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To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

Guidance Document
Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule C Drugs

GUI-0026

Supersedes:
March 1, 2002 edition

Date Issued:
November 19, 2010

Date of Implementation:
November 19, 2010

Disclaimer
This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

Canada

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1.0 Introduction

Radiopharmaceuticals, kits, and generators are listed in Schedule C to the *Food and Drugs Act* (http://laws-lois.justice.gc.ca/eng/F-27/index.html) and are regulated under the *Food and Drug Regulations* (http://laws-lois.justice.gc.ca/eng/C.R.C.-c.870/index.html). The *Regulations* which pertain to Schedule C drugs are found within Divisions 1A, 2, 3,5, and 8. Section 12 to the *Food and Drugs Act* prohibits the sale of drugs unless the premises in which the drug is manufactured and the process and conditions of manufacture therein are suitable to ensure that the drug will not be unsafe for use.

The guidance included in this Annex when placed in context with the "Good Manufacturing Practices (GMP) Guidelines (GUI-0001)" (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php), should facilitate compliance with Division 2 of the *Food and Drug Regulations*. The application of Division 2 to Schedule C drugs may be different from its application to pharmaceuticals due to the unique production and handling characteristics of the former. This Annex is intended to highlight the aspects of GMP that have a bearing on this class of drug. In order to avoid repetition, only those interpretations that are additional to those included in the "GMP Guidelines (GUI-0001)" are contained in this Annex. **Therefore, unless otherwise stated in this Annex, all interpretations included in the "GMP Guidelines (GUI-0001)" are applicable to Schedule C drugs and their bulk process intermediates.** Interpretations are written in general terms to allow establishments to adopt and justify procedures appropriate for their products and operations. The use of alternative approaches is justified and be consistent with the market authorization for the product.

Radiation safety requirements are not covered in this Annex. The Canadian Nuclear Safety Commission (CNSC) provides Regulations and guidance documents which are applicable to this subject matter. More specifically, the CNSC *GD-52: Design Guide for Nuclear Substance Laboratories and Nuclear Medicine Rooms* (http://nuclearsafety.gc.ca/eng/lawsregs/guidancedocuments/published/html/gd52/index.cfm) is applicable to the following sections of the GMP guidance: Premises, Equipment (Fume Hood, Plumbing, Storage and Security), Sanitation (handling and storage of radioactive wastes and personnel behavior), and Manufacturing Control (procedure writing related to management of rejected materials). Standard Operating Procedures concerning conditions of transportation are defined under the Raw Material Testing section of the "GMP Guidelines (GUI-0001)" and should follow recommendations from the CNSC Packaging and Transport Licensing Division. Radioactive contamination of the environment in which a drug is prepared can directly affect its quality. Thus, in addition to CNSC requirements, it is essential to follow GMP for Schedule C drugs.

Most radiopharmaceuticals are used as **diagnostic** agents and contain minute quantities of radionuclides, on a weight basis, in the final drug product. In addition to chemical or other (for example, biological) impurities, radiopharmaceuticals may also contain radioactive (radionuclidic and radiochemical) impurities. Such impurities may have a detrimental effect on both the utility and reliability of the drug as a diagnostic agent, and possibly on the radiation dose to the patient. Radiopharmaceuticals that are used as **therapeutic** agents require additional consideration as they contain high energy and long lived radionuclides and thus they present greater radiation doses to the patient.

Since most radiopharmaceuticals have a short shelf-life, they are often administered to patients within a short time after fabrication or reconstitution. Release of the product before completion of certain quality control tests might be necessary in these situations. For these reasons, the continuous assessment of the effectiveness of the quality assurance program becomes very important.

The guidance given in this document has been written with a view to harmonize with GMP principles incorporated in international documents (for example, Australian, European, Pharmaceutical Inspection Co-operation Scheme (PIC/S), World Health Organization (WHO), and United States GMP guidance documents for radiopharmaceuticals).

2.0 Purpose

To provide additional interpretive guidance for Part C, Division 2, of the *Food and Drug Regulations* for Schedule C drugs. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

3.0 Scope

The guidance provided in this Annex is applicable to the manufacture and control of bulk intermediates and finished Schedule C drugs. Due to the unique aspects of manufacture and quality control processes associated with their extremely short radioisotope half-life and thus shelf-life of Positron Emitting Radioisotopes and Radiopharmaceuticals (PERs), a separate GMP Annex has been published for this class of Schedule C drugs, and thus PERs are beyond the scope of this Annex.

4.0 Interpretation of Regulations

Premises

C.02.004

1. Radiopharmaceuticals and radionuclide generators are fabricated, packaged/labelled, stored and tested in facilities which prevent the contamination of drugs with unwanted sources of radioactivity such as radionuclidic and radiochemical contamination.

2. Facilities used for the handling of radioactivity are identified and access is restricted to authorised personnel involved in the process taking place.

3. Airflow patterns do not present a contamination risk while providing the necessary protection for the product during critical operations.

4. Positive pressure areas are used to process sterile products which are not radiolabelled but negative pressure is used in specific areas at points of risk for exposure to radioactivity.

5. Air handling filtration units are dedicated to specific processing areas.

6. Where negative pressure areas or safety cabinets are used, such as a hot-cell and a total containment glove box, the area(s) is surrounded by a positive pressure zone.

Equipment

C.02.005

1. Radiopharmaceuticals and radionuclide generators are fabricated, packaged/labelled, stored and tested with equipment which prevents the contamination of drugs with unwanted sources of radioactivity such as radionuclidic and radiochemical contamination. Dedicated equipment is recommended for campaign production to minimize the risk of cross-contamination.

2. Radioactivity measuring equipment, such as radionuclide dose calibrators and gamma counters, is available for fabrication and control operations. These devices are:

    2.1 shielded or located to avoid any source of background radiation.

    2.2 regularly calibrated for accuracy and precision by competent personnel. Corresponding records are maintained.

    2.3 subject to installation and operational qualification. Equipment qualification is documented.

Personnel

C.02.006

1. For the fabricator, packager/labeller and tester, qualified individuals in respect of the drug and GMPs should be in charge of and retained in the manufacturing department and the quality control department.

2. Personnel (including those involved in cleaning and maintenance) working in areas where radioactive materials are handled are given specific radiation safety training in accordance with other applicable Federal jurisdictions. Canadian Nuclear Safety Commission regulations and guidelines on radiation safety should be consulted.

3. Personnel have appropriate training for handling of radioactive materials.

Sanitation

C.02.007 and C.02.008

1. The sanitation program also includes procedures and practices in accordance with other applicable Federal jurisdictions. Canadian Nuclear Safety Commission regulations and guidelines on radiation safety should be consulted.

2. Environmental monitoring of the work areas includes programs addressing radioactive, microbial and particulate matter contamination.

3. Material and reagents used in the manufacture of radiopharmaceuticals as well as the exposure to the products themselves may present health hazards for employees. Consideration of these hazards is reflected in the environmental and personal protective procedures and controls. Proper personnel gowning prior to facility entry should be enforced.

4. Personnel involved in production, quality control and maintenance activities should be monitored for possible contamination and/or radiation exposure.

Raw Material Testing

C.02.009 and C.02.010

1. On arrival, packages containing radioactive raw materials (such as ^{99}Mo) are initially processed in accordance with other applicable Federal jurisdictions. Canadian Nuclear Safety Commission regulations and guidelines on radiation safety should be consulted.

2. Notwithstanding subsection C.02.009 (1), each lot or batch of raw materials containing a radionuclide where the physical half-life does not permit the completion of its tests under that subsection, may be used in the fabrication of a drug prior to the completion of its tests provided such testing is completed as soon as possible. Confirming the identity and purity of the raw materials prior to their use is the primary objective of this section. This requirement is usually a part of the premarket authorization review.

3. Non-radioactive raw materials that are manufactured in-house should have appropriate Master Production Documents including specifications, details of their method of manufacture and of the controls used to ensure their suitability for use. This requirement is usually a part of the premarket authorization review.

Manufacturing Control

C.02.011 and C.02.012

1. Checks on yields and reconciliation of quantities are carried out at appropriate stages of the process to ensure that yields are within acceptable limits for kits. Checks on yields and reconciliation of quantities do not apply to radiopharmaceuticals and radionuclide generators in cases where the radioactive components decay, with time, at a rate which makes this task unrealistic.

2. At all times during processing, all shielded containers are identified with the name of the contents and the batch or lot number.

3. In the case of a packaged radiopharmaceutical drug, the master formula also includes for each product, package size, and type, the specific activity and/or radioactive concentration (at calibration), total volume and radioactivity in the final container, and the type of shielding.

Quality Control Department

C.02.013 to C.02.015

1. The individual or authorized alternate making decisions concerning the release of a particular lot of raw material, packaging material or packaged Schedule C drug, is a person distinct from those that fabricate, package/label or sell the same lot.

2. All finished products are held in quarantine and are so identified until released by the quality control department. Where sterility and/or endotoxin testing is conducted on specific lots of short-lived radiopharmaceuticals, such lots may be released prior to completion of sterility and/or endotoxin testing, provided such testing is completed as soon as possible.

3. Radiopharmaceuticals are stored, transported and handled in strict compliance with the market authorization and other applicable Federal jurisdictions.

4. A procedure is in place describing the measures to be taken in the event that unsatisfactory/out of specification test results are obtained for batches that are released prior to complete testing. This procedure includes provisions for reporting to the proper regulatory authority by the authorized person.

Packaging Material Testing

C.02.016 and C.02.017

1. The reuse of lead shielding is permitted only after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision is made for such in the premarket authorization.

2. Compatibility studies are conducted on all materials in direct contact with the drug (for example, vials/stoppers for drugs with no-carrier-added radionuclides).

Finished Product Testing

C.02.018 and C.02.019

1. The written specifications contain a description of the drug in dosage form, which includes all properties and attributes including total radioactivity, specific activity or radioactive concentration, together with tolerances and a description of all tests or analyses used to determine those properties and attributes, in sufficient detail to permit performance by qualified personnel. Such analyses include the monitoring of generator eluate.

2. Sterility and/or endotoxin tests are conducted on batches of short-lived radiopharmaceuticals according to finished product specifications. Such batches may be released prior to completion of sterility and/or endotoxin testing, provided this overall process has been validated in advance and such testing is completed as soon as possible.

3. Batches of radiopharmaceuticals containing radionuclides of long half-life are tested for all test parameters before release, if time permits, to confirm that they meet the finished product specifications.

Records

C.02.020 to C.02.024

1. For imported Schedule C drugs, detailed summaries of marketing authorization of the current fabrication, packaging, labelling and testing procedures are maintained by the legal agent in Canada.

Samples

C.02.025 and C.02.026

1. A sample of each lot or batch of radioactive raw material used in the fabrication of a drug is retained by the fabricator of the drug for a period of three months after this lot or batch is last used in the fabrication of the drug unless otherwise specified in the fabricator's establishment licence. Conditions for specifying raw material sample retention in the fabricator's establishment licence, may be due to, but is not limited to a short physical half-life, excessively small amounts of the raw material and high radiation exposure pursuant to the retention process. These considerations would normally be addressed at the time of the premarket authorization specific to a given product upon written request and based on appropriate justification.

2. Every distributor referred to in paragraph C.01A.003(*b*) and importer of a kit retains in Canada a sample of each lot or batch of the packaged/labelled kit for a period of at least one year after the expiration date on the label of the kit unless otherwise specified in the distributor's or importer's establishment licence.

Stability

C.02.027 and C.02.028

1. The aspects of the stability program of the drug are determined prior to marketing and prior to adoption of significant changes in formulation, fabrication procedures, or packaging materials that may affect the shelf-life of the drug. Any significant change in the source of radionuclide or any packaging components will necessitate repeat assessment of the stability.

    1.1 The shelf-life of non-reconstituted kits is established from the date/time of fabrication of the kit.

    1.2 The shelf-life of radiopharmaceuticals or generators is established from the date/time of fabrication or calibration.

    1.3 The shelf-life of reconstituted kits is established from the time of radiolabelling or calibration.

    1.4 The stability protocol is designed such that data cover at least the highest specific activity, total radioactivity or radioactive concentration to be used for the preparation of the radiopharmaceutical. This design assumes that the stability of the intermediate condition samples is represented.

    1.5 The stability of reconstituted kits is demonstrated. Reconstitution is performed using the extremes of the reconstitution conditions. Tests for radiochemical purity/impurity, pH, and appearance are performed both at the time of reconstitution and at the time of expiry of the reconstituted drug. If the reconstituted drug is to be transferred to a secondary container or syringe for storage or distribution, stability and/or compatibility in that container or syringe is validated.

2. Where a drug is transferred to a second container, the stability for the storage time in that container is demonstrated. The stability is determined for the final packaged dosage form.

3. Stability data are available to support the labelled shelf-life of the product in its final container.

4. For radiopharmaceuticals supplied in multi-dose vials, stability data are available to support that multiple penetrations of the vial do not adversely affect the stability of the drug up to its labelled shelf-life.

5. These stability requirements are subject to premarket authorization.

Sterile Products

C.02.029

1. The preparation of radiopharmaceuticals can be undertaken in qualified aseptic systems such as unidirectional flow (laminar flow) cabinets or total containment glove boxes that ensure a Grade A environment.

2. Activities performed in aseptic systems/areas may include, but are not limited to:

    2.1 Aseptic addition of a sterile diluent to a sterile vial using a syringe.

    2.2 Aseptic attachments of sterile components and devices such as connecting a sterile syringe or

a sterile filter device to a sterile needle; inserting a sterile needle through a sanitized stopper into a vial; and any penetration of, or creation of an open pathway into a sealed container-closure system after filling, as might occur with some postfilling sampling techniques.

3. Air velocity in aseptic areas (for example, laminar flow hoods) is sufficient to sweep particulate matter away from the filling and closing area. Whenever possible, equipment configuration does not disrupt the laminar flow. Different areas in the fabricating process are separated by physical barriers whenever possible and may be supplemented by partial physical barriers (for example, air curtains) where needed.

4. Radiochemical synthesis and High Performance Liquid Chromatography (HPLC) purification can be performed in a hot-cell with a Grade B or C environment. The hot-cell should meet a high degree of air cleanliness with filter feed air, and is placed in a room with air classification of at least Grade C. However, all aseptic activities are carried out in a Grade A environment.

5. In cases where terminal steam sterilization is not possible or practical, due to the short physical half-life of the radionuclide involved or the thermal instability of the drug, additional measures are taken to minimize contamination. Such measures may include, but are not limited to, the use of closed systems of fabrication and sterile filtration. Such equivalence is validated and subsequent filling operations or any further operations involving the entry or opening of sterile closed containers are performed under aseptic conditions.

Appendix A

Glossary of Terms
The following additional definitions supplement the definitions provided under the Glossary of Terms in the main "GMP Guidelines (GUI-0001)".

Aseptic System - A set of equipment with related controls and procedures used to achieve a sterile environment free from contaminating organisms or particles.

Carrier - A stable element that is added, in detectable quantities, to a radionuclide of the same element, usually to facilitate processing of the radionuclide.

Component - "A unit of a drug, other than a radionuclide, separately packaged in a kit for use in the preparation of a radiopharmaceutical, or an empty vial or other accessory item in a kit ." (C.03.205)

Cross-Contamination - Contamination of a drug or raw material or in-process intermediate with another drug, raw material or in-process intermediate. In multi-product facilities, potential cross-contamination can occur throughout the manufacturing process.

Dedicated - Facility or piece of equipment used only in the fabrication of a particular product or a closely related group of products.

Drug - "A drug listed in Schedule C to the Act that is in dosage form, or a drug that is a bulk process intermediate, that can be used in the preparation of a drug listed in Schedule C to the Act that is of biological origin." (C.03.001)

Half-Life - Time during which an initial radioactivity of a radionuclide is reduced to one half.

Hot Cell - A total containment cabinet or workstation shielded with lead used for manufacturing (radiosynthesis) and/or purification of radiopharmaceuticals.

Kit - "A package that contains one or more separately packaged units of a drug, other than a radionuclide, and that may contain empty vials or other accessory items, for use in the preparation of radiopharmaceuticals." (C.03.205)

Master Formula - A document or set of documents specifying the raw materials with their quantities, their radioactivity and the packaging materials, together with a detailed description of the procedures and precautions required to fabricate a specified quantity of a finished product as well as the processing instructions, including in-process controls.

Multiple-Dose Container - Container that permits withdrawal of successive portions of the contents without changing the strength, quality or purity of the remaining portion for articles intended for parenteral use only.

No-Carrier-Added - Indicates the status of a radionuclide sample where no stable atom of the same element has been added purposely.

Pharmaceutical - "A drug other than a drug listed in Schedule C or D to the Act." (C.01A.001)

Radioactive Concentration - Amount of radioactivity per unit volume such as mCi/mL or MBq/mL.

Radioactivity - The number of disintegrations per unit of time given in Becquerel (Bq) or Curie (Ci) units.

Radiochemical Purity - The extent to which a drug is free from undesirable or adulterating radiochemicals as defined by specifications.

Radionuclide - A nuclide with an unstable or excited nucleus (imbalance of protons and neutrons) which will undergo spontaneous transformation with emissions of subatomic particles and/or photons of energy.

Radionuclide Dose Calibrator - Device measuring the radioactivity in Becquerels (Bq) or Curies (Ci), of a radioactive sample.

Radionuclide Generator - "A radioactive parent and daughter contained in an ion exchange column or dissolved in a suitable solvent in a liquid-liquid extraction system where the radioactive daughter is separated from its parent by elution from the ion exchange column, or a solvent extraction procedure." (C.03.001)

Radionuclidic Purity - The extent to which a drug radioisotope is free from undesirable or adulterating radionuclides as defined by specification expressed as a percentage of the radioactivity of the specified radionuclide to the total radioactivity of the source.

Radiopharmaceutical - "A drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons." (C.03.201)

Specific Activity - Amount of radioactivity per unit mass or per mole such as mCi/mg, MBq/mg or mCi/mole, Mbq/mole.

Total Containment Glove Box - An aseptic suite of totally enclosed environment at negative pressure, whose primary purpose is to maintain a sterile environment with the additional purpose of radioactivity workspace localization.

Total Radioactivity - Amount of radioactivity present in the total volume of a reconstituted preparation or total volume of an eluate or solution used for reconstitution/labelling purposes, expressed as mCi/total volume (mL) or MBq/total volume (mL).