Guidance on post-notice of compliance changes: Quality for Schedule C drugs

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Également disponible en français sous le titre :
Ligne directrice sur les changements survenus après l'avis de conformité : Qualité des médicaments de l'Annexe C

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Document change log

Date	Nature of and/or 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	• Appendices 1, 2, 3, 4, 7, 8

	categories, and the supporting data required • Appendix 7: Addition of an example, modification of existing examples • Appendix 8: Revision to an existing acronym and the addition of new acronyms • Rewording of various sections to add clarity to existing text and to provide consistency with notices or policies that have been issued since the last update • Updating text to reflect Health Canada's adoption of ICH guidelines or annexes (such as Q4B, Q8 and Q11) • Clarifying when Level III changes should be filed and what documentation should be submitted	
July 22, 2021	Under drug product - Kits/radiopharmaceuticals: • **Added Change 28b**: Change in the specifications of the elastomeric	• Generation of the companion document for Schedule C drugs

	component of a closure system • **Change 35**: Added examples to the list Under generators: • **Change 4b**: Added examples to the list • **Change 5**: Added examples to the list	
May 15, 2026	• **New format**	• Whole document

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Introduction

Health Canada's companion 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.

General information

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

In the guidance below, a radiolabeled product resulting from reconstitution of a kit is referred to as a "reconstituted final drug product" to distinguish it from a pre-radiolabeled drug product (radiopharmaceutical). These two types of radiopharmaceutical products are

handled together whereas generators are handled separately. The examples are grouped, in order, as follows:

- Drug substance - Kits or radiopharmaceuticals containing drug substance of chemical origin
- Drug substance - Kits or radiopharmaceuticals containing drug substance of biological origin
- Drug product - Kits or radiopharmaceuticals containing drug substance of chemical or biological origin
- Drug product - Generators

The information summarized in the tables provides recommendations for:

a. the conditions to be fulfilled for a given change to be classified as either Level I, II, or III change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Level II - Notifiable change are not fulfilled, the change is considered a Level I - Supplement. Similarly, if any of the conditions recommended for a Level III – Annual Notification are not fulfilled, the change would warrant the filing of a notifiable change.
b. the supporting data for a given change, either to be submitted to Health Canada and/or maintained by the sponsor. Where applicable, the corresponding modules of the common technical document (CTD) for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided. 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 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.
c. the reporting category (such as supplement, notifiable Change or annual notification).

For convenience, the change examples are organized according to the format defined by the common technical document (CTD), refer to the guidance for industry:

- Radiopharmaceuticals, kits, and generators: Submission information for Schedule C drugs

Level III changes – Notifications (minor quality changes)

For Radiopharmaceuticals (Schedule C drugs), all Level III changes should be reported as annual notification unless the minor quality change is classified as immediate notification in the guidance or 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 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.

For further guidance, sponsors are also encouraged to consult Health Canada's:

- Guidance on the Lot Release Program for Schedule D (biologic) drugs

On-site evaluation

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 – Kits or radiopharmaceuticals containing drug substance of chemical origin

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 the information on the drug substance has not changed as a result of the change [e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved.]

Supporting data

1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] or Package Insert for veterinary drugs, and Inner and Outer Labels.
2. (S.1.1) Information on the proposed nomenclature of the drug substance [e.g., chemical name(s), compendial name] and evidence that the proposed name for the drug substance is recognized (e.g., Recommended INN, USAN, BAN).

Manufacture

Table 2: Replacement or addition of a manufacturing site and/or manufacturer

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Production of the starting material, intermediate, or drug substance	None	1-9	Supplement
	3,5	2-9	Notifiable change
	1-5	3-7	Annual notification

Table 3: Deletion of a manufacturing site or manufacturer for the starting material, intermediate, or drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Deletion of a manufacturing site or manufacturer for the starting material, intermediate, or drug substance	None	None	Annual notification

Conditions

1. No Level I or Level II changes in the drug substance specifications.
2. No change in the route of synthesis, physical characteristics, and impurity profile of the drug substance [that is (i.e.,) no new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within ICH limits].

3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment of viral safety data or TSE risk assessment is required.
4. The change does not concern a sterile drug substance.
5. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting data

1. (1, 5) Viral safety data (ref. Condition 3) or supporting or comparative bioavailability data (ref. Condition 5) (whichever is applicable to be included in CTD modules 1 and 5).
2. (1.2.5) GMP and EL information.
3. (S) Updated or new DMF (with a Letter of Access provided in Module 1), any relevant drug substance information should be provided where available.
4. (S.2) Confirmation that the synthetic route, process controls, control of materials, and specifications of the intermediate or drug substance (as appropriate) in the manufacturing process of the proposed drug substance are the same as those previously approved or revised information if any of the attributes have changed.
5. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and testing.
6. (S.2.3) For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance) should be provided where available.
7. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for one batch of the currently approved and proposed drug substance manufacturing sites. If a batch size range is proposed, then a batch from the lowest and highest scale should be provided.
8. (S.7.3) Stability data from one (1) batch with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.
9. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance into the long term stability program (bracketing and matrixing with justification would be acceptable for multiple strength products).

Table 4: Change in the manufacturing process for the drug substance or intermediate

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the manufacturing process for the drug substance or intermediate	1	1-11	Supplement
	1-4,8	2-9,11	Notifiable change
	1-8	2-6,8-9,11	Annual notification

Conditions

1. No change in the identicality of the drug substance (as defined in the Health Canada policy Interpretation of “Identical Medicinal Ingredient”).
2. No change in the physical state (e.g. crystalline, amorphous, solid, semi-solid, liquid or gas) of the drug substance.
3. For low solubility drug substances, no change in the polymorphic form or no change in the particle size distribution of the drug substance.
4. Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No Level I or Level II changes in the drug substance specifications.
6. No change in the route of synthesis (i.e., intermediates remain the same), physical characteristics, and impurity profile of the drug substance (no new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within ICH limits).
7. The change does not concern a sterile drug substance.
8. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting data

1. (1.5) Viral safety data (ref. Condition 4) or supporting clinical or comparative bioavailability data (ref. Conditions 3,8) (whichever is applicable to be included in CTD modules 1&5).

2. (S) Updated or new DMF (with a Letter of Access provided in Module 1) or relevant drug substance information.
3. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es), including comparison with the approved process.
4. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance.
5. (S.2.3) For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance) should be provided where available.
6. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance, including comparison with the approved controls.
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.
8. (S.3.1) Evidence for elucidation of structure, where applicable.
9. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for at least one (1) batch of the currently approved and proposed processes.
10. (S.7.3) Results of two (2) batches with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.
11. (P.8.2) Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of the drug product, manufactured using the proposed drug substance, into the long term stability program.

Table 5: Change in the batch size for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the batch size for the drug substance	None	1-4	Notifiable change
	1-8	1-4	Annual notification

Conditions

1. No change in the proportionality of the raw materials.
2. Changes to the method of manufacture are only those necessitated by change in batch size (e.g., use of different-sized equipment).
3. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
4. No Level I or Level II changes in the drug substance specifications.
5. The change does not affect the sterilization procedures of a sterile drug substance.
6. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).
7. The change does not concern a sterile drug substance.
8. There is no change in the stability profile of the drug substance manufactured using the new batch size.

Supporting data

1. (S.2.2) A brief narrative description of the proposed manufacturing process(es).
2. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.
3. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a tabular format, for at least one batch compared to the previous batch size.
4. (S.7.3) Stability data from one (1) batch with a minimum of three (3) months of accelerated (or intermediate as appropriate) and three (3) months of long term testing of the proposed drug substance.

Table 6: Change in the controls for the materials used in the manufacture of the drug substance (such as raw materials, starting materials, solvents, reagents, catalysts) or the controls performed at critical steps in the process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the controls for the materials used in the manufacture of the drug substance (such as raw materials, starting materials, solvents, reagents, catalysts) or the controls performed at critical steps in the process	None	1 or 2-4	Notifiable change
	1-5	1 or 2,4	Annual notification

Conditions

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

Supporting data

1. (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed drug substance.
2. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
3. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization.
4. (S.4.4) Description of the batches, certificates of analyses or batch analysis report, and summary of results, in a comparative tabular format, for at least one batch of each of the drug substance manufactured by the current and proposed methods.

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 7: 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 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.

Supporting data

1. (S.2.5) Information demonstrating technology transfer qualification for the non-pharmacopoeial assays or verification for the pharmacopoeial assays.
2. Evidence that the new company/building is GMP compliant.

Table 8: Change in the standard claimed for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the standard claimed for the drug substance (e.g., from a Professed to Schedule B pharmacopoeial standard or from one Schedule B standard to a different Schedule B standard)	1-3	1-4	Annual notification

Table 9: Change in the specification for the drug substance to comply with an updated Schedule B pharmacopoeial monograph

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the specification for the drug substance to comply with an updated Schedule B pharmacopoeial monograph	1-2	1-4	Annual notification

Conditions

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

Supporting data

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

4. (S.4.5) Justification of the proposed drug substance specification (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities).

Table 10: Change in the drug substance release or shelf-life specifications involving test and acceptance criteria

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. For sterile drug substances, replacing the sterility test with process parametric release	None	1-7	Supplement
b. Deletion of a test	None	2,7	Notifiable change
	1-2,5	2,7	Annual notification
c. Replacement of a test	1-7	2-5,7	Annual notification
d. Addition of a test	1,3-4,6-7	2-5,7	Annual notification
e. Relaxation of an acceptance criterion	None	2,7	Notifiable change
	1,4,6-7	2,7	Annual notification
f. Tightening of an acceptance criterion	2	2,7	Annual notification

Conditions

1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the impurity profiles that impacts safety of the drug substance. Acceptance criterion for any Class 3 residual solvent is within the ICH limits (the

relaxation of an acceptance criterion for a Class 1 or 2 solvent should be filed as a Notifiable Change).

5. The deleted test has been demonstrated to be redundant with respect to the remaining tests and does not impact the safety or overall quality of the product (e.g., removal of an organic volatile solvent test after at least 10 commercial scale batches tested and meet acceptance criteria, or provide valid scientific justification).
6. The change does not concern sterility testing.
7. The change concerns drug substances that are discrete chemical entities (i.e., this does not include polymeric complexes).

Supporting data

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

Table 11: Change in the drug substance release and shelf-life specifications involving analytical procedures

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

Conditions

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

Supporting data

1. (S.4.1) Updated, QC approved, proposed drug substance specification.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (S.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (S.4.3) Comparative analytical results demonstrating that the approved and proposed analytical procedures are equivalent.

Container closure system

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

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

Conditions

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

Supporting data

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

Stability

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Extension	None	1-4	Notifiable change
	1-2,4-6	1-4	Annual notification
b. Reduction	None	1-4	Notifiable change
	1,3,5	1-4	Annual notification

Conditions

1. No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance.
2. The approved re-test period (or shelf-life) is at least 24 months.
3. Full long term stability data is available covering the proposed re-test period (or shelf-life) and is based on stability data generated on at least three commercial scale batches.
4. Full long term stability data is available covering the proposed re-test period (or shelf-life) or is based on stability data generated on at least three commercial scale batches. If the proposed re-test period (or shelf-life) is beyond the available long term data, the extrapolation is in accordance with ICH's Q1E guideline.
5. Stability data was generated in accordance with the approved stability protocol.
6. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.

Supporting data

1. (S.7.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. (S.7.1) Proposed storage conditions and re-test period (or shelf-life, as appropriate).

3. (S.7.2) Updated post-approval stability protocol and stability commitment.
4. (S.7.3) Results of stability testing generated on at least two pilot and/or commercial scale batches with stability data to support the proposed re-test period or shelf-life, inverted and upright except for lyophilized powder.

Table 14: Change in the labelled storage conditions for the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the labelled storage conditions for the drug substance, involving: addition/deletion of a cautionary statement or relaxation/tightening of a temperature criterion (e.g., from 15-25° C to 15-30°C)	None	1	Annual notification

Conditions

None

Supporting data

1. (S.7.3) If applicable, stability testing results to support the change to the storage conditions on not less than two (2) lots (pilot or commercial scale).

Table 15: Change to the post-approval stability protocol or stability commitment

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change to the post-approval stability protocol or stability commitment	None	1-2	Annual notification

Conditions

None

Supporting data

1. (S.7.2) QC approved updated post-approval stability protocol and stability commitment.
2. (S.7.2) Justification of the change to the post-approval stability protocol or stability commitment.

Drug substance - Kits or radiopharmaceuticals containing drug substance of biological origin

Refer to the 'Drug substance' section of the *Guidance on post-notice of compliance changes: Quality for biologics*.

Drug product - Kits or radiopharmaceuticals containing drug substance of either chemical or biological origin)

Description and composition of the drug product

Table 16: Addition or modification of radioactive strength

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition or modification of radioactive strength	None	1-13	Supplement
	1-5	1,3-6,12-13	Notifiable change

Conditions

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

Supporting data

1. Supporting batch analyses data to demonstrate the chemical equivalence with approved product for all parameters except total radioactivity, radioactive concentration and specific activity.
2. (1.2.6) Letters of Access [(e.g., Drug Master Files (DMFs)] or detailed information, if new excipients are included such as preservatives, radioprotective agents or reducing agents.
3. (1.3) Product Monograph (title page, "Dosage Forms, Composition, and Packaging" section).
4. (1.3) Inner and Outer Labels.
5. (S) Confirmation that the information on the drug substance has not changed as a result of the change.
6. (P.1) For radiopharmaceuticals, description of the new radioactive strength.
7. (P.2) Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients).
8. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies.
9. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
10. (P.5) Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), Batch Analyses for one (1) production scale batch.
11. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
12. (P.8.1) Stability Summary and Conclusions, [e.g. for reconstituted final product, or radiopharmaceutical, test results including storage conditions for at least three (3) final product lots in upright and inverted vial orientations, including a minimum of three (3) time points (including the zero time point)], as well as commitment to notify Health Canada of any failures in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
13. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and commitment to place the first commercial scale batch of the drug product manufactured using the proposed drug substance into the long term stability program.

Table 17: Change in the formulation of a kit or radiopharmaceutical

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the formulation of a kit or radiopharmaceutical	None	1-12	Supplement
	1-8	2,11	Notifiable change

Conditions

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

Supporting data

1. Supporting in vivo clinical and/or bioequivalence/chemical equivalence data or a request for a waiver of in vivo studies.
2. (1.2.6) Letters of Access [e.g., Drug Master Files (DMFs)] detailed information, if new excipients are included such as preservatives, radioprotective agents or reducing agents.
3. (1.3) Product Monograph (title page, "Dosage Forms, Composition, and Packaging" section).
4. (S) Confirmation that the information on the drug substance has not changed as a result of the change.
5. (P.1) Description of each ingredient in the new formulation of the kit or radiopharmaceutical.

6. (P.2) Discussion of function of each component of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in-vitro testing for the approved and changed products, discussion of any in vitro and/or in vivo studies, results of preservative effectiveness testing (if applicable).
7. (P.4) Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
8. (P.5) Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), Batch Analyses for one (1) commercial scale batch.
9. (P.7) Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
10. (P.8.1) Stability Summary and Conclusions, e.g. for reconstituted final product, or radiopharmaceutical, test results including storage conditions for at least three (3) final product lots in upright and inverted vial orientations, including a minimum of three (3) time points. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
11. (P.8.2) Updated, QC approved post-approval stability protocol and stability commitment.
12. (P.8.3) Results of a minimum of three (3) months of accelerated and three (3) months of long term testing of the proposed formulation of kit or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify Health Canada of any failures in the ongoing long term stability studies.

Table 18: Change of a radioisotope either for reconstitution of a kit or preparation of a radiopharmaceutical

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition or replacement of a radioisotope	None	1-12	Supplement
b. Deletion of a radioisotope	1-5	2,4,6-7,9-11	Notifiable change

Conditions

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

Supporting data

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

11. (P.8.1) Stability Summary and Conclusions, [e.g. for reconstituted final product, or radiopharmaceutical, test results including storage conditions for at least three (3) final product lots in upright and inverted vial orientations, including a minimum of three (3) time points or longer if less than three (3) time points are available (including the zero time point)], as well as commitment to notify Health Canada of any failures in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified (refer to ICH Q1D).
12. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Pharmaceutical development

Table 19: 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 20: Replacement or addition of a drug product manufacturer / manufacturing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Production of a kit or radiopharmaceutical	None	1-8	Supplement
b. Primary packaging (other than vial and stopper such as radiopharmaceutical in syringe)	1-3	2-3,5-6,8	Notifiable change
c. Secondary packaging which impacts temperature control during shipping	1-3	2-3,5	Notifiable change
d. Labelling	1-3	2-3,5	Notifiable change
e. Storage and distribution	1-3	2-3,5	Annual notification

Table 21: Deletion of any drug product manufacturer / manufacturing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Deletion of any drug product manufacturer / manufacturing site	None	None	Annual notification

Conditions

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

3. No change in the product shelf-life for the kit, reconstituted final product or radiopharmaceutical.

Supporting data

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

Table 22: Change in the batch size for the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Up scaling or down scaling in the batch size	1-4	1-5	Notifiable Change

Conditions

1. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch-size, [e.g., use of different sized equipment (i.e., the same formulation, controls, standard operating procedures (SOPs) are utilized)].
2. The change should not be a result of recurring events arising during manufacture or because of stability concerns.

3. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the kit, reconstituted final product or radiopharmaceutical.
4. The change does not affect the shelf-life of Kit, reconstituted final product or radiopharmaceutical.

Supporting data

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

Table 23: Change in the drug product manufacturing process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the drug product manufacturing process	None	1-7	Supplement
	1-5	1-7	Notifiable change

Conditions

1. No Level I changes made to the drug product manufacturing process.
2. The change is not the result of recurring events arising during manufacture or because of stability concerns.

3. The change does not involve the packaging or labelling where the primary packaging provides a syringe for patient administration purposes.
4. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the kit, reconstituted final product or radiopharmaceutical.
5. The change does not affect the shelf-life of kit, reconstituted final product or radiopharmaceutical.

Supporting data

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

Table 24: Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Deletion of an in-process test	4-5	3	Annual notification
b. Replacement or addition of an in-process test	1-4,6	1-2,4	Annual notification
c. Relaxation of an acceptance criterion	None	1,3-4	Notifiable change
d. Tightening of an acceptance criterion	None	1,3-4	Notifiable change
	2	1	Annual notification

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the kit, reconstituted final product or radiopharmaceutical.
5. The deleted test has been demonstrated to be redundant with respect to the remaining analytical tests.
6. The replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Supporting data

1. (P.3.3) Description of the proposed process controls or acceptance criteria.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (P.5.4) Data to show that the relaxation or deletion has not a negative impact on the quality of the batch. Results for at least one (1) commercial scale batch are required.
4. Rationale for the change supported by data.

Table 25: Major change to process validation protocols used during the manufacture of the kit, reconstituted final product or radiopharmaceutical

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Major change to the following process validation protocols used during the manufacture of the kit, reconstituted final product or radiopharmaceutical: introduction of product into an approved multi-product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)	None	1-2	Notifiable change

Conditions

None

Supporting data

1. (P.3.5) Proposed validation protocol. Process validation and/or evaluation studies could be requested.
2. Rationale for the change in the validation protocol.

Control of excipients

Table 26: 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 27: 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 28: 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	3	1,3-4	Annual notification
b. Addition of a test	2,5	1-4	Annual notification
c. Replacement of an analytical procedure	5,8-9	1-2	Annual notification
d. Minor changes to an approved analytical procedure	5-7,10	1-2	Annual notification
e. A change from a House/Professed analytical procedure to a Schedule B analytical procedure	5-6,10	1-2	Annual notification
f. To reflect a pharmacopoeial monograph update	5	1	Annual notification
g. Relaxation of an acceptance criterion	2,4	1,3-4	Annual notification
h. Tightening of an acceptance criterion	1-2	1	Annual notification

Conditions

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

Supporting data

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

Table 29: 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 (e.g., animal) source

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 (e.g., animal) source	None	2-8	Supplement

Table 30: 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	3	1,3,5-7	Notifiable change

Table 31: 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)	3,7-8	2-6,8	Annual notification

Table 32: 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
	3	3,5-8	Notifiable change
	1-4	3,5	Annual notification

Table 33: Change in supplier for a human plasma-derived excipient (e.g., human serum albumin)

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
	5-6	5-7,10	Notifiable Change

Table 34: 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)	1,4	3	Annual notification

Conditions

1. No change in the specifications of the excipient or drug product outside of the approved ranges.
2. No negative impact on the chemical and radiochemical purity/impurity or stability of the drug product.

3. The change does not concern a human plasma-derived excipient.
4. Properties of the proposed excipient are not different from those of the approved excipient.
5. The excipient from the new supplier is a Health Canada approved excipient.
6. No chemistry and manufacturing changes were made by the supplier of the new excipient since its last approval in Canada.
7. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material.
8. The new excipient does not require the assessment of viral safety data.

Supporting data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source or the excipient (e.g., animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient.
4. (P.3.3) Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient.
5. (P.4.5) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient.
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 minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) batches of the drug product with the proposed excipient, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify Health Canada of any failures in the ongoing long term stability studies.
8. (A.2) Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk).
9. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
10. Letter from the supplier certifying that no changes were made to the excipient since its last approval in Canada (DIN provided).

Control of drug product

Table 35: Changes affecting the quality control (QC) testing of the drug product

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 or to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable change
	1	1-2	Annual notification
b. Transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	2	1-2	Annual notification

Conditions

1. The transfer involves 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.

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 36: 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 37: 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.
3. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a Schedule B pharmacopoeial standard/monograph.
4. No deletion or change to any analytical procedures, except to comply with a Schedule B pharmacopoeial standard/monograph.

Supporting data

1. (1.3) Product Monograph [e.g., Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels.
2. (P.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.5.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
4. (P.5.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
5. Justification of specifications with data.

Table 38: Change in the drug product release and 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	1-2,5,7-8	Supplement
b. Deletion of a test	None	2,7-8	Notifiable change
c. Addition of a test	1-2	2-4,7	Annual notification
d. Replacement of an analytical procedure	None	2-4,6	Notifiable change
e. Minor changes to an approved analytical procedure	3-6	3-4,6	Annual notification
f. Change from a House/Professed analytical procedure to a Schedule B analytical procedure or change from an approved compendial analytical procedure to an harmonized compendial procedure	3,6	2-4	Annual notification
g. Relaxation of an acceptance criterion	None	2,7-8	Notifiable change

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
h. Tightening of an acceptance criterion	7-8	2	Annual notification

Conditions

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

Supporting data

1. (P.3.5) Process validation and/or evaluation studies or validation protocol of the proposed drug product.
2. (P.5.1) Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
3. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
4. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
5. (P.5.4) Description of the batches and summary of results as quantitative data, of a sufficient number of batches to support the process parametric release.
6. (P.5.6) Justification for the change to the analytical procedure (e.g., demonstration of the suitability of the analytical procedure to monitor the drug product, including the degradation products).

7. (P.5.6) Justification of the proposed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).
8. Declaration that consistency of quality and of the production process is maintained.

Reference standards or materials

Table 39: 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 40: 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 41: Qualification of a new lot of reference standard against the approved reference standard

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Qualification of a new lot of reference standard against the approved reference standard	1	2	Annual notification

Table 42: Extension of reference standard shelf-life

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Extension of reference standard shelf-life	2	3	Annual notification

Conditions

1. Qualification of the reference standard is performed according to the approved protocol (i.e., no deviation from the approved protocol).
2. The extension of the shelf-life or re-test period is made in accordance with the Health Canada approved protocol.

Supporting data

1. (1.3) Revised Product monograph to reflect the change in reference standard.
2. (P.6) Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis).
3. (P.8.1) Summary of stability testing and results to support the extension of reference standard shelf-life.

Container closure system

Table 43: Change in the primary container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a container closure system	None	1-5	Notifiable change
	1-6	1,3-5	Annual notification
2. Change in the specifications of the elastomeric component of a closure system	1-6	1, 4, 5	Annual notification

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
3. Deletion of a container closure system	None	1	Annual notification

Table 44: Change in the package size

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Change in the fill weight / fill volume/total radioactivity	None	1-2,4-5	Notifiable change
b. A change in the number of units (e.g., vials) per package	None	1-2,4-5	Notifiable change
	1-6	1,3	Annual notification

Conditions

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

Supporting data

1. (1.3) Product Monograph [e.g., Title Page, Storage and Stability (Part I), Dosage Forms, Composition and Packaging (Part I)] and Inner and Outer Labels.
2. (P.3.5) Process validation and/or evaluation studies.
3. (P.7) Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications, including results of transportation studies, if appropriate).
4. (P.8.1) Stability Summary and Conclusions.

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

Table 45: Change in the materials of construction of any primary or functional secondary container closure component

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the materials of construction of any primary or functional secondary container closure component	None	1-7	Supplement
	1-4	1-5	Notifiable change

Conditions

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

Supporting data

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

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

Table 46: 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	1-6	Notifiable change
	1-6	1	Annual notification
b. Deletion of a supplier	None	None	Annual notification

Conditions

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

Supporting data

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

Table 47: 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	6-8	1-3	Annual notification
d. Minor changes to an analytical procedure	4-8	1-3	Annual notification
e. Relaxation of an acceptance criterion	None	1-2	Notifiable change
f. Tightening of an acceptance criterion	9	1	Annual notification

Conditions

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

Supporting data

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

Stability

Table 48: Change in the shelf-life for the drug product such as kit, reconstituted final product or radiopharmaceutical

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Extension	None	1-2,6-7	Notifiable change
	1-5,7-9	1-2,5,7	Annual notification
b. Reduction	None	1-5,7	Notifiable change
	6	2-4	Annual notification

Conditions

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

9. The change does not affect the specific activity, injection volume, chemical or radiochemical purity/impurity of the reconstituted final drug product or radiopharmaceutical.

Supporting data

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

Table 49: 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

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	4-5	Annual notification

Conditions

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

Supporting data

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

Table 50: Change in the labelled storage conditions for the drug product or the reconstituted final drug product or radiopharmaceutical

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	1-6,8	Notifiable change
	1-2	1,3-5	Annual notification
b. Addition of a cautionary statement	None	1-3,5-6	Notifiable change
	1	1-3,5-6	Annual notification
c. Deletion of a cautionary statement	None	1-3,5,7	Annual notification

Conditions

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

Supporting data

1. (1.3) Revised Product Monograph (e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section) and Inner and Outer Labels, as applicable.
2. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
3. (P.8.1) Proposed storage conditions and shelf-life, as appropriate.
4. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

5. (P.8.2) Justification of the change in the labelled storage conditions/cautionary statement.
6. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on one (1) commercial scale batch).
7. (P.8.3) Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).
8. (P.8.3) For reconstituted final product or radiopharmaceutical, test data up to the proposed expiry for three (3) commercial scale batches in vial orientation of upright and inverted.

Drug product – Generators

Description and composition of the generator

Table 51: Addition or modification of radioactive strength (total radioactivity of the generator)

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition or modification of radioactive strength (total radioactivity of the generator)	None	1-9	Supplement
	1-6	1-4, 8-9	Notifiable change

Conditions

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

Supporting data

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

Table 52: Change in the formulation

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the formulation	None	1-8	Supplement
	1-8	2-8	Notifiable change

Conditions

1. No change in the origin or supplier of parent radionuclide.
2. No change in generator shelf-life.
3. No change in elution methodology.
4. No change in column, elution vial, tubing, needle or other generator accessories.
5. No qualitative change in the formulation.

6. No change in the specifications of the drug product outside of the approved ranges.
7. The change does not affect negatively the physicochemical characteristics of the eluate (e.g., pH, appearance, parent radionuclidic breakthrough, radionuclidic and radiochemical purity of the daughter radionuclide).
8. No change in the principle of the sterilization procedures.

Supporting data

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

Pharmaceutical development

Table 53: 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 54: Replacement or addition of a generator component manufacturer/manufacturing site

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Supplier of parent radionuclide	None	1-7	Supplement
b. Primary packaging including accessories (generator casing, lead shielding and other materials used in	1-3	2-3	Notifiable change

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
the manufacture of the generator, including tubing and elution vials)			
c. Secondary packaging (if any)	1-3	2-3	Annual notification
d. Labelling	2	2-3	Notifiable change
e. Storage and distribution	1-3	2-3, 5	Annual notification
f. Deletion of generator component manufacturer/ manufacturing site including supplier of parent radionuclide	None	None	Annual notification

Conditions

1. No change in the Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, or generator Specifications outside of the approved ranges.
2. No significant change in the container closure system.
3. No change in the generator shelf-life, including the shelf-life of evaluate (if applicable).

Supporting data

1. (1.2.5) GMP and EL information.
2. (P) Confirmation that information on the generator has not changed as a result of the submission (e.g., other than change in site) or revised information on the generator, if any of the attributes have changed.
3. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed generators. This should include data from radiolabeling of kits that contain ligands that are anionic, cationic and neutral.
4. (P.3) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and testing.

5. (P.3.5) Process validation and/or evaluation studies. The proposed validation protocol may be sufficient, but data could be requested.
6. (P.5.4) Batch Analyses for three (3) commercial scale batches.
7. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Table 55: Change in the generator manufacturing process

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Change in the generator manufacturing process, including column loading with the parent radionuclide	None	1-7	Supplement
	1-5	1-5, 7	Notifiable change

Conditions

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

Supporting data

1. (P.2.2) Comparative full release test data for one (1) batch of each of the approved and proposed generator and eluate. For eluate, test should include appearance, pH, parent radionuclide breakthrough, radionuclidic and radiochemical purity/impurity, sterility and apyrogenicity.
2. (P) Confirmation that the information on the parent radionuclide has not changed as a result of the change.
3. (P.2) Discussion of the development of the manufacturing process for the approved and proposed generator.

4. (P.3) Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation Studies.
5. (P.5) Specification(s) (if specification(s) have changed), Batch Analyses for three (3) commercial scale batches.
6. (P.8.1) Stability Summary and Conclusions.
7. (P.8.2) QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.

Table 56: Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Deletion of an in-process test	4-5	3	Annual notification
b. Replacement or addition of an in-process test	1-4, 6	1-2,4	Annual notification
c. Relaxation of an acceptance criterion	None	1,3-4	Notifiable change
d. Tightening of an acceptance criterion	None	1,3-4	Notifiable change
	2	1	Annual notification

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the generator or its eluate.
5. The deleted test has been demonstrated to be redundant with respect to the remaining analytical tests.

6. The replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Supporting data

1. (P.3.3) Description of the proposed process controls or acceptance criteria.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.4) Release data for at least one (1) commercial scale batch to show that the relaxation or deletion has no negative impact on the quality of the batch.
4. Rationale for the change supported by data.

Table 57: Major change to the process validation protocols used during the manufacture of the generator

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Major change to the following process validation protocols used during the manufacture of the generator: introduction of product into an approved multi-product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)	None	1-2	Notifiable change

Conditions

None

Supporting data

1. (P.3.5) Proposed validation protocol. Process validation and/or evaluation studies could be requested.
2. Rationale for the change in the validation protocol.

Control of parent radionuclide

Table 58: Change in the standard/monograph (i.e., specifications) claimed for the parent radionuclide

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

Table 59: Change in the specification for the parent radionuclide 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 parent radionuclide to comply with an updated Schedule B pharmacopoeial standard/monograph	2-3	1-2, 4	Annual notification

Conditions

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

Supporting data

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

Table 60: Change in the specifications used to release the parent radionuclide

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Deletion of a test	2	1,3	Annual notification
b. Addition of a test	4	1-3	Annual notification
c. Replacement of an analytical procedure	4, 7-9	1-2	Annual notification
d. Minor changes to an approved analytical procedure	4-5, 7-9	1-2	Annual notification
e. Change from a House/Professed analytical procedure to a Schedule B analytical procedure	4-9	1-2	Annual notification
f. To reflect a pharmacopoeial monograph update	4	1	Annual notification
g. Relaxation of an acceptance criterion	3	1, 3	Annual notification
h. Tightening of an acceptance criterion	1	1	Annual notification

Conditions

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

Supporting data

1. (P.4.1) Updated specifications of the parent radionuclide.
2. (P.4.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
3. (P.4.3) Justification of the proposed specifications for the parent radionuclide.

Table 61: Addition or replacement of the source of a parent radionuclide

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Addition or replacement of the source of a parent radionuclide	None	1-6	Supplement

Table 62: Deletion of the source of a parent radionuclide

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Deletion of the source of a parent radionuclide	1	7	Immediate notification

Conditions

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

Supporting data

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

Control of generator

Table 63: Changes affecting the quality control (QC) testing of the generator

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 or to a different building within the same company or to a different laboratory within the same building	None	1-2	Notifiable change
	1	1-2	Annual notification
b. Transfer of the QC testing activities for a pharmacopoeial assay to a new company not listed on the Establishment Licence of the manufacturer/sponsor	None	1-2	Annual notification

Conditions

1. The transfer involves only the relocation of the equipment and laboratory staff to the new laboratory or building.

Supporting data

1. (P.3.5) Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant.

Table 64: Change in the standard/monograph (i.e., specifications) claimed for the generator 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 65: Change in the specifications for the generator 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 generator to comply with an updated Schedule B pharmacopoeial standard/monograph	1-2	1-3	Annual notification

Conditions

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

Supporting data

1. (1.3) Product Monograph [e.g., Where applicable, Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section] and Inner and Outer Labels.
2. (P.4.3) Copies or summaries of validation reports, if new analytical procedures are used.
3. (P.5.1) Updated, QC approved copy of the proposed generator specifications and its eluate specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
4. (P.5.3) Where a House analytical procedure is used and a Schedule B standard is claimed, results of an equivalency study between the House and compendial methods.
5. Justification of specifications with data.

Table 66: Change in the specifications for the generator

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacing the sterility test with process parametric release for ultra-short lived daughter radionuclide	None	1-2, 5-6	Supplement
b. Deletion of a test	None	2, 6	Notifiable change
c. Addition of a test	1-2	2-4, 6	Annual notification
d. Replacement of an analytical procedure	None	2-4, 6-7	Notifiable change
e. Minor changes to an approved analytical procedure	5-8	3-4, 7	Annual notification
f. Change from a House/Professed analytical procedure to a Schedule B analytical procedure or change from an approved compendial analytical procedure to an harmonized compendial procedure	5, 7	2-4	Annual notification

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
g. Relaxation of an acceptance criterion	None	2, 6-7	Notifiable change
h. Tightening of an acceptance criterion	3-4	2	Annual notification

Conditions

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

Supporting data

1. (P.3.5) Process validation and/or evaluation studies or validation protocol of the proposed generator.
2. (P.5.1) Updated, QC approved copy of the proposed generator specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval).
3. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
4. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
5. (P.5.4) Description of the batches, certificates of analyses, and summary of results, of a sufficient number of batches to support the process parametric release.

6. (P.5.6) Justification of the proposed generator specifications (e.g., demonstration of the suitability of the monograph to control the generator and its eluate, including parent radionuclide breakthrough).
7. (P.5.6) Justification of the proposed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).

Reference standards or materials

Table 67: 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 68: 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 69: Qualification of a new lot of reference standard against the approved reference standard

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Qualification of a new lot of reference standard against the approved reference standard	1	2	Annual notification

Table 70: Extension of reference standard shelf-life

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Extension of reference standard shelf-life	2	3	Annual notification

Conditions

1. Qualification of the reference standard is performed according to the approved protocol (i.e., no deviation from the approved protocol).
2. The extension of the shelf-life or re-test period is made in accordance with the Health Canada approved protocol.

Supporting data

1. (1.3) Revised Product monograph to reflect the change in reference standard.
2. (P.6) Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis).
3. (P.8.1) Summary of stability testing and results to support the extension of reference standard shelf-life.

Generator accessories

Table 71: Change in the container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of elution or collection container closure system	None	1-5	Notifiable change
b. Deletion of elution or collection container closure system	None	1	Annual notification

Table 72: Change in chromatography column and tubing

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. A change in chromatography column	None	1-5	Notifiable change
b. A change in the column tubing, elution needle	None	1-5	Notifiable change
	1-5	1,3-5	Immediate notification

Conditions

1. No change in the type of container closure or materials of construction for chromatography column, column tubing or elution needle.
2. No change in the shape or dimensions of the vial, stopper, chromatography column, column tubing or elution needle.
3. No change in the principle of the sterilization procedures and no impact on the apyrogenicity of the eluate.
4. The change is within the range of approved package sizes.
5. All the accessories of the generator, such as vial, stopper, chromatography column, column tubing and elution needle, are compatible with the eluate.

Supporting data

1. (1.3) Relevant sections of the Product Monograph and Inner and Outer Labels affected by the proposed change.
2. (P.3.5) Process validation and/or evaluation studies.
3. (P.7) Information on the changed components such as vial, stopper, chromatography column, column tubing and elution needle (e.g., description, materials of construction, specifications, including results of compatibility studies).
4. (P.8.1) Stability Summary and Conclusions.
5. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment (if any).

Table 73: Change in the supplier for vial, stopper, chromatography column, column tubing or elution needle

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Replacement or addition of a supplier	None	1-2	Notifiable change
	1-2	2	Annual notification
b. Deletion of a supplier	None	None	Annual notification

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or specifications.
2. The change does not concern a sterile container closure component.

Supporting data

1. (P.3.5) Process validation and/or evaluation studies.
2. (P.7) Information on the proposed components such as vial, stopper, chromatography column, column tubing or elution needle (e.g., description, materials of construction, specifications, including results of compatibility studies).

Stability

Table 74: Change in the shelf-life for the generator

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Extension	None	1-2, 5	Notifiable change
b. Reduction	1-3	1-5	Annual notification

Conditions

1. No change to the recommended storage condition of the generator.
2. Change does not affect the parent radionuclide breakthrough, radionuclidic or radiochemical purity of the eluate.
3. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns.

Supporting data

1. (P.8.1) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. (P.8.1) Proposed storage conditions and shelf-life.
3. (P.8.1) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
4. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment.
5. (P.8.3) Results of stability testing (i.e., full long term stability data covering the proposed shelf-life generated on at least three (3) commercial scale batches).

Table 75: Change in the post-approval stability protocol of the generator

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 within or beyond the approved shelf-life	None	2-3	Annual notification

Conditions

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.

Supporting data

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

Table 76: Change in the labelled storage conditions for the generator

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
a. Addition or change of storage condition for the generator (e.g., relaxation or tightening of a temperature criterion)	1-5	1-5,7	Annual notification
b. Addition of a cautionary statement	4	1-2,5-6	Annual notification
c. Deletion of a cautionary statement	None	1-2,5,7	Annual notification

Conditions

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

Supporting data

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

Appendix 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).
- Rooms upgrades, such as installation of improved finishes on floors/walls.
- Addition of a new GMP storage warehouse for raw materials, master and working cell banks and drug substance.
- Installation of non-process-related equipment or rooms to improve the facility, such as warehousing refrigerators or freezers.
- Replacement of equipment with an identical equipment.
- Change in specifications for a compendial raw material to comply with an updated Schedule B pharmacopoeial standard/monograph.
- For biologics and radiopharmaceuticals, with the exception of a potency assay or a bioassay, transfer of the QC testing activities for a pharmacopoeial assay to a different laboratory within the same building, to a different building within the same company or to a different company listed on the sponsor’s establishment licence.

- Change in supplier for non-critical excipients.
- Change in tertiary packaging components of drug substance or drug product that do not affect stability.

Appendix 2: Recommendations for conducting and assessing comparative dissolution profiles

Below are recommendations when conducting comparative dissolution profiles:

- The resulting comparative dissolution profiles should be considered *similar* using the following equation which defines a similarity factor (f_2):

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

  where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are *similar*.

- At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the % coefficient of variation at the earlier point should be not more than 20% and at other time points should be not more than 10%.

- The dissolution measurements of the two products (e.g., test and reference, pre- and post- change, two strengths) should be made under the same test conditions. The dissolution time points for both the profiles should be the same, e.g., for immediate release products: 15, 30, 45 and 60 minutes, for extended release products: 1, 2, 3, 5 and 8 hours.

- Adequate sampling should be performed until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

- Because f_2 values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution of the product.

- If the individual data for both the test and reference products show more than 85% dissolution within 15 minutes, the profiles are considered *similar* (no calculations are necessary).

- When multi-media dissolution profiles are recommended, these studies should be performed in at least three (3) media covering the physiological range (pH 1.2 - 6.8), e.g., water, 0.1N HCl, and pharmacopoeial buffer media for the test and reference products.

- When delayed-release products (e.g., enteric coated) are being compared, it is acceptable to consider either multi-point testing in the acid phase as one of these media, or alternatively for coated products, to compare testing in 3 media once the coating disintegrates (e.g., pH 4, 5 and 6.8).

Summary of dissolution documentation:

Drug permeability/solubility	Comparative dissolution data
Case A: High Permeability, High Solubility Drugs	Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below).
Case B: Low Permeability, High Solubility Drugs	Multi-point dissolution profile should be performed in the submission/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.
Case C: High Permeability, Low Solubility Drugs	Multi-point dissolution profiles should be performed in at least three (3) media covering the physiological range (pH 1.2 - 6.8), e.g., 0.1N HCl, and pharmacopoeial buffer media for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached.

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

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

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

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.