kits, the approved shelf-life is at least 24 months.
4. The deletion of time points is made according to ICH Q5C.

Supporting Data

1. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
2. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.8.1) Proposed storage conditions and or shelf-life, as appropriate.
4. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
5. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment.
6. (P.8.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
35. Change in the labelled storage conditions for the drug product or the reconstituted final drug product or radiopharmaceutical, involving:			
a. addition or change of storage condition for the drug product (e.g., relaxation or tightening of a temperature criterion)	None	1-6,8	Notifiable Change
	1-2	1,3-5	Annual Notification
b. addition of a cautionary statement	None	1-3,5-6	Notifiable Change
	1	1-3,5-6	Annual Notification
c. deletion of a cautionary statement	None	1-3,5,7	Annual Notification

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change consists in the tightening of a temperature criterion within the approved ranges.

Supporting Data

1. (1.3) Revised Product Monograph (e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section) and Inner and Outer Labels, as applicable.
2. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
3. (P.8.1) Proposed storage conditions and shelf-life, as appropriate.
4. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
5. (P.8.2) Justification of the change in the labelled storage conditions/cautionary statement.
6. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on one (1) commercial scale batch).
7. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).
8. (P.8.3) For reconstituted final product or radiopharmaceutical, test data up to the proposed expiry for three (3) commercial scale batches in vial orientation of upright and inverted.

3.2.P Drug product (generators)

3.2.P.1 Description and composition of the generator

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Addition or modification of radioactive strength (total radioactivity of the generator)	None	1-9	Supplement
	1-6	1-4, 8-9	Notifiable Change

Conditions

1. No change in the origin or supplier of parent radionuclide.
2. No change in the formulation.
3. No change in generator shelf-life.
4. No change in elution methodology.
5. No change in radiochemical purity and/or impurity specifications outside of the approved ranges.
6. No change in column, elution vial, tubing, needle and other generator accessories.

Supporting Data

1. Supporting comparative Batch Analyses data for *chemical equivalence*.
2. (1.3) Revised Product Monograph (title page, ''Dosage Forms, Composition, and Packaging'' section).
3. (1.3) All applicable Labels.
4. (P.3) Batch formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies.
5. (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 one (1) production scale batch to be provided in section 3.2.R.3).
6. (P.5) Description of elution and quality control procedure, if these procedures have changed.
7. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
8. (P.8.1) Stability data, Summary and Conclusions. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
9. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Change in the formulation	None	1-8	Supplement
	1-8	2-8	Notifiable Change

Conditions

1. No change in the origin or supplier of parent radionuclide.
2. No change in generator shelf-life.
3. No change in elution methodology.
4. No change in column, elution vial, tubing, needle or other generator accessories.
5. No qualitative change in the formulation.
6. No change in the specifications of the drug product outside of the approved ranges.
7. The change does not affect negatively the physicochemical characteristics of the eluate (e.g., pH, appearance, parent radionuclidic breakthrough, radionuclidic and radiochemical purity of the daughter radionuclide).
8. No change in the principle of the sterilization procedures.

Supporting Data

1. Supporting comparative Batch Analyses data for chemical equivalence.
2. (1.3) Revised Product Monograph (title page, ''Dosage Forms, Composition, and Packaging'' section).
3. (P) Confirmation that the information on the parent radionuclide has not changed as a result of the change (e.g., cross reference(s) should be provided to the previously approved parent radionuclide, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved) or revised information on the parent radionuclide, if any of the attributes have changed.
4. (P.2) Description of the proposed formulation of the generator.
5. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
6. (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 three (3) commercial scale batches to be provided in section 3.2.R.3).
7. (P.8.1) Stability data, Summary and Conclusions. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
8. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

3.2.P.2 Pharmaceutical development

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
3. Change in the approved design space, involving:			
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	1	1	Annual Notification
Conditions			
1. The reduction in design space is not necessitated by recurring problems having arisen during manufacture.			
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).			

3.2.P.3 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
4. Replacement or addition of a generator component manufacturer/manufacturing site, involving:			
a. supplier of parent radionuclide	None	1-7	Supplement
b. primary packaging (including generator casing, lead shielding and other materials used in the manufacture of the generator)	1-3	2-3	Notifiable Change
c. secondary packaging (if any)	1-3	2-3	Annual Notification
d. labelling	2	2-3	Notifiable Change
e. storage and distribution	1-3	2-3, 5	Annual Notification
f. deletion of generator component manufacturer/ manufacturing site including supplier of parent radionuclide	None	None	Annual Notification
Conditions			
1. No change in the Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, or generator Specifications outside of the approved ranges. 2. No significant change in the container closure system. 3. No change in the generator shelf-life, including the shelf-life of evaluate (if applicable).			
Supporting Data			
1. (1.2.5) GMP and EL information. 2. (P) Confirmation that information on the generator has not changed as a result of the submission (e.g., other than change in site) or revised information on the generator, if any of the attributes have changed. 3. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed generators. This should include data from radiolabeling of kits that contain ligands that are anionic, cationic and neutral. 4. (P.3) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and testing. 5. (P.3.5) Process validation and/or evaluation studies. The proposed validation protocol may be sufficient, but data could be requested. 6. (P.5.4) Batch Analyses (certificate of analyses for three (3) commercial scale batches to be provided in section 3.2.R.3). 7. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
5. Change in the generator manufacturing process	None	1-7	Supplement
	1-5	1-5, 7	Notifiable Change

Conditions

1. The same standard operating procedures (SOPs), process controls and formulation are used on the approved and proposed generator. The equipment used to produce the proposed generator may vary in capacity, but are of the same design and operating principles.
2. The change is not the result of recurring events arising during manufacture or because of stability concerns.
3. The change does not involve the packaging or labelling.
4. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the generator.
5. The change does not affect the shelf-life of the generator.

Supporting Data

1. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed generator and eluate. For eluate, test should include appearance, pH, parent radionuclide breakthrough, radionuclidic and radiochemical purity/impurity, sterility and apyrogenicity.
2. (P) Confirmation that the information on the parent radionuclide has not changed as a result of the change.
3. (P.2) Discussion of the development of the manufacturing process for the approved and proposed generator.
4. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies.
5. (P.5) Specification(s) (if specification(s) have changed), Batch Analyses (certificate of analyses for three (3) commercial scale batches to be provided in section 3.2.R.3).
6. (P.8.1) Stability Summary and Conclusions.
7. (P.8.2) QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
6. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
a. deletion of an in-process test	4-5	3	Annual Notification
b. replacement or addition of an in-process test	1-4, 6	1-2,4	Annual Notification
c. relaxation of an acceptance criterion	None	1,3-4	Notifiable Change
d. tightening of an acceptance criterion	None	1,3-4	Notifiable Change
	2	1	Annual Notification

Conditions

1. The change is not necessitated by recurring events 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 principle of the sterilization procedures and no impact on the apyrogenicity of the generator or its eluate.
5. The deleted test has been demonstrated to be redundant with respect to the remaining analytical tests.
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.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.4) Release data for at least one (1) commercial scale batch to show that the relaxation or deletion has no negative impact on the quality of the batch.
4. Rationale for the change supported by data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
7. Major change to the following process validation protocols used during the manufacture of the generator: introduction of product into an approved multi-product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)	None	1-2	Notifiable Change
Conditions			
None			
Supporting Data			
1. (P.3.5) Proposed validation protocol. Process validation and/or evaluation studies could be requested. 2. Rationale for the change in the validation protocol.			

3.2.P.4 Control of parent radionuclide

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
8. Change in the standard/monograph (i.e., specifications) claimed for the parent radionuclide	None	1-4	Notifiable Change
	1-5	1-4	Annual Notification
9. Change in the specification for the parent radionuclide to comply with an updated Schedule B pharmacopoeial standard/monograph	2-3	1-2, 4	Annual Notification

Conditions

1. The change is from a House/Professed to a Schedule B pharmacopoeial standard/monograph.
2. The change is made exclusively to comply with a Schedule B pharmacopoeial standard/monograph.
3. The change to the specifications does not affect negatively the radionuclidic or chemical purity of the parent radionuclide.
4. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
5. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting Data

1. (P.4.1) Updated excipient specifications.
2. (P.4.3) Where a House analytical procedure is used and a Schedule B standard/monograph is claimed, results of an equivalency study between the House and compendial methods.
3. (P.4.4) Justification of the proposed specifications for the parent radionuclide (e.g., demonstration of the suitability of the monograph to control the parent radionuclide and potential impact on the performance of the drug product).
4. Declaration that consistency of quality and of the production process of the parent radionuclide is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
10. Change in the specifications used to release the parent radionuclide, involving:			
a. deletion of a test	2	1,3	Annual Notification
b. addition of a test	4	1-3	Annual Notification
c. replacement of an analytical procedure	4, 7-9	1-2	Annual Notification
d. minor changes to an approved analytical procedure	4-5, 7-9	1-2	Annual Notification
e. change from a House/Professed analytical procedure to a Schedule B analytical procedure	4-9	1-2	Annual Notification
f. to reflect a pharmacopoeial monograph update	4	1	Annual Notification
g. relaxation of an acceptance criterion	3	1, 3	Annual Notification
h. tightening of an acceptance criterion	1	1	Annual Notification

Conditions

1. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the parent radionuclide.
2. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
3. The change to the specifications does not negatively affect the radionuclidic purity or radiochemical purity of the parent radionuclide.
4. The change does not concern sterility testing.
5. No change in the acceptance criteria outside of the approved ranges.
6. The method of analysis has not changed.
7. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
8. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
9 The change does not concern test for radionuclidic or radiochemical purity.

Supporting Data

1. (P.4.1) Updated specifications of the parent radionuclide.

2. (P.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. (P.4.3) Justification of the proposed specifications for the parent radionuclide.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
11. Addition or replacement of the source of a parent radionuclide	None	1-6	Supplement
12. Deletion of the source of a parent radionuclide	1	7	Annual Notification[12]

Conditions

1. The change does not affect the physicochemical properties or specifications of the generator.

Supporting Data

1. (S) Detailed information of facility, radioisotope production, quality control and transportation procedure from the manufacturer/supplier of the parent radionuclide or Letter of Access from the supplier to access any existing file with Health Canada for the above information.
2. (S) Detailed information on storage, processing, and manufacturing process, or confirmation that these steps remain unchanged (cross-reference to the existing information of the same generator approved by Health Canada (File number, Control number, date of approval, product name, sponsor name).
3. (S.3.1) Information demonstrating comparability in term of physicochemical characterization and impurity profile of the proposed parent radionuclide with the approved parent radionuclide.
4. (P.5.4) Comparative release test data for the proposed generator eluate and the approved eluate to demonstrate chemical equivalence.
5. (P.5.4) Batch analyses data for at least three (3) commercial scale batches of the proposed generator.
6. (P.8.3) Stability test data to support the claimed expiry of the proposed generator.
7. Rationale for the deletion of the source of a parent radionuclide.

3.2.P.5 Control of generator

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
13. Changes affecting the quality control (QC) testing of the generator, involving			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable Change
	1	1-2	Annual Notification
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	None	1-2	Annual Notification
Conditions			
1. The transfer involves the relocation of the equipment and laboratory staff to the new laboratory or building.			
Supporting Data			
1. (P.3.5) Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
14. Change in the standard/monograph (i.e., specifications) claimed for the generator product, involving:			
a. a change from a Schedule B pharmacopoeial standard/monograph to a House standard	None	1-5	Notifiable Change
b. a change from a House/Professed standard to Schedule B pharmacopoeial standard/ monograph or from one Schedule B standard/monograph to a different Schedule B standard/monograph)	1-4	1-3	Annual Notification
15. Change in the specifications for the generator to comply with an updated Schedule B pharmacopoeial standard/monograph	1-2	1-3	Annual Notification

Conditions

1. The change is made exclusively to comply with a Schedule B pharmacopoeial standard/monograph.
2. The change to the specifications does not result in a potential impact on the performance of the eluate.
3. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
4. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting Data

1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels.
2. (P.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.5.1) Updated, QC approved copy of the proposed generator specifications and its eluate specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
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. Justification of specifications with data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
16. Change in the specifications for the generator, involving:			
a. replacing the sterility test with process parametric release for ultra-short lived daughter radionuclide	None	1-2, 5-6	Supplement
b. deletion of a test	None	2, 6	Notifiable Change
c. addition of a test	1-2	2-4, 6	Annual Notification
d. replacement of an analytical procedure	None	2-4, 6-7	Notifiable Change
e. minor changes to an approved analytical procedure	5-8	3-4, 7	Annual Notification
f. change from a House/Professed analytical procedure to a Schedule B analytical procedure or change from an approved compendial analytical procedure to an harmonized compendial procedure	5, 7	2-4	Annual Notification
g. relaxation of an acceptance criterion	None	2, 6-7	Notifiable Change
h. tightening of an acceptance criterion	3-4	2	Annual Notification

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.
3. The change is within the range of approved acceptance criteria.
4. Parent radionuclide breakthrough in the eluate is within the acceptance limit specified by Health Canada.
5. No change in the acceptance criteria outside of the approved ranges.
6. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. The change does not concern sterility testing.
8. The change does not concern test for radionuclidic identity or purity or radiochemical purity.

Supporting Data

1. (P.3.5) Process validation and/or evaluation studies or validation protocol of the proposed generator.
2. (P.5.1) Updated, QC approved copy of the proposed generator specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
3. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

4. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used. 5. (P.5.4) Description of the batches, certificates of analyses, and summary of results, of a sufficient number of batches to support the process parametric release. 6. (P.5.6) Justification of the proposed generator specifications (e.g., demonstration of the suitability of the monograph to control the generator and its eluate, including parent radionuclide breakthrough). 7. (P.5.6) Justification of the proposed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).

3.2.P.6 Reference standards or materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
17. Change the reference standards from pharmacopoeial to House	None	1-2	Notifiable Change
18. Change the reference standards from House/Professed to pharmacopoeial	1	1-2	Annual Notification
19. Qualification of a new lot of reference standard against the approved reference standard	1	2	Annual Notification
20. Extension of reference standard shelf-life	2	3	Annual Notification
Conditions			
1. Qualification of the reference standard is performed according to the approved protocol (i.e., no deviation from the approved protocol). 2. The extension of the shelf-life or re-test period is made in accordance with the Health Canada approved protocol.			
Supporting Data			
1. (1.3) Revised Product monograph to reflect the change in reference standard. 2. (P.6) Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis). 3. (P.8.1) Summary of stability testing and results to support the extension of reference standard shelf-life.			

3.2.P.7 Generator accessories

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
21. Change in the container closure system, involving:			
a. replacement or addition of elution or collection container closure system	None	1-5	Notifiable Change
b. deletion of elution or collection container closure system	None	1	Annual Notification
22. Change in chromatography column and tubing, involving:			
a. a change in chromatography column	None	1-5	Notifiable Change
b. a change in the column tubing, elution needle	None	1-5	Notifiable Change
	1-5	1,3-5	Annual Notification[13]
Conditions			
1. No change in the type of container closure or materials of construction for chromatography column, column tubing or elution needle. 2. No change in the shape or dimensions of the vial, stopper, chromatography column, column tubing or elution needle. 3. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the eluate. 4. The change is within the range of approved package sizes. 5. All the accessories of the generator, such as vial, stopper, chromatography column, column tubing and elution needle, are compatible with the eluate.			
Supporting Data			
1. (1.3) Relevant sections of the Product Monograph and Inner and Outer Labels affected by the proposed change. 2. (P.3.5) Process validation and/or evaluation studies. 3. (P.7) Information on the changed components such as vial, stopper, chromatography column, column tubing and elution needle (e.g., description, materials of construction, specifications, including results of compatibility studies). 4. (P.8.1) Stability Summary and Conclusions. 5. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment (if any).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
23. Change in the supplier for vial, stopper, chromatography column, column tubing or elution needle, involving:			
a. replacement or addition of a supplier	None	1-2	Notifiable Change
	1-2	2	Annual Notification
b. deletion of a supplier	None	None	Annual Notification
Conditions			
1. No change in the type of container closure, materials of construction, shape, dimensions or specifications. 2. The change does not concern a sterile container closure component.			
Supporting Data			
1. (P.3.5) Process validation and/or evaluation studies. 2. (P.7) Information on the proposed components such as vial, stopper, chromatography column, column tubing or elution needle (e.g., description, materials of construction, specifications, including results of compatibility studies).			

3.2.P.8 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
24. Change in the shelf-life for the generator, involving:			
a. extension	None	1-2, 5	Notifiable Change
b. reduction	1-3	1-5	Annual Notification
Conditions			
1. No change to the recommended storage condition of the generator. 2. Change does not affect the parent radionuclide breakthrough, radionuclidic or radiochemical purity of the eluate. 3. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns.			
Supporting Data			
1. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained). 2. (P.8.1) Proposed storage conditions and shelf-life. 3. (P.8.1) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) 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 (i.e., full long term stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
25. Change in the post-approval stability protocol of the generator, involving:			
a. major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature	None	3-6	Notifiable Change
	1	1-2, 4-5	Annual Notification
b. addition of time point(s) into the post-approval stability protocol	None	4-5	Annual Notification
c. addition of test(s) into the post-approval stability protocol	2	4-5	Annual Notification
d. deletion of time point(s) from the post-approval stability protocol within or beyond the approved shelf-life	None	2-3	Annual Notification
Conditions			
1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.			
Supporting Data			
1. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used. 2. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used. 3. (P.8.1) Proposed storage conditions and or shelf-life, as appropriate. 4. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment. 5. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment. 6. (P.8.3) If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
26. Change in the labelled storage conditions for the generator, involving:			
a. addition or change of storage condition for the generator (e.g., relaxation or tightening of a temperature criterion)	1-5	1-5,7	Annual Notification
b. addition of a cautionary statement	4	1-2,5-6	Annual Notification
c. deletion of a cautionary statement	None	1-2,5,7	Annual Notification

Conditions

1. Full stability data for the generator are available and covers the proposed shelf-life and are based on stability data generated on three (3) commercial scale batches.
2. Stability data was generated in accordance with the approved stability protocol.
3. Stability data for the generator was generated post calibration with the approved quantity of parent radionuclide.
4. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
5. The change consists in the tightening of a temperature criterion within the approved ranges.

Supporting Data

1. (1.3) Revised Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels, as applicable.
2. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
3. (P.8.1) Proposed storage conditions and shelf-life, as appropriate.
4. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
5. (P.8.2) Justification of the change in the labelled storage conditions/cautionary statement.
6. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on one (1) commercial scale batch).
7. (P.8.3) Results of stability testing [i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches].

Appendix 5: Recommendations for conducting and assessing comparative dissolution profiles

Below are 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):

  $f_2 = 50 \text{ LOG } \{[1+1/n \Sigma^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$

  where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two 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 two products (e.g., test and reference, pre- and post-change, two strengths) should be made under the same test conditions. The dissolution time points for both the profiles should be the same, e.g., 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 three (3) media covering the physiological range (pH 1.2 - 6.8), e.g., water, 0.1N HCl, and pharmacopoeial buffer media for the test and reference products.
- When delayed-release products (e.g., 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 (e.g., 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.
Case C: High Permeability, Low Solubility Drugs	Multi-point dissolution profiles should be performed in at least three (3) media covering the physiological range (pH 1.2 - 6.8), e.g., 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^{o}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^{o}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 6: Changes to excipients

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

* 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 (e.g., microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (e.g., ±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 (e.g., 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 7: 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 biologics and radiopharmaceuticals, 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.

Appendix 8: Glossary

Acronyms:

ASMF
Active Substance Master File

ANDS
Abbreviated New Drug Submission

BGTD
Biologics and Genetic Therapies Directorate

BSE
Bovine Spongiform Encephalopathy

CPSFI
Changes in Product-Specific Facility Information

CQA
Critical Quality Attribute

CTD
Common Technical Document

DMF
Drug Master File

DPIF
Drug Product Information Form

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

QC
Quality Control

Q1A
ICH guideline entitled “Stability testing of New Drug Substances and Products”

Q1D
ICH guideline entitled “Bracketing and Matrixing Designs for Stability Testing of New Drug Substance and Drug Product”

Q1E
ICH guideline entitled “Evaluation of stability data”

Q4b
ICH guideline entitled “Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions”

Q5A
ICH guideline entitled “Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin”

Q5B
ICH guideline entitled “Analysis of the expression construct in cells used for production of r-DNA derived protein products”

Q5C
ICH guideline entitled “Stability testing of biotechnological/biological products”

Q5D
ICH guideline entitled “Derivation and characterisation of cell substrates used for production of biotechnological/biological products”

Q5E
ICH guideline entitled “Comparability of biotechnological / biological products”

Q8(R2)
ICH guideline entitled “Pharmaceutical Development”

Q11
ICH guideline entitled “Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)”

SUPAC-MR
Scale-up and Post-approval Changes - Modified Release Solid Oral Dosage Forms (U.S. FDA guideline)

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 (e.g., 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 (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (e.g., cell substrate, host/vector production cells, eggs, viral strains, etc.).

Carrier:
An edible material (e.g., 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 (e.g., 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.

Equivalency of method:
The proposed analytical method has been validated and demonstrated to be equivalent to the approved method in term 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 (e.g., 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 (e.g., pharmaceutical and biological drugs).

Non-critical area:
Area that does not encompass process steps.

Non-critical excipient:
Excipient with no active function, e.g., 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 (e.g., 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 (e.g., United States Pharmacopeia, European Pharmacopoeia).

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

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.

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[1] The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the Food and Drug Act.

[2] Data should be presented under Module 1.0.7 for human drugs.

[3] Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs).

[4] Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs).

[5] Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

[6] This application consists of the review of the CPID-B only. Therefore, the supporting data recommended for this change should not be submitted but should be available upon request.

[7] This application consists of the review of the CPID-B only. Therefore, the supporting data recommended for this change should not be submitted but should be available upon request.

[8] Change from end-product testing to upstream controls for some tests is not considered a change in in-process test and/or acceptance criteria but instead a change in control strategy (see Change 24).

[9] Change in a component of a biological adjuvant system may require the filing of a NDS. Sponsors are encouraged to contact Health Canada for further guidance.

[10] Note that a biological diluent is considered itself a drug product.

[11] Change from end-product testing to upstream controls for some tests is not considered a change in in-process test and/or acceptance criteria but instead a change in control strategy (see Change 61).

[12] Notification is required immediately after the change is made.

[13] Notification is required immediately after the change is made.