Guidance on post-notice of compliance changes: Quality for biologics

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Ligne directrice sur les changements survenus après l'avis de conformité : Qualité des produits biologiques

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Document change log

Date	Nature of and reason for change	Location
September 15, 2009	• Administrative changes	• Whole document
October 15, 2013	• Appendix 1 to 4: Revisions or clarifications for various quality changes • Appendix 7: Additional examples of Level IV changes • Appendix 8: Addition of one definition	• Appendices 3, 7, 8
February, 2016	• Appendices 1, 2, 3: Further revisions or clarifications for various quality changes • Appendix 8: Addition of acronyms and definitions	• Appendices 1, 2, 3, 8
October 19, 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	• Appendices 1, 2, 3, 4, 7, 8

Date	Nature of and reason for change	Location
	been issued since the last update • Updating text to reflect Health Canada's adoption of ICH guidelines or annexes (such as Q4B, Q8 and Q11) • Clarifying when Level III changes should be filed and what documentation should be submitted	
July 22, 2021	• **Change 2a** (new DS site) and **changes 4-5** (Change in manufacturing process): Removal of the requirement to provide three (3) DP batches • **Certificates of analysis** don't need to be provided anymore • When **process evaluation and/or evaluation studies** are required, removal of the sentence **"The proposed validation is acceptable, but data could be requested"**:This applies to changes 3, 17, 43, 45 • **Change 16** (new cell bank/seed bank qualification protocol): Added the requirement to provide one batch in support of the new protocol • **Change 21**: Corrected the CTD section for Supporting data #1 (S.4.3 instead of S.2.5) • **Change 35**, supporting data #6: Replaced "i.e." by "e.g." to provide more flexibility • **Change 38b** (Change in fill volume): Added the option to file the change as a notifiable change if issuance of a new DIN is not required for the new fill volume (such as for vials)	• Generation of the biologics companion document

Date	Nature of and reason for change	Location
	• **Change 44**: Deletion of condition #3 • **Change 45b**: Clarified that the change was applicable to both product-contact and non product contact-equipment • **Change 45b**, condition #5: Added that for product-contact equipment, the size of the equipment is bracketed by the approved scales of the manufacturing process (such as new 300 L formulation tank for use in formulation process with an approved scale of 50 – 500L) • **Change 58**: Corrected the CTD section for supporting data #1 (P.5.3 instead of P.3.5) • **Change 79** (Change in the labelled storage conditions) : Added change in the in-use shelf-life, addition of or change to controlled temperature chain conditions as part of the example	
May 15, 2026	• **Change 12c and 13b**: Downgraded the reporting category from notifiable change to annual notification • **Change 27 and 32**: Deletion of condition #2 • **Change 38**: Removal of the requirement to provide certificates of analysis • **Change 64 and 69**: Deletion of condition #2	• Whole document

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Introduction

Health Canada's guidance document *Guidance on post-notice of compliance changes: Overall quality document for biologic and Schedule C drugs for human use* should be consulted for general information on Post-NOC changes and the classification of changes.

Scope

This guidance should be used to assess changes to biological products by the Biologics and Radiopharmaceuticals Drug Directorate (BRDD). This guidance only clarifies the reporting category for the quality related changes. These quality related changes may affect other regulatory aspects of the product such as administrative, labelling, or Good Manufacturing Practices (GMP) requirements. The referenced guidances should be consulted to determine the reporting requirements for these changes.

Post-drug identification number changes

In the absence of a guidance specific to quality changes to drugs which were approved through a drug identification application - biologics (DIN-B drugs), the quality 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.

General information

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:

- 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 III - Annual Notification are not fulfilled, the change would warrant the filing of Level II – Notifiable Change.

- The supporting data for a given change 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. As described in the Overall document, any data that may have been generated by the sponsor in support of a Level III change – Annual Notification or Level III change – Immediate Notification 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.
- The reporting category (e.g., Supplement, Notifiable Change, Annual Notification or Immediate 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: Biotherapeutic and Blood 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.

Level III changes – Notifications (minor quality changes)

For Biologics (Schedule D drugs), all Level III changes should be reported as Annual Notification unless the minor quality change results from the downgrade of a major or moderate quality change to minor quality change due to the execution of an approved post-approval change management protocol when the reporting categories have been negotiated to be classified as immediate notification rather than a higher typical reporting category.

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.

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 and may do so for 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.

On-site evaluation

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.

Drug substance

General information

Table 1: Change in the name of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).

Manufacture

Table 2: Change to a drug substance manufacturing facility

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a manufacturing facility for the bulk drug substance, or any intermediate of the drug substance	None	1-7,9-13,15	Supplement
	1-5	3,7,9-12,18	Notifiable change
b. Introduction of microbial hosts into a multi-product mammalian cell culture suite or vice versa	None	13-14	Supplement
c. Conversion of production and related area(s) from campaign to concurrent for a multi-product facility	5-6	16-17	Notifiable change
d. Conversion of a drug substance manufacturing facility from single-product to multi-product	5	13,15	Notifiable change
e. Addition of product(s) to an approved multi-product manufacturing facility	4-5,7	13,16	Annual notification
f. Introduction of a different host/media-type into an approved multi-product facility	7	8,15	Annual notification
g. Deletion of a manufacturing facility or manufacturer for a bulk intermediate, or drug substance	None	None	Annual notification
h. Replacement or addition of a storage facility/area for the bulk drug substance, or any intermediate of the drug substance	None	1,3	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.
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.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.
12. (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.
13. (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.
14. (A.1) Results of the environmental monitoring studies in critical classified areas.
15. (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.
16. (A.1) Data demonstrating lack of carry-over or cross-contamination.
17. Description of the segregation procedures to avoid cross-contamination.
18. Rationale for considering the proposed equipment as equivalent, if applicable.

Table 3: Modification to a facility involved in the manufacture of a drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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) Summary of the process validation and/or evaluation studies (e.g., equipment qualification). The complete report with all raw data could be requested during review.
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.

Table 4: Change to the drug substance fermentation process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. A critical change (e.g., incorporation of disposable bioreactor technology)	None	1-3,7-8, 10,12	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

Table 5: Change to the drug substance purification process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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	1-2,5,7-8,10,12-13	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	1-2,7-8,11-12	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

Table 6: Change in scale of the manufacturing process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. At the fermentation stage	10-11	3,7-8, 10,12,14	Notifiable change
b. At the purification stage	1,3,5,7	7-8, 10,12	Notifiable change

Table 7: Introduction of reprocessing steps

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Introduction of reprocessing steps	12	5, 9,11,12	Annual notification

Table 8: Change in the parameters of an approved holding step or addition of a new holding step

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.
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.
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.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.
13. (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.
14. Rationale for regarding the bioreactors as similar/comparable, if applicable.

Table 9: Change in the auxiliary materials/reagents of biological origin (e.g., foetal calf serum, insulin)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in **supplier**	None	2,6,8-9	Notifiable change
	1	2,6	Annual notification
b. Change in **source** (i.e., different country of origin, different animal species)	None	2,7-9	Notifiable change
	1	2,7	Annual notification

Table 10: Change in specification for the materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 11: Change in raw materials testing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.
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.
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.

Table 12: Changes to the cell banks

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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	Annual notification
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

Table 13: Changes to the seed banks

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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	Annual notification

Table 14: Change in cell bank/seed bank manufacturing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in cell bank/seed bank manufacturing site	None	1-2,13	Notifiable change

Table 15: Change in cell bank/seed bank testing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in cell bank/seed bank testing site	6	13	Annual notification

Table 16: Change in cell bank/seed bank qualification protocol

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in cell bank/seed bank qualification protocol	None	3-4,7	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.2.6) 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.
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.

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.
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.

Table 17: Change in product-contact equipment/material used in the drug substance manufacturing process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.
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.

Table 18: Change in the controls (in-process tests and/or acceptance criteria) applied during the drug substance manufacturing process or on intermediates

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 19: Change in in-process controls testing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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 change outside the range of approved acceptance criteria 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.

Table 20: Change in the approved design space

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

Characterisation

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

Control of the drug substance

Table 21: Changes affecting the quality control (QC) testing of the drug substance (release and stability)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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 only 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.4.3) 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.

Table 22: Change in the standard/monograph (i.e., specifications) claimed for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 23: Change in the specifications for the drug substance to comply with an updated Schedule B pharmacopoeial standard/monograph

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.

Table 24: Changes in the control strategy of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.

Table 25: Change in the drug substance release or shelf-life specifications

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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	3,7	1-3	Annual notification

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
approved compendial analytical procedure to an harmonized compendial procedure			
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).

Reference standards or materials used in the release of the drug substance

Table 26: Change the reference standards from pharmacopoeial to House

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change the reference standards from pharmacopoeial to House	None	1-2	Notifiable change

Table 27: Change the reference standards from House/Professed to pharmacopoeial

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change the reference standards from House/Professed to pharmacopoeial	1	1-2	Annual notification

Table 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)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. A reference standard used in a qualitative test	1	2	Annual notification
b. A reference standard used in a physicochemical test	1-3	2	Annual notification
c. A reference standard used in a semi-quantitative or quantitative biological assay.	1-3	2	Annual notification

Table 30: Change to reference standard qualification protocol (except for a bacterial or viral vaccine, bacterial toxin or blood product)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change to reference standard qualification protocol (except for a bacterial or viral vaccine, bacterial toxin or blood product)	None	3-4	Notifiable change
	4	4	Annual notification

Table 31: Change to reference standard qualification protocol for a bacterial or viral vaccine, bacterial toxin or blood product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. A reference standard used in a qualitative test	None	3-4	Annual notification
b. A reference standard used in a physicochemical test	4	3-4	Annual notification
c. A reference standard used in a semi-quantitative or quantitative biological assay.	2-4	3-4	Annual Notification

Table 32: Extension of the reference standard shelf-life or retest period

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Extension of the reference standard shelf-life or retest period	5	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 used to calculate the potency of the drug substance or intermediate.
3. The reference standard is not used to generate the calibration curve in test for a critical quality attribute or critical process parameter.
4. 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).
5. 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.

Container closure system

Table 33: Change in the primary container closure system(s) for the storage and shipment of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1-2,4	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.

Table 34: Change in the supplier for a primary container closure

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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:
    - accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and
    - 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.

Stability

Table 35: Change in the shelf-life for the drug substance or for a stored intermediate of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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. There are 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 (e.g., batch analysis on three (3) commercial scale batches).

Table 36: Change in the post-approval stability protocol of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).

Table 37: Change in the labelled storage conditions for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).

Drug product

Description and composition of the drug product

Table 38: Change in the description or composition of the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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
	1	2-4,6,8-11	Notifiable change
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

1. The change does not require issuance of a new Drug Identification Number (DIN) (e.g., same concentration, different volume for vials).

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 for at least three (3) consecutive commercial scale batches of the proposed drug product. 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.

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.

Table 39: Change involving a chemical/synthetic adjuvant

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 40: Change involving a biological adjuvant

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.
11. Supporting non-clinical and clinical data, if applicable.

Description and composition of the drug product

Table 41: Change to diluent

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.
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.

Pharmaceutical development

Table 42: Change in the approved design space

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

Manufacture

Table 43: Change involving a drug product manufacturer/manufacturing facility

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).
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. 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:
    - accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and
    - 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.

Table 44: Effect on the existing drug products in a drug product manufacturing facility involving introduction of a new product or change in concurrence

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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	2-3	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 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).

Table 45: Change in the drug product manufacturing process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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 product-contact and non-product contact 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) and the size of the equipment is bracketed by the approved scales of the manufacturing process (e.g. new 300 L formulation tank for use in formulation process with an approved scale of 50 – 500L).
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) Summary of the 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.

Table 46: Change in the controls (in-process tests and/or acceptance criteria) applied during the drug product manufacturing process or on intermediates

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 47: Change in in-process controls testing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.

Control of excipients

Table 48: Change in the standard/monograph (i.e., specifications) claimed for the excipient

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the standard/monograph (i.e., specifications) claimed for the excipient	None	1-4	Notifiable change
	1-5	1-4	Annual notification

Table 49: Change in the specification for the excipient to comply with an updated Schedule B pharmacopoeial standard/monograph

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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. (P.4.4) Declaration that consistency of quality and of the production process of the excipient is maintained.

Table 50: Change in the specifications used to release the excipient

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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. (P.4.4) Declaration that consistency of quality and of the production process of the excipient is maintained.

Table 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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 52: Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 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)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 54: Change in manufacture of a biological excipient

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in manufacture of a biological excipient	None	3-8	Supplement
	2	3,5-8	Notifiable change
	1-2	3,5	Annual notification

Table 55: Change in supplier for a human plasma-derived

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 56: Change in supplier of an excipient of non-biological origin or of biological origin (excluding human plasma-derived excipient)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 57: Change in excipient testing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.
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.
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.

Control of drug product

Table 58: Changes affecting the quality control (QC) testing of the drug product (release and stability)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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 only 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.5.3) 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.

Table 59: Change in the standard/monograph (i.e., specifications) claimed for the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 60: Change in the specifications for the drug product to comply with an updated Schedule B pharmacopoeial standard/monograph

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.

Table 61: Changes in the control strategy of the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.

Table 62: Change in the drug product release or shelf-life specifications

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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. (P.5.4) 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).

Reference standards or materials used in the release of the drug product

Table 63: Change the reference standards from pharmacopoeial to House

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change the reference standards from pharmacopoeial to House	None	1-2	Notifiable change

Table 64: Change the reference standards from House/Professed to pharmacopoeial

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change the reference standards from House/Professed to pharmacopoeial	1	1-2	Annual notification

Table 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)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. A reference standard used in a qualitative test	1	2	Annual notification
b. A reference standard used in a physicochemical test	1-3	2	Annual notification
c. A reference standard used in a semi-quantitative or quantitative biological assay.	1-3	2	Annual notification

Table 67: Change to reference standard qualification protocol (except for a bacterial or viral vaccine, bacterial toxin or blood product)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change to reference standard qualification protocol (except for a bacterial or viral vaccine, bacterial toxin or blood product)	None	3-4	Notifiable change
	4	4	Annual notification

Table 68: Change to reference standard qualification protocol for a bacterial or viral vaccine, bacterial toxin or blood product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. A reference standard used in a qualitative test	None	3-4	Annual notification
b. A reference standard used in a physicochemical test	4	3-4	Annual notification
c. A reference standard used in a semi-quantitative or quantitative biological assay.	2-4	3-4	Annual notification

Table 69: Extension of the reference standard shelf-life or re-test period

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Extension of the reference standard shelf-life or re-test period	5	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 used to calculate the potency of the drug product.
3. The reference standard is not used to generate the calibration curve in test for a critical quality attribute or critical process parameter.
4. 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).
5. 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.

Container closure system

Table 70: Modification of a primary container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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	None	1-7	Notifiable change
	1-3	1,3	Annual notification

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
only a vial) is considered a change in presentation (see change 38.d).			

Table 71: Addition of a secondary container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition of a secondary container closure system	None	1-3,7	Supplement
	4	1,3	Annual notification

Table 72: Change from a reusable container to a disposable container with no changes in product-contact material

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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

Table 73: Change from approved single-dose container to multi-dose container

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change from approved single-dose container to multi-dose container	None	1-7	Notifiable change

Table 74: Deletion of a container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).

Table 75: Change in the supplier for a primary container closure component

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).

Table 76: Change in the specifications used to release a primary or functional secondary container closure component

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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.

Stability

Table 77: Change in the shelf-life for the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Extension	None	1-4,6	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.

Table 78: Change in the post-approval stability protocol of the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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).

Table 79: Change in the labelled storage conditions for the drug product or the diluted or reconstituted product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition or change of storage condition for the drug product (e.g., relaxation or tightening of a temperature criterion, change in the in-use shelf-life, addition of or change to controlled temperature chain conditions)	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 1: Examples of Level IV changes (changes not reported)

- 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).
- Room 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.

Note about guidance documents in general

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

Guidance documents are administrative, not legal, instruments. This means that Health Canada may consider alternative approaches to meeting the regulatory requirements that stakeholders may propose. However, to be acceptable, alternative approaches to the principles and practices described in this document must be supported by adequate justification. Stakeholders should discuss their proposals with the relevant program area in advance so that Health Canada can determine whether the applicable statutory or regulatory requirements can be met.

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