Health Canada Santé Canada

Annex 3A to the Good manufacturing practices guide - Schedule C drugs (GUI-0026)

GUI-0026

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Également disponible en français sous le titre: Annexe 3A des Lignes directrices sur les bonnes pratiques de fabrication – drogues de l’annexe C (GUI-0026)

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Purpose

This document is for people who work with Schedule C drugs (radiopharmaceuticals) as:

- fabricators
- packagers
- labellers
- testers
- distributors
- importers

It is an annex to the latest version of 2 guidance documents:

- Good manufacturing practices guide for drug products (GUI-0001)
- Good manufacturing practices guidelines for active pharmaceutical ingredients (GUI-0104)

The annex will help you understand and comply with Part C, Division 2 of the *Food and Drug Regulations*. For definitions to terms used in this guide, please refer to the glossary.

Scope

This annex provides additional guidance for the manufacture and control of bulk intermediates and finished Schedule C drugs. To understand all relevant guidelines, you must read the annex together with the *Good manufacturing practices guide for drug products (GUI-0001)*.

Note: The scope does not include establishment licensing. To understand how to comply with Good Manufacturing Practices (GMP) requirements to get an establishment licence, please refer to the Guidance on drug establishment licences (GUI-0002).

Health Canada took into account the GMP principles and concepts adopted internationally for radiopharmaceuticals when developing this annex. For related international GMP guidance documents for radiopharmaceuticals, refer to the reference section.

Table 1: Applying GMP principles to radiopharmaceutical fabrication

Type of Activity	Non-GMP[1]	Subject to GMP • Good manufacturing practices guide for drug products (GUI-0001), • Good manufacturing practices guidelines for active pharmaceutical ingredients (GUI-0104), • relevant annexes Increasing GMP requirements from the first to last manufacturing steps			
Manufacturing of radiopharmaceuticals or radioactive Precursors	Reactor/cyclotron production	Chemical synthesis	Purification	Processing, formulation, and dispensing	Aseptic or final sterilization
Manufacturing of generators	Reactor/cyclotron production	Manufacturing			

[1] The target, target material and system of transfer from cyclotron may be subject to oversight under good manufacturing practices. This guidance will help clarify expectations.

Note: The fabricator of the radiopharmaceutical should describe and justify which GMP guidance is appropriate for specific process/manufacturing steps that define the manufacture of the:

- active ingredient (GUI-0104)
- finished dosage form (GUI-0001)

Note also that radiation safety requirements are also not within the scope of this annex. For more information on radiation safety, consult the Canadian Nuclear Safety Commission's (CNSC) web site and review its regulations, policies and guidance documents.

Specifically, CNSC's GD-52: Design guide for nuclear substance laboratories and nuclear medicine rooms applies to the following sections of GUI-0001:

- premises
- equipment
  - fume hood, plumbing, storage and security
- sanitation
  - handling and storage of radioactive wastes and personnel behaviour
- manufacturing control
  - procedure writing for managing rejected materials

The raw material testing section of GUI-0001 provides information on standard operating procedures for conditions of transportation. The transportation conditions should follow the recommendations of CNSC's Packaging and Transport Licensing Division.

Positron-emitting radioisotopes and radiopharmaceuticals (PERs) are beyond the scope of this annex. Because of their extremely short radioisotope half-life and shelf life, these drugs have unique manufacture and quality control requirements.

For guidance on this class of Schedule C drugs, consult:

- Annex 3B to the Good manufacturing practices guide – Positron-emitting radiopharmaceuticals (GUI-0071)

Introduction

Radiopharmaceuticals, kits and generators are listed in Schedule C to the *Food and Drugs Act* (act) and are regulated under the *Food and Drug Regulations*. The following 2 guidance documents apply to these drugs:

- Good manufacturing practices guide for drug products (GUI-0001)
- Good manufacturing practices guidelines for active pharmaceutical ingredients (GUI-0104)

Some drugs have unique properties that require additional guidelines. This annex to GUI-0001 clarifies the good manufacturing practices (GMP) that concern the manufacture of finished Schedule C drugs and bulk intermediates.

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 and biological impurities, radiopharmaceuticals may also contain radioactive (radionuclidic and radiochemical) impurities. These impurities may have a detrimental effect on the usefulness and reliability of the drug as a diagnostic agent as well as the radiation dose given to the patient.

Radiopharmaceuticals used as **therapeutic** agents require additional consideration. They contain high energy and long-lived radionuclides, which 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. In these situations, the product may need to be released before certain quality control tests are completed. For these reasons, it is important to continually assess the effectiveness of the quality assurance program for radiopharmaceuticals.

Unless otherwise stated in this annex, all interpretations included in both guidance documents (GUI-0001 and GUI-0104) apply to Schedule C drugs. To avoid repetition, only those interpretations that are in addition to (or different from) the those in these guidance documents are included in this annex.

Note about guidance documents in general

Guidance documents like this one help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff so that the regulations are enforced fairly, consistently and effectively across Canada.

Health Canada inspects establishments to assess their compliance with the *Food and Drugs Act* and associated regulations. Our inspectors will use this document as a guide to assess your compliance with GMP requirements for sterile drugs.

These guidelines are not the only way to interpret GMP regulations and do not cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for a flexible approach. Use this guide to help you develop specific approaches to meet your unique needs.

Guidance

For each of the following sections, Health Canada's interpretations of Part C, Division 2 of the *Food and Drug Regulations* (regulations) are provided. Unless otherwise noted, the following interpretations are **in addition to** those in the Good manufacturing practices guide for drug products (GUI-0001).

Premises

C.02.004

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

2. Identify facilities used for handling radioactivity and restrict access to authorized personnel involved in the process.

3. Ensure airflow patterns do not present a contamination risk, while providing the needed protection for the product during critical operations.

4. Use:

- positive pressure areas to process sterile products that are not radiolabelled
- negative pressure in specific areas at points of risk for exposure to radioactivity

5. Ensure air handling filtration units are dedicated to specific processing areas.

6. Surround the negative pressure areas or safety cabinets (such as a hot-cell and a total containment glove box) with area(s) with a positive pressure zone.

Equipment

C.02.005

1. Ensure radiopharmaceuticals and radionuclide generators are fabricated, packaged/labelled, stored and tested with equipment that 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. Ensure radioactivity measuring equipment (such as radionuclide dose calibrators and gamma counters) is available for fabrication and control operations, and that these devices are:

- shielded or located to avoid any source of background radiation
- calibrated regularly for accuracy and precision by competent personnel (maintain corresponding records)
- subject to installation and operational qualification (document the equipment qualification)

Personnel

C.02.006

1. For the fabricator, packager/labeller and tester, ensure qualified individuals (experienced with the product and GMP) are in charge of the manufacturing and quality control departments.

2. Ensure personnel working in areas where radioactive materials are handled (including those involved in cleaning and maintenance) are given specific radiation safety training in accordance with other applicable federal guidelines.

For more information on radiation safety, consult:

- Canadian Nuclear Safety Commission (CNSC) regulations and guidelines

3. Ensure personnel have appropriate training for handling radioactive materials.

Sanitation

C.02.007 and C.02.008

1. Ensure your sanitation program includes procedures and practices in accordance with other applicable federal guidelines.

For more information on radiation safety, consult:

- CNSC regulations and guidelines

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

3. Ensure that health hazards posed by material and reagents used to manufacture radiopharmaceuticals and exposure to the products themselves is reflected in your environmental and personal protective procedures and controls.

- Enforce proper personnel gowning before entering the facility

4. Monitor staff involved in production, quality control and maintenance activities for possible contamination and/or radiation exposure.

Raw material testing

C.02.009 and C.02.010

1. Ensure packages containing radioactive raw materials (such as Molybdenum 99) are initially processed on arrival in accordance with other applicable federal guidelines.

For more information on radiation safety, consult:

- CNSC regulations and guidelines

2. The main objective of subsection C.02.009 (1) is to confirm the identity and purity of raw materials before their use. However, a lot or batch of raw materials that contains a radionuclide with a short physical half-life which does not allow tests to be completed before use may be used to fabricate a drug before all tests are completed. The provision is that such testing should be completed as soon as possible.

- Usually a part of the premarket authorization review

3. Ensure that non-radioactive raw materials manufactured in-house have proper master production documents, including specifications, details of their method of manufacture and details of the controls used to ensure their suitability for use.

- Usually a part of the premarket authorization review

Manufacturing control

C.02.011 and C.02.012

1. Carry out checks on yields and reconcile quantities at appropriate stages of the process to ensure that yields are within acceptable limits.

- Does not apply to radiopharmaceuticals and radionuclide generators in cases where the radioactive components decay at a rate that makes this task unrealistic

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

3. Ensure the master formula for a packaged radiopharmaceutical drug also includes for each product, package size and type:

- specific activity and/or radioactive concentration (at calibration)
- total volume and radioactivity in the final container
- type of shielding

Quality control department

C.02.013 to C.02.015

1. Ensure the individual (or authorized alternate) making decisions about the release of a particular lot of raw material, packaging material or packaged Schedule C drug is not the person who fabricates, packages/labels or sells the same lot.

2. Hold all finished products in quarantine and identify with a quarantine status until released by the quality control department.

- Where sterility and/or endotoxin testing is conducted on specific lots of short-lived radiopharmaceuticals, you may release the lots before sterility and/or endotoxin testing is completed (to be completed as soon as possible)

3. Ensure radiopharmaceuticals are stored, transported and handled in strict compliance with the market authorization and other applicable federal guidelines.

4. Ensure 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 released before complete testing.

- Procedure must include provisions for the authorized person to report to the proper regulatory authority

Packaging material testing

C.02.016 and C.02.017

1. Conduct a full evaluation of the risks involved, including any possible deleterious effects on product integrity, before the reuse of lead shielding is allowed.

- Make sure specific provision is made for this in the premarket authorization

2. Conduct compatibility studies on all materials in direct contact with the drug.

- For example, vials and stoppers for drugs with no-carrier-added radionuclides

Finished product testing

C.02.018 and C.02.019

1. Ensure written specifications describe the drug in dosage form, including all properties and attributes (for example, total radioactivity, specific activity or radioactive concentration), together with tolerances.

- Include a description of all tests or analyses used to determine those properties and attributes (in enough detail to allow performance by qualified personnel)
- Ensure analyses include the monitoring of generator eluate

2. Conduct sterility and/or endotoxin tests on batches of short-lived radiopharmaceuticals according to finished product specifications.

- Such batches may be released before sterility and/or endotoxin testing are completed, provided:
  - the overall process has been validated in advance and
  - testing is completed as soon as possible

3. Test batches of radiopharmaceuticals containing radionuclides of long half-life for all test parameters before release (if time permits) to confirm that they meet finished product specifications.

Radiopharmaceuticals and radionuclide generators that have a useful life of no more than 30 days

1. Exemptions from confirmatory testing and identity testing apply to the packager/labeller, distributor or importer of radiopharmaceuticals and radionuclide generators that have a useful life of no more than 30 days. These exemptions apply if the packager/labeller, distributor or importer has evidence that the drug has been:

- tested against the specifications for that drug and
- transported or stored under conditions that will not adversely impact the drug's quality

2. Imported radiopharmaceuticals and radionuclide generators that have a useful life of no more than 30 days may be shipped directly to the point of use (such as nuclear medicine departments). Direct shipping facilitates access to these radiopharmaceuticals and radionuclide generators. It also minimizes the risk of potential exposure by keeping the distribution chain as lean as possible.

3. However, before importing the drug, the importer must:

- receive and review documentation that demonstrates that the drug complies with the specifications for that drug
- have measures in place to ensure that all requirements of the *Food and Drug Regulations* (regulations) for importing the drug are met

    - must identify roles and responsibilities and have appropriate quality agreements between all parties, including the foreign fabricator, importer and receiver of the product

For information on quality agreements, consult:

- Good manufacturing practices guide for drug products (GUI-0001), section C.02.012

4. The importer must release the product before it can be administered to the patient. Its release, along with certain other activities (for example, reviewing and approving specifications, shipping, storing documentation, other documentation), can be done remotely by the importer.

5. In some cases, the Canada Border Services Agency (CBSA) will refer a shipment to Health Canada to verify if the requirements for import are satisfied. We recommend that direct shipments be accompanied by the following information:

- a statement that the importer is shipping directly to the point of use and not to the importer's warehouse
- the invoice that includes the importer's drug establishment licence (DEL) number
- a copy of the importer's DEL

For more information on importing health products into Canada, consult:

- GUI-0117: Importing and exporting health products for commercial use

Records

C.02.020 to C.02.024

1. For imported Schedule C drugs, keep in Canada detailed summaries of marketing authorization for current fabrication, packaging, labelling and testing procedures.

Samples

C.02.025 and C.02.026

1. Fabricators of drugs must retain a sample of each lot or batch of radioactive raw material used to fabricate a drug for 3 months after this lot or batch is last used to fabricate the drug (unless otherwise specified on the fabricator's DEL).

- Conditions for specifying raw material sample retention requirements on the fabricator's DEL may be due to, for example, a short physical half-life, excessively small amounts of the raw material and high radiation exposure from the retention process

- These considerations should normally be addressed in a written request at the time of the premarket authorization, specific to a given product and based on appropriate justification

2. Distributors (referred to in paragraph C.01A.003(*b*)) and importers of a kit must retain in Canada a sample of each lot or batch of the packaged/labelled kit for at least 1 year after the kit label's expiration date.

- Unless otherwise specified on the distributor's or importer's DEL

Stability

C.02.027 and C.02.028

1. Generate stability data for a drug before marketing and before making significant changes in formulation, fabrication procedures or packaging materials that may affect the drug's shelf life.

2. Any significant change in the source of radionuclide or packaging components will require repeat assessment of stability.

- Establish the shelf life of non-reconstituted kits from the date/time of fabrication of the kit
- Establish the shelf life of radiopharmaceuticals or generators from the date/time of fabrication or calibration
- Establish the shelf life of reconstituted kits from the time of radiolabelling or calibration
- Ensure the stability protocol is designed so that the data cover at least the highest specific activity, total radioactivity or radioactive concentration to be used for preparing the radiopharmaceutical
    - design assumes that the stability of the intermediate condition samples is represented
- Demonstrate the stability of reconstituted kits by performing reconstitution using the extremes of reconstitution conditions and performing tests for radiochemical purity/impurity, pH and appearance, 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, validate stability and/or compatibility in that container or syringe

3. Demonstrate the stability for the storage time in the second container if a drug is transferred to a second container.

- Determine the stability for the final packaged dosage form

4. Ensure stability data are available to support the labelled shelf life of the product in its final container.

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

Note: These stability requirements are subject to premarket authorization.

Sterile products

C.02.029

1. Manufacture radiopharmaceuticals in qualified aseptic systems that ensure a Grade A environment, such as unidirectional flow (laminar flow) cabinets or total containment glove boxes.

2. Activities performed in aseptic systems/areas may include:

- aseptic addition of a sterile diluent to a sterile vial using a syringe
- 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 creating an open pathway into, a sealed container-closure system after filling, as might occur with some post-filling sampling techniques

3. Ensure 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, make sure equipment configuration does not disrupt the laminar flow
- separate different areas in the fabricating process with physical barriers whenever possible and supplement these with partial physical barriers (for example, air curtains) where needed

4. Perform radiochemical synthesis and high-performance liquid chromatography (HPLC) purification 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 be placed in a room with air classification of at least Grade C
- all aseptic activities must be carried out in a Grade A environment

5. Take additional measures to minimize contamination 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). Measures may include using closed systems of fabrication and sterile filtration.

- Validate the equivalence of these measures and ensure subsequent filling operations (or any further operations involving the entry or opening of sterile closed containers) are performed under aseptic conditions

Acronyms and abbreviations

Bq: Becquerel
Ci: Curie
CNSC: Canadian Nuclear Safety Commission
GBq: Gigabecquerel
GMP: good manufacturing practices
HPLC: high performance liquid chromatography
MBq: Megabecquerel
mCi: Millicurie
PET: positron emission tomography
PER: positron-emitting radiopharmaceutical

Definitions

These definitions explain how terms are used in this document. They apply to the terms used in this annex and may have different meanings in other contexts. Definitions quoted from other documents are identified in brackets at the end of the definition. If there is a conflict with a definition in the *Food and Drugs Act* (act) or *Food and Drug Regulations* (regulations), the definition in the act or regulations prevails.

More applicable definitions can be found in the Good manufacturing practices guide for drug products (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; 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 that is listed in Schedule C to the act that is in dosage form or a drug that is an active ingredient of biological origin that can be used in the preparation of a drug listed in that Schedule. (C.03.001)

Half-life: Time during which the 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 is intended to be used in the preparation of radiopharmaceuticals and that contains 1 or more separately packaged units of a drug, other than a radionuclide, and may contain empty vials or other accessory items. (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: A 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: An unstable atom that undergoes spontaneous transformation with emissions of subatomic particles and/or photons of energy.

Radionuclide dose calibrator: Device measuring the radioactivity of a radioactive sample in Becquerels (Bq) or Curies (Ci).

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, expressed as mCi or MBq.

References

Legislation

- *Food and Drugs Act*
- *Food and Drug Regulations*

Health Canada GMP guidance documents

- Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)
- Annex 3B to the Good manufacturing practices guide – Positron-emitting radiopharmaceuticals (GUI-0071)
- Good manufacturing practices guide for drug products (GUI-0001)
- Good manufacturing practices guidelines for active pharmaceutical ingredients (GUI-0104)
- Guidance on drug establishment licences (GUI-0002)
- Importing and exporting health products for commercial use (GUI-0117)

International guidance documents

- International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products
- Guide for good manufacturing practice for medicinal products – Annex 3 – Manufacture of radiopharmaceuticals (Pharmaceutical Inspection Cooperation Scheme (PIC/S))
- Guidelines to good manufacturing practice medicinal products for human and veterinary use: Annex 3: Manufacture of radiopharmaceuticals (European Commission)

Other related documents

- Canadian Nuclear Safety Commission (CNSC)
- GD-52: Design guide for nuclear substance laboratories and nuclear medicine rooms (CNSC)