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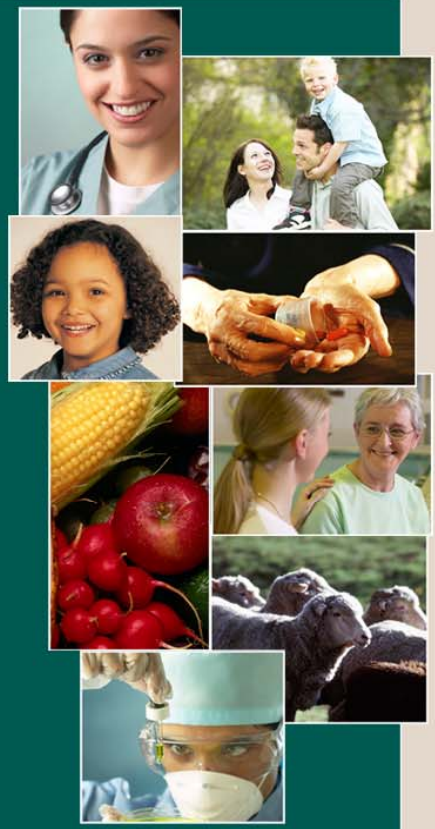

Quality: Post-NOC Changes for Schedule C Drugs

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Schedule C drugs are:

- **Radiopharmaceuticals**: They are pre-radiolabelled drugs ready for patient administration, may contain a drug substance of either chemical or biological origin.
- **Kits:** They are preformulated drug product containing drug substances of either chemical or biological origin. They need to be reconstituted with a radioisotope prior to patient administration.
- **Generators:** They contain a parent radionuclide which is decayed to a daughter radionuclide and is eluted for use either in reconstitution of a kit or for direct patient administration.

These products are listed in Schedule C to the Food and Drugs Act and regulated under the Food and Drug Regulations

Development of Examples for Schedule C Drugs

- Appendix 3 lists the example of changes, conditions and supporting data for Schedule C drug products
- For Kits and radiopharmaceuticals containing a drug substance of chemical origin, drug substance part of Appendix 1 (pharmaceutical) is applicable
- For kits and radiopharmaceuticals containing a drug substance of biological origin, drug substance part of Appendix 2 (biologics) is applicable.
- For kits and radiopharmaceuticals containing drug substances of either chemical or biological origin drug product part of the Appendix 3 is applicable. This will be the focus of this presentation.
- Note: PET/PERs specific examples will be included later as an Annex to Appendix 3.

DRUG PRODUCT
(Kits/Radiopharmaceuticals)

Description and Composition of the Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Addition of radioactive strength	None	1-14	Supplement
	1-5	1,3,4,5,6,12, 13,14	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 for reconstituted final product or radiopharmaceutical			

Description and Composition of the Drug Product (continued...)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the formulation	1	1-13	Supplement
	1-9	2-9,11,12	Notifiable Change

Conditions

1. None of the excipients are prohibited by the Food and Drug Regulations.
2. No qualitative change in the formulation.
3. The changed excipient(s) does/do not function to affect the physicochemical properties of the drug substance.
4. The changed excipient(s) does/do not function to affect the solubility of the drug substance.
5. The changed excipient(s) does/do not function as a preservative or preservative enhancer or as radioprotective or reducing agent.
6. No change in the specifications of the changed excipient(s) or the drug product.
7. No change to the physical and radiochemical characteristics of the drug product (e.g., pH, chemical and radiochemical purity/impurity, specific activity, osmolality).
8. The change does not concern sterility or apyrogenicity of the drug product.
9. The change does not affect the shelf-life of the Kit, reconstituted final product or radiopharmaceutical

Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Replacement or addition of a drug product manufacturer / manufacturing site, involving:			
a. production of a Kit or radiopharmaceutical	1,2,3	1-9	Supplement
b. primary packaging (other than vial and stopper such as radiopharmaceutical in syringe)	1,2,3	2,3,5,6,8	Notifiable Change
c. secondary packaging which impacts temperature control during shipping	1,2,3	2,3,5	Notifiable Change
d. labelling	1,2,3	2,3,5	Notifiable Change
e. testing (e.g., release, stability)	1,2,3	2,3,4,5	Notifiable Change
f. storage and distribution	1,2,3	2,3,5	Annual Notification
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. 2.No change in the container closure system. 3.No change in the product shelf-life for the kit, reconstituted final product or radiopharmaceutical.			

Manufacture (cont`d)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the batch size for the drug product, involving			
upscaling or down scaling in the batch size	1-4	1-6	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 (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized). 2.The change should not be a result of unexpected events arisen during manufacture or because of stability concerns. 3.The change does not affect the sterility and 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.			

Manufacture (cont`d)

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

Conditions

1.The same standard operating procedures (SOPs), process controls, formulation, and manufacturing procedures are used on the approved and changed products. The equipment used to produce the changed product may vary in capacity, but are of the same design and operating principles.
2.The change is not the result of unexpected 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.The change does not affect the sterility and 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.

Control of Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specification for the drug product, involving:			
a. replacing the sterility test with process parametric release	None	1-3,5-7	Supplement
b. deletion of a test	5-9	2-4,6,7	Notifiable Change
c. replacement or addition of a test	None	2-4,6,7	Notifiable Change
d. relaxation of an acceptance criterion	None	2-4,6,7	Notifiable Change
e. tightening of an acceptance criterion	1-4,6,7	2-4,6,7	Annual Notification

Conditions

1.The change is not necessitated by unexpected 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.Acceptance criterion for any Class 3 residual solvent is within the ICH limits.
5.The deleted test has been demonstrated to be redundant with respect to the remaining test procedures.
6.The change to the specifications does not affect the functional controls of the excipient nor result in a potential impact on the purity and stability of the drug product.
7.The change does not concern sterility testing.
8.The change does not concern radionuclidic identity and purity test and/or radiochemical purity tests.
9.The change does not concern tests for osmolality, residual solvents and pH for radiopharmaceutical drug products.

Control of Drug Product (cont`d)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specification for the drug product, for analytical procedures involving:			
a. deletion of an analytical procedure	1,5,6,7	1-5	Notifiable Change
b. replacement or addition of an analytical procedure	1,3	1-5	Notifiable Change
c. minor changes to an approved procedure	1-7	1-5	Annual Notification
Conditions			

1.No change in the approved acceptance criteria.
2.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.
3.Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4.Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5.The change does not concern sterility testing.
6.The change does not concern test for radionuclidic identity and purity or radiochemical purity.
7.The change does not concern tests for osmolality, residual solvent or pH for reconstituted final product or radiopharmaceutical.

Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the container closure system, involving:			
a. replacement or addition of a container closure system	4	1-5	Notifiable Change
	1,3,4,5	1,3,4,5	Annual Notification
b. deletion of a container closure system	4	1,3	Annual Notification
Change in the package size, involving:			
a. change in the fill weight / fill volume/total radioactivity	4,5	1-5	Notifiable Change
b. a change in the number of units (e.g., vials) per package	4	1-5	Notifiable Change
	1-5	1,3,4,5	Notifiable Change

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.The change does not concern sterility and stability of the drug product.
5.The change is within the range of approved package sizes.

Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the shelf life for the drug product such as kit, reconstituted final product or radiopharmaceutical, involving:			
a. Extension	1,4,5,6,7,8,9	1-4,6,7	Notifiable Change
b. Reduction	1,5-9	1-7	Notifiable Change

Conditions

1.No change to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2.The approved shelf life is at least 24 months for the kit and 8 hours for the reconstituted final product or 3 days for the radiopharmaceutical.
3.Full long term stability for kit *is* available covering the changed shelf life and is based on stability data generated on at least three production scale batches.
4.Full long term stability data for kit *is not* available covering the changed shelf life or *is not* based on stability data generated on at least three production scale batches. If the proposed 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.
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.Change does not affect the specific activity, injection volume, chemical or radiochemical purity/impurity of the reconstituted final drug product or radiopharmaceutical.

DRUG PRODUCT (GENERATORS)

Description and Composition of the Generator

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Addition of radioactive strength (total radioactivity of the Generator)	None	1-10	Supplement
	1-6	1,2,3,4,9,11	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
6. No change in column, elution vial, tubing, needle and other Generator accessories.

Description and Composition of the Generator (continued...)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the formulation	1,5	1-9	Supplement
	1-9	2-9	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 and other Generator accessories.
5.None of the excipients are prohibited by the Food and Drug Regulations.
6.No qualitative change in the formulation
7.No change in the specifications of the changed excipient(s)
8.The change does affect the physicochemical characteristics of the eluate (e.g., pH, parent radionuclidic breakthrough, radionuclidic and radiochemical purity of the daughter radionuclide).
9. The change does not affect the sterility of the eluate.

. Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Replacement or addition of a Generator manufacturer/manufacturing site involving:			
a. supplier of parent radionuclide	1,3	1-8	Supplement
b. primary packaging (including generator casing, lead shielding and other materials used in the manufacture of the generator)	1,2,3	2,3,	Notifiable change
c. secondary packaging (if any)	1,2,3	2,3,	Annual Notification
d. labelling	2	2,3	Notifiable change
e. testing (e.g., calibration, release, stability)	1,2,3	2-6	Notifiable change
f. storage and distribution	1,2,3	2,3,5	Annual Notification
Deletion of Generator 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.
2. No change in the container closure system.
3. No change in the generator shelf-life, including the shelf-life of eluate (if applicable)

Manufacture (continued...)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the generator manufacturing process	None	1-8	Supplement
	1-5	1-5,8	Notifiable Change
Conditions			
1.The same standard operating procedures (SOPs), process controls and formulation are used on the approved and changed generator. The equipment used to produce the changed generator may vary in capacity, but are of the same design and operating principles. 2.The change is not the result of unexpected events arising during manufacture or because of stability concerns. 3.The change does not involve the packaging or labelling. 4.The change does not affect the sterility and apyrogenicity of the generator. 5.The change does not affect the shelf-life of the generator.			

Control of Parent Radionuclide

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specification for the parent radionuclide, involving:			
a. deletion of a test procedure	4	1-3	Notifiable Change
a. replacement or addition of a test procedure	None	1-3	Notifiable Change
a. relaxation of an acceptance criterion	None	1-3	Notifiable Change
	1-3,5,6	1-3	Annual Notification
a. tightening of an acceptance criterion	1-3	1-3	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture, shipping, and storage of the parent radionuclide.
2. The change is within the range of approved acceptance criteria.
3. Any new test procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The deleted test procedure has been demonstrated to be redundant with respect to the remaining test procedures.
5. The change to the specifications does not affect radionuclidic purity or radiochemical purity of the parent radionuclide.
6. The change does not concern sterility testing..

Control of Parent Radionuclide (cont`d)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Addition or replacement of the source of a parent radionuclide	1	1-6	Supplement
Deletion of the source of a parent radionuclide	2	7	Annual Notification[1]
Conditions			
1.Parent radionuclidic breakthrough in the eluate is within the Health Canada specified limits. 2.Does not affect the physicochemical properties or specification of the generator.			
[1]Notification is required immediately after the change has been made			

Control of Generator

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specification of generator, involving:			
a. replacing the sterility test with process parametric release for ultra short lived daughter radionuclide	None	1-6	Supplement
b. deletion of a test procedure	5	2-4,6	Notifiable Change
c. replacement or addition of a test procedure	None	2-4,6	Notifiable Change
d. relaxation of an acceptance criterion	7,8	2-4,6	Notifiable Change
e. tightening of an acceptance criterion	1-4,6,7	2-6	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new test procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. Parent radionuclide breakthorugh in the eluate is within the acceptance limit specified by Health Canada
5. The deleted test procedure has been demonstrated to be redundant with respect to the remaining test procedures.
6. The change to the specifications does not affect the functional controls of the generator nor result in a potential impact on the purity or stability of the eluate.
7. The change does not concern sterility testing.
8. The change does not concern radionuclidic identity or purity test or radiochemical purity tests.

Generator Accessories

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the container closure system, involving:			
a. replacement or addition of elution or collection container closure system	4,5	1-5	Notifiable Change
a. deletion of elution or collection container closure system	3	1,3	Annual Notification
Change in chromatography column and tubing, involving:			
a. change in chromatography column	4,5	1-5	Notifiable Change
a. a change in the column tubing, elution needle	4,5	1-5	Notifiable Change
	1-5	1,3,4,5	Annual Notification[2]
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. The change does not affect the sterility or 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.			

Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the shelf life for the generator, involving:			
a.Extension	1-5	1-5	Notifiable Change
a.Reduction	1,5	1-5	Notifiable Change
Conditions			
1.No change to the recommended storage condition of the generator. 2.Full stability data for the generator *is* available and covers the changed shelf life and *is* based on stability data generated on three production scale batches. 3.Stability data was generated in accordance with the approved stability protocol. 4.Stability data for the generator was generated post calibration with the approved quantity of parent radionuclide. 5.Change does not affect the parent radionuclide breakthrough, radionuclidic or radiochemical purity of the eluate.			

Conclusion

- The presentation did not include the required supporting data for changes
- For supporting data consult Appendix 3 of the Guidance document
- The presentation did not cover all aspects of the changes listed in Appendix 3
- For details consult Appendix 3 of the Guidance document

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