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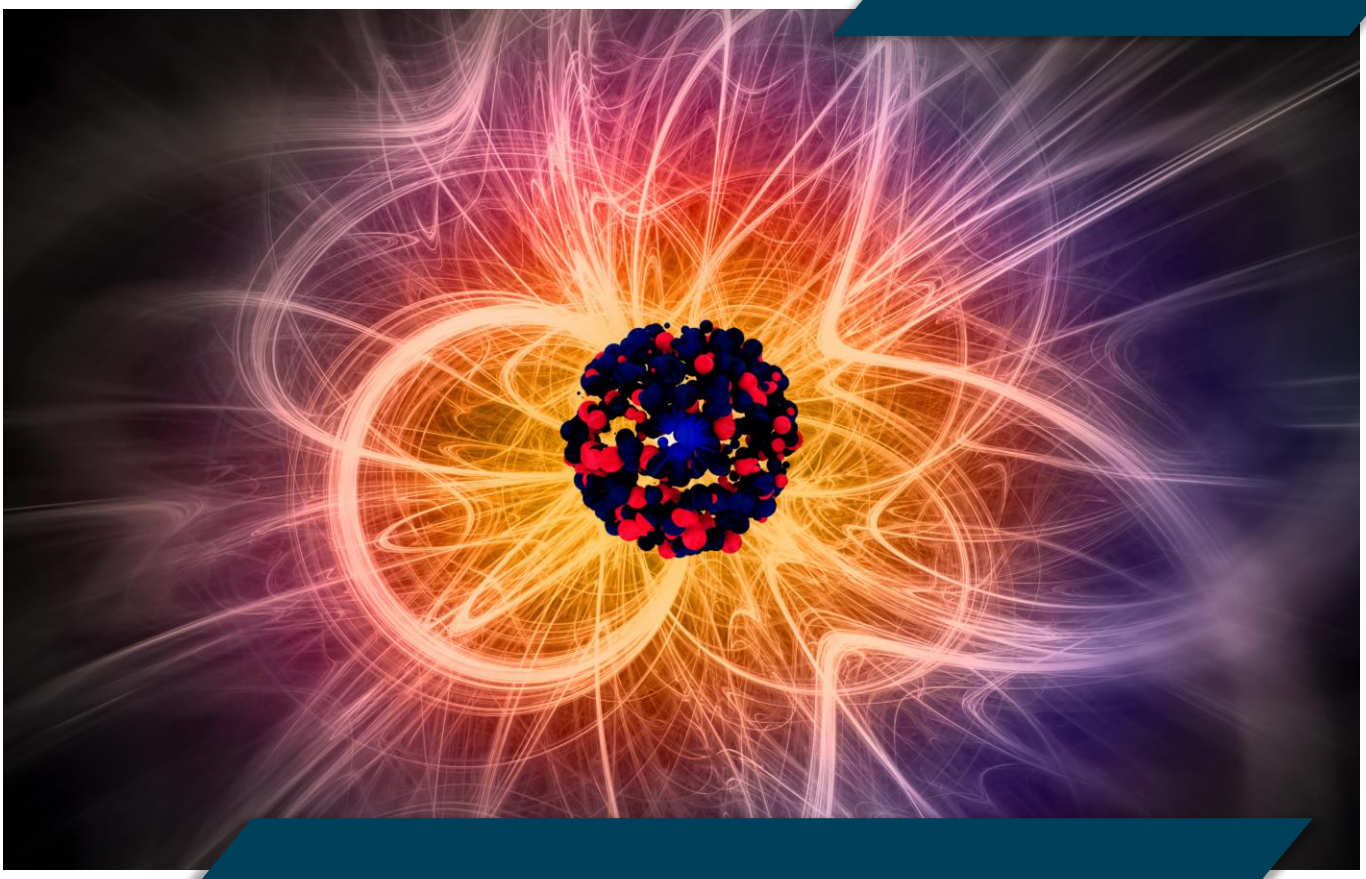
Annex 3B to the *Good manufacturing practices guide* – Positron-emitting radiopharmaceuticals



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Annexe 3B aux Lignes directrices sur les Bonnes pratiques de fabrication - Produits radiopharmaceutiques émetteurs de positrons

For more information, please contact:

Health Canada
Address Locator 0900C2, Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
Email: publications@hc-sc.gc.ca

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Disclaimer

This document does not constitute part of the *Food and Drugs Act* (the Act) or its regulations and in the event of any inconsistency or conflict between the 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.

Table of contents

The following table shows the two types of icons used in this document, and the way they are intended to be used.

Important: Key or cautionary information for people to know.

Information: Supplementary information like quotes and legal references.

About this document

1. Purpose

This document is for people who work with positron-emitting radiopharmaceuticals (PERs) as:

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

It is an annex to the latest version of the *Good manufacturing practices guide for drug products (GUI-0001)* and *Good manufacturing practices for active pharmaceutical ingredients (API) (GUI-0104)*. It will help you understand and comply with Part C, Division 2 of the Food and Drug Regulations (the Regulations). You can find definitions to terms used in this guide under Appendix A.

2. Scope

These guidelines apply to positron-emitting radiopharmaceuticals (PERs) which include positron-emitting radionuclide generators (generators).

The provisions specified in C.02.019, C.02.025, and C.02.026 of this guide do not apply to PERs for basic research or clinical trials involving human subjects. You can find more information on this in C.03.311(i) or C.05.010(j) of the Regulations. For PERs for basic research or clinical trials involving human subjects, this Guidance document should be read in conjunction with *Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines: Drugs Used in Clinical Trials (GUI-0036).* In these cases, the term "clinical trial authorization" can be used interchangeably with the term "market authorization" which has been used in this guide to facilitate readability.

The scope of this document does not include:

Establishment licensing — To understand how to comply with good manufacturing practices (GMP) to get an establishment licence, see *Guidance on Drug Establishment Licences (GUI-0002)*.

The GMP principles and concepts adopted internationally for radiopharmaceuticals and PERs were taken into account in the development of this annex. (See Appendix B – References for related international GMP guidance documents for radiopharmaceuticals.)

Table 1: Application of GMP to radiopharmaceutical fabrication

Type of Activity	Non-GMP[1]	Subject to GMP *Good manufacturing practices guide for drug products (GUI-0001)*, *Good manufacturing practices for active pharmaceutical ingredients (API) (GUI-0104)*, and relevant Annexes as appropriate with increasing GMP requirements from the first to last manufacturing steps.			
Manufacturing of PERs	Reactor/cyclotron /accelerator production	Chemical synthesis	Purification	Processing, formulation, and dispensing	Aseptic or final sterilization
Manufacturing of positron emitting radionuclide generators	Reactor/cyclotron /accelerator Production	Manufacturing			

[1] The target, target material and system of transfer from cyclotron may be subject to oversight under GMP. This guidance will help clarify expectations. In-situ cyclotron production (for example, O-15 production within the target) of an active ingredient, finished product, or intermediate thereof is subject to GMP.

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

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

Radiation safety requirements are not within the scope of this annex. For more information on radiation safety, please see the Canadian Nuclear Safety Commission (CNSC) website and review its regulations, policies and guidance documents.

For guidance on other Schedule C drugs, see: *Annex 3A to the Good manufacturing practices guide for drug products – Schedule C drugs (GUI-0026)*.

3. Introduction

Positron emitting radiopharmaceuticals (PERs) are Schedule C drugs to the *Food and Drugs Act* (the *Act*) and are regulated under Part C of the Regulations. The *Good manufacturing practices guide for drug products (GUI-0001)* and *Good manufacturing practices for active pharmaceutical ingredients (API) (GUI-0104)* apply to these drugs. But some drugs have unique properties that require additional guidance. This annex clarifies those aspects of GMP that are relevant to PERs.

PERs have unique production, quality control and handling characteristics. They are used in positron emission tomography (PET) as diagnostic agents and as tools in research. In addition to chemical impurities, the finished product may contain impurities of radioactive origin (such as radionuclidic and/or radiochemical impurities). These impurities may have a detrimental effect on the utility, quality, safety and reliability of the drug as a diagnostic agent, and possibly on the radiation dose to the patient.

Most PERs have a relatively short half-life and therefore a short shelf-life. They are often administered to patients within a short time after fabrication (production). The product may need to be released before certain quality control tests are completed, to maintain the appropriate radioactive dose regimen. For these reasons, it is vital to continually assess the effectiveness of the quality assurance program for PERs.

These guidelines interpret the requirements for GMP in Part C, Division 2 of the Regulations. They were developed by Health Canada in consultation with stakeholders.

Unless otherwise stated in this annex, all interpretations included in the *Good manufacturing practices guide for drug products (GUI-0001)* or *Good manufacturing practices for active pharmaceutical ingredients (API) (GUI-0104)* also apply.

To avoid repetition, only those interpretations that are in addition to (or different from) the ones in GUI-0001 or GUI-0104 are included in this annex.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

Health Canada inspects establishments to assess their compliance with the *Act* and associated regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to 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. For investigational or research PERs, you may wish to consider other guidance such as the United States Pharmacopeia in particular ⟨823⟩ Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses.

PER drug fabrication can be performed on a small scale such as that in provincial health care establishments. It may be important for stakeholders to note that there are no prohibitions preventing the sharing of scientific information among stakeholder groups.

Where shared information has relevance, it may be applied by more than one location to support compliance with the Regulations. There are numerous aspects where such information may help reduce individual burdens ranging from vendor qualification to justifying the allowable elapse time before a sterility test begins. Ensure such records are appropriately maintained to satisfy regulatory requirements.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. So use this guide to help you develop specific approaches that meet your unique needs.

Guidance

4. Modified interpretations

Unless otherwise noted, the following interpretations are **in addition to** those in the *Good manufacturing practices guide for drug products (GUI-0001)* or *Good manufacturing practices for active pharmaceutical ingredients (API)* (GUI-0104). Therefore the numbering does not correspond to the numbering of these guides, unless specifically noted.

Premises

C.02.004

1. Ensure PERs are fabricated, packaged/labelled, stored and quality tested in a way that prevents:
    - cross-contamination and mix-up of drugs
    - radioactivity from unwanted sources
    - residual contamination from other agents including those that may be chemical, radionuclidic, radiochemical or radiopharmaceutical

2. Identify facilities used for handling radioactivity. Restrict access to people involved in the process taking place. Although you may designate the same room or area for various purposes (such as radiochemical synthesis, quality control, packaging and storage), separate each area by a physical barrier. A line of demarcation may be appropriate where there is no risk of cross contamination.

3. Ensure airflow patterns and ventilation do not present a contamination risk for the products, but still provide the needed protection from radioactive airborne exposure to personnel during critical operations.

4. Ensure and maintain aseptic work areas for processing sterile PERs:
    a. Use positive pressure areas to process sterile products that are not radiolabeled.
    b. Use negative pressure in areas specifically designed for the containment of radioactivity.

c. Carry out production in negative pressure areas or safety cabinets (e.g. hot cell, total containment glove box, etc.), surrounded by a positive pressure zone (ensuring proper air quality requirements).

d. Dedicate air handling filtration units to specific processing areas (such as radioactive or non-radioactive). Ensure that air from any operations containing radioactivity is exhausted through appropriate filters. Check the filters routinely for efficiency. Ensure that exhausted air is not re-circulated and that air outlets are designed to avoid environmental contamination with radioactive particles or gases. Ensure that a system is in place to prevent air from entering aseptic areas if the air exhaust is not functioning. Alarms and systems need to be in place to alert of changes in air flow patterns in the event of exhaust failure.

e. Clean transfer lines in a way that ensures no contaminant is introduced into the final radiopharmaceutical product.

f. Store and sample raw materials in a separate area or containment vessel. If sampling is performed in the storage area, ensure it is conducted in a way that prevents contamination or cross-contamination. Mark all materials clearly and maintain a log sheet for each material.

Equipment

C.02.005

1. Radionuclide production target – When a positron-emitting radionuclide is produced in an in-house accelerator/cyclotron, ensure that:

    a. Targets are operated in a way that mitigates risks of product contamination by residual radionuclidic, radiochemical, or chemical contaminants. You should pay particular attention to reusable targets.

    b. Standard operating procedures (SOPs) are available that describe the responsibility for and frequency of cleaning and maintaining the target.

You are required to have knowledge about the quality of the radionuclide and potential contamination risks.

When a positron-emitting radionuclide (e.g. F-18) is obtained from an outsourced accelerator/cyclotron then appropriate agreements and other controls should be established in consideration to the quality of the radionuclide. This should include knowledge of the cleaning, maintenance, and reuse of critical equipment.

This guideline does not apply to the maintenance and operation of the cyclotron.

2. Radiosynthesis apparatus (including dedicated radiosynthesis units) – Ensure you have SOPs for the operation, maintenance and cleaning of all radiosynthesis apparatus, including dedicated radiosynthesizer units (RSUs). Before their initial use in manufacturing and production, validate the manufacturing process against the specifications for the PERs being manufactured. In particular, you must demonstrate that a sterile and pyrogen-free PER can be produced repeatedly.

   Perform the following for any RSU:

   a. Clean/flush the RSU as per the user's manual.
   b. Connect all tubing (including replacement reaction vessels, if needed), manifold/cartridges, purification columns, and final product collection vials.
   c. Ensure that monitoring and/or recording devices for various important chemical synthesis parameters (such as temperature, pressure, flow rate, time and date) are calibrated and functioning properly.
   d. Ensure that controlling computer systems and software (if applicable) are validated for the intended uses.
   e. Assemble any closed system in an environment complies with requirements in the Sterile Products section of this guide.

3. Critical components - Health care establishments that use commercially available critical components such as transfer lines, aseptic filters, and syringes used for obtaining quality control samples should pay attention to the following:

   a. Critical components are sourced from reputable suppliers in accordance with the market authorization and a written procedure. You should source critical components that are sold in compliance with the Canadian Medical Devices Regulations where possible.
   b. You should request vendors to notify you of changes in manufacturing of an item.
   c. Where available, sterile critical components should be used during nonsterile fabrication steps (e.g. sterile transfer lines prior to a sterilising filter).
   d. Each lot of critical components are subject to acceptance testing prior to a documented release for use in the fabrication of PERs:
      i. You should ensure that each lot received complies with current specifications and the market authorization. A certificate of analysis should be available.
      ii. Ensure that identity is confirmed prior to use. You may use visual

identification where appropriate.

iii. Ensure that critical components are stored under appropriate conditions.

e. You can use commercially available pre-sterilized sterilizing grade filters specified in your market authorization.

f. You should consider the use of disposable critical components. SOPs are available that describe the responsibility for and frequency of cleaning and maintaining of critical components.

g. Changes in the supply or specification of a critical component are subject to change control processes.

4. Ensure PERs are fabricated, packaged, stored and tested with equipment that does not contribute to the cross-contamination of drugs with unwanted sources including those that are radionuclidic, radiochemical, and chemical in nature.

5. Shield or locate radioactivity-measuring equipment so as to avoid any source of background radiation.

6. Calibrate all equipment regularly for accuracy, precision and reproducibility. Maintain corresponding records.

7. Ensure critical equipment undergoes design, installation, operational and performance qualification. Document results.

Personnel

C.02.006

1. In a PERs manufacturing establishment (regardless of whether it is a hospital, centralized radiopharmacy, nuclear centre or institution, industrial manufacturer, or contract manufacturer), there must be a head of the establishment who is a professionally qualified person with knowledge in PERs and PET. It is reasonable to expect that this person's qualifications include experience in radiopharmaceutical sciences and/or nuclear medicine.

2. For the fabricator, packager/labeller and tester, you must have qualified individuals in PERs manufacturing and quality control.

3. You must have a minimum of two qualified people involved to support production and quality control of PERs. The person responsible for production must have adequate education in radiochemistry, including specialized training in PET chemistry and

experience in the manufacturing of PERs. The person responsible for quality control and batch release must have specialized knowledge, education and experience/training in the quality control of PERs and radiopharmaceuticals. At health care establishments involved in basic research or clinical trial drug fabrication, for more efficient management, outsourced quality control support may be considered with an appropriate rationale.

4. Ensure personnel working in areas where radioactive materials are handled are given specific safety training in accordance with other applicable federal guidelines. See the Canadian Nuclear Safety Commission (CNSC) regulations and guidelines on radiation safety for more information.

Sanitation

C.02.007 and C.02.008

1. Your sanitation program must include procedures and practices in accordance with other applicable federal regulations. See the CNSC regulations and guidelines on radiation safety for more information.

2. You must use specialized disposal systems for radioactive effluents in accordance with other applicable federal regulations. See the CNSC regulations and guidelines on radiation safety for more information.

3. You must validate cleaning procedures for manufacturing equipment to mitigate contamination risks (e.g. radionuclidic, radiochemical, chemical, and microbial). You should consider:

    a. sterilizing or depyrogenating certain equipment used in non-sterile production processes (e.g. transfer lines prior to sterile filtration and reusable manifolds)

    b. cleaning reusable transfer lines to minimize microbial contamination with organic solvents after use, rinsing with water for injection, flushing with a volatile solvent, and drying under an inert gas

Raw material testing

C.02.009 and C.02.010

Interpretations in section C.02.009 of GUI-0001 not applicable are those that specify requirements for:

- establishing an impurity profile for each API based on the marketing authorization (Interpretation 8)
- testing a representative sample of each lot of raw material fully against specifications, using a statistically valid plan (Interpretation 9)

1. Maintain detailed approved specifications (including the source, origin and—where applicable—method of manufacture, test data, suitable storage conditions and expiry dates) for all materials and components. This includes starting materials and/or precursor used in the production of PERs. This is to ensure their suitability for use in production or testing.

2. When you have a vendor qualification program and the vendor is qualified, you can rely on a certificate of analysis or quality testing data provided from the supplier to satisfy testing requirements. If these are not available or if the material is produced in-house, the PER manufacturing facility is responsible for testing to full specifications of the material.

For health care establishment manufacturing of PERs using an automated RSU, raw material testing obligations under C.02.009 and C.02.010 may be considered reasonably satisfied when the raw material (e.g. USP Sterile Water for Injection or USP 0.9% Sodium Chloride) has been obtained as a drug in dosage form on the Canadian market in compliance with the Regulations (e.g. labelled with a Drug Identification Number). The use of the drug in dosage form must be appropriate for the intended purpose and in accordance with market authorization for the manufacture of the PERs drug.

Appropriate documentation should be retained to provide evidence of the marketing authorization (e.g. package insert).

3. Depending on the state of vendor qualification, you may need to do acceptance testing for the target material or other critical materials if there is a potential impact on the quality of the final PER product.

4. Document any recycling method of O-18 water. Ensure acceptance criteria and specifications are well defined and met.

5. On arrival, ensure packages containing radioactive materials—such as off-site PER radionuclides (e.g. F-18, Ga-68, or I-124)—are initially processed in accordance with other applicable federal guidelines. See the CNSC regulations and guidelines on radiation safety for more information.

6. The PER manufacturing facility must establish the reliability of the supplier of critical materials (i.e. radionuclide, target material, precursor) by performing full testing against supplier specifications for the first three lots and having a vendor certification program in place. This reliability may be established on a concurrent basis at the time each lot is received. The vendor certification should include a written evaluation of evidence that the supplier can consistently provide material meeting the specifications. Confirmatory testing of critical materials should be performed at appropriate interval thereafter:
    a. radionuclide, annual or when target material has changed
    b. target material and precursor, annually

7. You must confirm the identity of raw materials before their use. Consider requirements to perform identity testing on each container (Interpretation 11) under C.02.009 in GUI-0001. Justify your approach to confirming identity of raw materials. With a validated procedure, you may apply other approaches to confirm the identity of raw materials containing a radionuclide where the physical half-life does not permit the completion of its tests.

8. For health care establishment based manufacturing using commercially available kits, you may consider the application of unique identifiers to confirm identity of precursors that are part of a kit for a commercially available RSU from qualified suppliers as permitted in your marketing authorization. You should qualify your suppliers by:
    a. initially confirming the identity of precursors before their use – usually part of a pre-approval authorization
    b. establishing mechanisms that allow for monitoring of precursors

Manufacturing control

C.02.011 and C.02.012

Interpretations in section C.02.011 in GUI-0001 not applicable are those that specify requirements for:

- ensuring processing operations are covered by a manufacturing master formula (Interpretation 26)
- writing the manufacturing master formula to provide not less than 100% of label claim (Interpretation 27)
- ensuring the packaging master formula also includes the package size expressed in terms of the number, weight or volume of the product in the final container (Interpretation 29d)
- requiring the name and batch number of the product being handled at each packaging station or line (Interpretation 39) when dedicated equipment is used to produce limited quantities

Manufacturing control is required to:

- Ensure consistent production of PERs drugs that comply with their established specifications for quality
- ensure proper labelling and prevent mix-ups
- ensure proper cleaning and sterility (since critical testing may be done retrospectively)
- prevent contamination

The following are guidelines for ensuring the above criteria:

1. Ensure your master production document includes (but is not limited to):
    a. each major production step
    b. critical process control parameters
    c. in-process controls
    d. weights of raw materials or precursors (where applicable)
    e. identification of radionuclides
    f. codes of components used
    g. identification of major equipment

h. packaging and labelling processes

2. In the case of a packaged drug, ensure the master formula also includes for each product (where applicable):
    a. package size and type
    b. the range of radioactivity
    c. concentration in the final container
    d. the type of radionuclide and shielding
3. At all times during processing, ensure shielded containers are identified with the name of the contents and the batch or lot number.
4. You must test the membrane filter used for the sterile filtration of the final product for filter integrity. Where permitted in marketing authorisation, you may consider refiltration (i.e. reprocess) if filter integrity does not meet specifications.
5. Validate computer systems used in the production of PERs with a production run, to demonstrate that they function as intended. You must re-validate changes to the computer system, including software upgrades.
6. Ensure an effective recall system is in place. The purpose of a recall system is to prevent the use of a PER product (rather than to retrieve it), since the return of a PER is not practical due to the radioactive nature of the product. However, in the event a sample is returned, you must ensure federal guidelines for transportation are followed. See the CNSC regulations and guidelines on radiation safety for more information.
7. In your recall system, ensure the chain of distribution for each batch of PER drug product can be readily determined to allow its recall if needed. A recall should consist of notifying Health Canada, the receiving facility, the radiopharmacist, and the patient's health care professional (if known). When the receiving facility disposes of the recalled drug, the PER drug producer should obtain a notification from the receiving facility confirming the recalled drug has been disposed of and describing the manner in which it was disposed.
8. In the event that an out-of-specification (OOS) product was administered to a patient — as may occur when results for certain tests can only be obtained after administration — you must report it to Health Canada as a recall.

For PERs produced by a health care establishment, the following are not considered to be outsourced activities requiring quality agreements where due diligence is applied in sourcing:

- Manufacture of commercially available RSU kits or components in the RSU kits (e.g. pre-sterilization of primary packaging material) when used in accordance with marketing authorization.
- Manufacture of pre-sterilized primary packaging material when used in accordance with marketing authorization.
- Manufacture of pre-sterilized syringes when used in accordance with marketing authorization and sold in compliance with the Canadian Medical Devices Regulations.

Quality control department

C.02.013 to C.02.015

Interpretations in section C.02.015 in GUI-0001 not applicable are those that specify requirements for:

- the person in charge of the quality control department to meet requirements described under C.02.006 Personnel when signing and dating decisions (Interpretation 1).

1. Ensure your quality control department is responsible for authorized decision-making about the release of a particular lot of raw material, packaging material or finished PERs.

2. Ensure that the person responsible for the release of product is a distinct person from the person(s) who fabricate, package/label or sell the same lot.

3. You should have a system in place to ensure that all finished products in quarantine (on-site or in transit) are identified accordingly and the receiving sites are aware of the release by your quality control department. If sterility and/or endotoxin testing is conducted on specific lots of PERs, those lots may be released before completion of sterility and/or endotoxin testing, provided such testing is validated beforehand and is completed as soon as possible.

4. Ensure PERs are stored, transported and handled in strict compliance with the market authorization and CNSC regulations.

5. Reject products that fail to meet acceptance criteria. Reprocessing is not allowed unless it has been defined in the marketing authorization.

6. You should have a procedure that describes the measures to be taken by your quality control department if unsatisfactory (out-of-specification) test results occur after product release. Investigate such events and document the corrective and preventive actions that should be taken to prevent future events.

Packaging material testing

C.02.016 and C.02.017

1. For products produced with an automated RSU by health care establishments, you may rely on testing described on certificates of analysis and/or quality testing data from vendors supplying packaging materials that are:
    a. part of a commercially available RSU kit that is used in accordance with marketing authorization, or
    b. sourced in a manner that complies with marketing authorization

2. You may only reuse lead shielding in generators after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision must have been made for this in your pre-market authorization.

3. Conduct compatibility and stability studies on all materials in direct contact with the PER drug product (such as vials and stoppers), as well as sterile filters, tubing, and so on for generators.

For products produced with an automated RSU by health care establishments, an establishment licence that lists the building where primary packaging material has been sterilized is not necessary for vendors supplying packaging materials that are:

- part of a commercially available RSU kit that is used in accordance with marketing authorization, or
- sourced in a manner that complies with marketing authorization

Finished product testing

C.02.018 and C.02.019

Interpretations in section C.02.019 of GUI-0001 not applicable are those that specify requirements for:

- confirmation of identity after the lot or batch is packaged (Interpretation 1)
- positive identification on a sample of each lot or batch in a drug shipment after you receive it on your site, as a packager/labeller or importer (Interpretation 6)

Because the production method for some PERs may vary in different manufacturing facilities, the testing for the final product may also vary. In general, use the following guidelines:

1. Include a description of the drug in dosage form in your written specifications. This may include (but is not limited to):
    a. total radioactivity
    b. specific activity or radioactive concentration
    c. radiochemical purity
    d. pH
    e. osmolality
    f. radionuclidic purity
    g. catalyst
    h. residual solvents

    Your description should also include tolerances and a description of all test methods or analyses used to determine those properties and attributes, in enough detail to allow analysis by qualified personnel. Such analyses should include the monitoring of generator eluate for purity, radioactivity, radioactive concentration and appearance.

2. Due to the short half-life of most radionuclides and the short shelf-life of most PERs, product release tests are typically based (in real time) on a limited number of tests. The remaining tests are performed on a retrospective basis. In order to determine which tests are done on a retrospective basis, you should prepare and document a rationale. Also, you must have a system in place to ensure the product is not used until it has been released by your quality control department.

3. You may ship finished radiopharmaceutical products under approved conditions allowed by the marketing authorization before appropriate testing is complete, as long as the product is not administered by the receiving site until satisfactory test results have been received and assessed by a designated person.

4. Conduct sterility and endotoxin tests on all batches of PERs according to finished product specifications.

    a. Perform Endotoxin testing prior to release, when possible. You should use an approved rapid limulus amebocyte lysate (LAL) test method whenever possible.

    b. Release batches before sterility and/or endotoxin testing is complete only when the overall process has been validated in advance and testing is completed as soon as possible.

    c. Begin sterility testing within 30 hours after completing sterile production unless a rationale is available supported by scientific evidence and as specified in your marketing authorization.

    d. Do not pool sterility samples unless a scientific rationale is available to support pooling.

    e. For products produced with an automated RSU by health care establishments, you may consider testing only the first batch prepared each day for that drug if you have established a history of successful sterility tests.

Records

C.02.020 to C.02.024.1

1. Maintenance of batch records at the PER manufacturing facility is important for all PER products, as most of them are released with retrospective testing. Ensure batch record information includes the following:

    a. list of tests that are performed before release

    b. list of tests that are performed retrospectively

    c. results of all the test parameters (as per product specification)

    d. record of any deviations and additional testing (if any)

    e. record of total amount of radioactivity per batch at the end of synthesis and at calibration time

    f. total volume per batch

    g. specific activity and/or radioactive concentration at calibration time

2. For PERs imported into Canada, the legal agent in Canada must maintain detailed summaries of marketing authorization for the current fabrication, packaging, labelling and testing procedures.

3. For PER radionuclides, the PET facility that acquires the radionuclide—either from within Canada or from a country outside of Canada—must maintain detailed information on the amounts received, used in fabrication, and disposed of.

Samples

C.02.025 and C.02.026

Interpretations in section C.02.025 of GUI-0001 not applicable are those that specify a requirement for:

- Retention in Canada a sample of each lot or batch of a finished product if you are a distributor (as described in paragraph C.01A.003(b)) or an importer of a drug (Interpretation 1)

1. Samples of radioactive raw material are not required.

2. The fabricator of a drug must retain a sample of each lot or batch of non-radioactive raw material used in the fabrication of that drug for a period of six months beyond the expiry of any finished product in which the lot or batch used (unless otherwise specified in the fabricator's establishment licence and as per the marketing authorization). Acceptable rationale for not retaining samples may include short shelf-life or extremely small amounts of raw material. These considerations should normally be addressed before market authorization, specific to a given product, upon written request, based on appropriate justification, and identified on your establishment licence.

3. Retain a sample of the final product for a minimum of six months beyond the shelf life of the drug unless otherwise justified through risk management. This retention period should be identified on your establishment licence.

Stability

C.02.027 and C.02.028

For PER drugs with a shelf life of less than 30 days, the interpretations provided under C.02.027 and C.02.028 of GUI-0001 do not apply. However, you must ensure stability studies and a continuing program are carried out on the drug in each package type in which it is to be sold in Canada.

1. Ensure all aspects of the stability program for a drug are determined before marketing and before adopting significant changes in formulation, fabrication procedures, or packaging materials that may affect the shelf-life of the drug. Any significant change in the radionuclide or any packaging components in direct contact with the product require repeat assessment of stability. You can find more information about what changes required additionally stability data in Health Canada's *Post-Notice of Compliance (NOC) Changes – Quality Guidance*.

2. Follow these guidelines for stability assessment:

    a. State the shelf-life based on the time and date of fabrication of the drug.

    b. Design the stability study so that the data cover at least the worst case scenario that is used for the acceptance of the PER drug product as per specification (such as the highest specific activity, total radioactivity, or radioactive concentration to total volume).

    c. Include in your stability testing a determination of the stopper and vial compatibility with the PER drug product (when in direct contact).

    d. Ensure stability testing addresses the situation of shipping conditions such as with exposure to extremes of temperature or other transport conditions that could affect quality, integrity of the products. When no testing for product quality will be performed by the receiving site (for example, by clinical nuclear medicine facilities), stability during shipping should be validated.

3. Perform stability studies at well-defined temperatures and humidity (as appropriate), and on at least three consecutive batches. Analyze appropriate parameters to establish the stability of the PER under the proposed conditions. The test parameters used in the stability study may include radiochemical purity, appearance, pH, sterility and endotoxin determination.

4. If a drug is transferred to a second container, demonstrate the stability for the storage time in that container. Determine also the stability for the final packaged dosage form.

5. Perform ongoing stability once a year or after any major change to the process (e.g. changes to synthesis process, vial and closure, target, etc.).

Sterile products

C.02.029

Unless otherwise specified in this section, you can find more information about sterile manufacturing in Health Canada's *Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119).*

1. You should maintain an appropriate level of environmental cleanliness for the type of operation being performed. In the case of closed and automated systems — chemical synthesis, purification, on-line sterile filtration — you can use a Grade C environment (usually a hot-cell). You should perform radiochemical synthesis and high performance liquid chromatography (HPLC) purification in a hot-cell.

2. Perform aseptic activities in aseptic systems/areas (Grade A) within a Grade B background environment. These include:
    a. aseptic addition of a sterile diluent to a sterile vial using a syringe
    b. assembly of product vials, i.e. aseptic attachment 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 post-filling sampling techniques)
    c. sampling for final product testing and partitioning of bulk PER into separate sterile primary packaging materials (e.g. vials) before release
    d. assembly of closed RSU manifolds and components of open systems
    e. sterility testing

Alternative environmental conditions can be acceptable when justified using quality risk management principles.

For products produced with an automated RSU that have a 12 hour expiry or less a Grade C/D background environment (i.e. ISO 8 under dynamic conditions) to a critical area is required as a minimum.

You must transfer components assembled in critical areas using a technique that maintains the required environmental classification to minimize the microbial contamination or ingress (e.g. sterile product vial assembly containing sterile filter and vent filter transferred to the hot cell in a sealed sterile pouch).

3. When possible, terminally sterilize the product. It is recognized that terminal steam sterilization is not possible or practical for some PERs due to the short physical half-life of the radionuclide involved and/or the thermal instability of the product. In these cases you should take additional measures to minimize contamination, such as the use of closed systems of fabrication and sterile filtration. Validate the equivalence of these measures. Perform subsequent filling operations or any further operations involving the entry or opening of sterile closed containers under aseptic conditions.

4. In cases where there are safety and contamination issues, you do not need to verify filter integrity before filtration. But you should have data from the filter manufacturer showing that the product and vent filters are supplied pre-assembled and individually integrity tested by the filter manufacturer. And you must conduct post-filtration filter integrity testing of the product filter.

5. The sterilizing filtration should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent. For products produced with an automated RSU, quality risk management principles may be applied to limit this to an appropriate post processing filter integrity test when using:
    a. a commercially available sterile filter in accordance with marketing authorization, and
    b. an appropriately qualified vendor.

6. You may apply quality risk management principles to determine the appropriate pressure differences, air flow direction and air quality. Ensure air velocity in aseptic areas (for example: biological safety cabinet) is sufficient to sweep particulate matter away from the filling and closing area. Whenever possible, ensure equipment configuration does not disrupt the unidirectional flow. Separate different areas in the fabricating process by physical barriers whenever possible. Supplement by partial physical barriers (for example: air curtains) where needed.

7. Ensure PERs comply with the test for sterility unless process parametric release is authorized. Even if process validation data (routine media fills using sterile media) demonstrate the facility's control of the overall aseptic fill operations, you still need to perform sterility tests on finished products. For more information on sterility testing,

refer to interpretation 4 under Finished Product Testing C.02.018 and C.02.019.

You can find more information about process parametric release in Health Canada's *Annex 17, Parametric Release - Guide to Good Manufacturing Practice for Medicinal Products Annexes.*

8. Use quality risk management principles in developing and implementing a program to regularly monitor for viable and non-viable particulates. For products produced with an automated RSU a recommendation is detailed in tables 2 and 3 below.

9. Each person performing aseptic procedures must be qualified by successfully performing process simulation tests (i.e. media fills). For health care establishment based sterile fabrication of PERs, you are recommended to ensure operators perform 3 initial process simulation tests on 3 separate days. Requalification should be performed at least annually thereafter.

10. When fabricating product with an automated RSU using hot cells and biologic safety cabinets that provide a Grade A environment for critical processes, gowning should at a minimum consist of:
    a. a clean laboratory coat, dedicated shoes and shoes covers
    b. sterile forearm sleeves when exposed in grade A environment
    c. hair cover
    d. beard/moustache covers as appropriate
    e. sanitized gloves that cover the wrist
    f. sterile gloves when working in the grade A area and performing critical processes

Table 2: Viable Environmental Monitoring[1]

Grade	Monitoring frequency
A	Perform monitoring using a program that has been developed using quality risk management principles that may include: • using settling plates to monitor critical areas during critical processes (e.g. aseptic assembly, aseptic connections, filtration, withdrawal of endotoxin and sterility samples, dispensing) • monitoring critical surfaces along with personnel glove prints daily at the end of critical processes if there is no risk of exposure

Table 2: Viable Environmental Monitoring[1]

Grade	Monitoring frequency
	• performing daily volumetric air sampling in critical areas prior to and at the end of manufacturing if there is no risk of exposure — you may reduce the frequency if justified based on scientific rationale and supported with historical data
Other	Perform periodic[2] monitoring using a program that has been developed using quality risk management principles that may include: • monthly settling plates of pre-determined locations with consideration to sampling during both at rest and in operation state • monthly contact plates of pre-determined locations with consideration to sampling during both at rest and in operation state • semi-annual viable particle air sampling performed at pre-determined locations throughout the laboratory with consideration to sampling during both at rest and in operation state

[1] This is an example based on fabrication using an automated RSU with aseptic assembly, sterile filtration, collection of QC samples, and dispensing performed under Grade A conditions. This recommendation may not be appropriate for all cases such as manual synthesis processes, fabrication of generators, or fabrication of C-11 and I-124 products. For all other cases refer to *Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)*.

[2] The term periodic has been used to allow for flexibility based on good scientific rationale.

Table 3: Non-viable Environmental Monitoring[1]

Grade	Monitoring frequency
A	Perform monitoring for non-viable particles using a program that has been developed using quality risk management principles that may include: • daily monitoring in critical areas prior to manufacturing and end of manufacturing

Table 3: Non-viable Environmental Monitoring[1]

Grade	Monitoring frequency
	Note: A reduction in frequency may be justified based on scientific rationale and supported with historical data
Other	Perform monitoring for non-viable particles using a program that has been developed using quality risk management principles that may include: • periodic[2] monitoring in non-critical areas

[1] This is an example based on fabrication using an automated RSU with aseptic assembly, sterile filtration, collection of QC samples, and dispensing performed under Grade A conditions. This recommendation may not be appropriate for all cases such as manual synthesis processes, fabrication of generators, or fabrication of C-11 and I-124 products. For all other cases refer to *Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)*.

[2] The term periodic has been used to allow for flexibility based on good scientific rationale.

Appendices

Appendix A – Glossary

Abbreviations and acronyms

Bq	Becquerel
Ci	Curie
CNSC	Canadian Nuclear Safety Commission
GBq	Gigabecquerel
GMP	Good manufacturing practices
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation
ISO	International Organization for Standardization
LAL	Limulus amebocyte lysate
MBq	Megabecquerel
mCi	Millicurie
NOC	Notice of Compliance
OOS	Out of Specification
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PET	Positron emission tomography
PER	Positron-emitting radiopharmaceutical
RSU	Radiosynthesizer unit
SOPs	Standard operating procedures

TGA	Australian Therapeutic Goods Administration
USP	United States Pharmacopeia

Terms

These definitions explain how terms are used in this document. They supplement the definitions provided in the *Good manufacturing practices guide for drug products (GUI-0001)*. They apply to the terms used in this Annex, and may have different meanings in other contexts.

If there is a conflict with a definition in the *Act* or the Regulations, the definition in the Act/Regulations prevails.

Accelerator – A device to accelerate energetic charged particles linearly or in circular paths by means of a radiofrequency field and an electromagnetic field in case of cyclotrons. The accelerated particles cause nuclear reactions in the atoms of targets placed in their path.

Batch – A defined quantity of final product produced in one production run often expressed either in mass (mg or g) or volume (mL or L) or total radioactivity (Ci or GBq), total number of vials or doses.

Calibration – The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. (International Council for Harmonisation (ICH) Q7)

Campaign production – Manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure. (TGA, Q&As)

Carrier – A stable element present with a radionuclide of the same element.

Catalyst – A substance usually used in small amounts relative to the reactants that modifies and increases the rate of a reaction without being consumed in the process.

Closed system – Closed system means that there is no opening or exposure of the product or the system to the environment. When the assembly of the Radiosynthesizer unit (RSU) and the connection to the filter/vial are completed, the system is considered closed.

Cross-contamination – Contamination of a drug or a radionuclide or a raw material or in-process intermediate with another drug, radionuclide, raw material or in-process intermediate. In multiproduct 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 – drug means 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 decays to one half.

Health care establishments - Establishments supplying medicinal products to their own patients in line with national legislation. (Pharmaceutical Inspection Co-operation Scheme (PIC/S))

Note: This may include facilities providing outsourced services to health care establishments.

Hot cell – Shielded workstations for manufacture and handling of radioactive materials. Hot-cells are not necessarily designed as an isolator. (PIC/S)

Manifold – A unit for connecting a cylindrical pipe fitting, having a number of lateral outlets, for connecting one pipe with several others used in the Radiosynthesizer Unit.

Master production document – A document or set of documents specifying 1) the raw materials with their quantities, their radioactivity and the packaging materials, 2) a detailed description of the procedures and precautions required to fabricate a specified quantity of a finished product, and 3) the processing instructions, including in-process controls.

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

Positron-emitting radiopharmaceutical (PER) – Drugs labelled with positron emitting radionuclides or containing positron emitting radionuclides that exhibit spontaneous transformation of unstable nuclei through positron decay.

Precursor – A chemical substance or molecule which exists as an ingredient, reactant, or intermediate that is used for the chemical or radiochemical synthesis of a particular desired end product.

Radioactive concentration – Amount of radioactivity per unit volume such as mCi/mL or MBq/mL.

Radioactivity – Spontaneous decay of unstable nuclei and is quantified as the number of disintegrations per unit of time as 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 is free from undesirable or adulterating radionuclides (as defined by a specification), expressed as a percentage of the radioactivity of the specified radionuclide to the total radioactivity of the source.

Radiosynthesizer unit (RSU) – A closed-system device for the synthesis of radioactive drug substances used in the manufacturing of PERs. The system may be controlled by graphical computer software programs.

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).

Starting material – Any substance entering a production facility for use in the production of a drug product.

Target material – A chemical substance which is bombarded with nuclear particles to produce a desired radionuclide.

Total containment glove box – A totally enclosed environment at negative pressure, whose primary purpose is 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.

Appendix B – References

Canada

Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)
canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-annex-1-manufacture-sterile-drugs-0119.html

Annex 3A to the Good manufacturing practices guide for drug products – Schedule C drugs (GUI-0026)
canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/annex-3-current-edition-guidelines-schedule-drugs-0026.html

Canadian Nuclear Safety Commission (CNSC)
nuclearsafety.gc.ca/eng/

Food and Drug Regulations
laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

Food and Drugs Act
laws-lois.justice.gc.ca/eng/acts/F-27/index.html

Good manufacturing practices guide for drug products (GUI-0001)
canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html

Good manufacturing practices for active pharmaceutical ingredients (API) (GUI-0104)
canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/guidelines-active-pharmaceutical-ingredients-0104.html

Guidance on Drug Establishment Licences (GUI-0002)
canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/guidance-drug-establishment-licences-drug-establishment-licensing-fees-0002.html

Other jurisdictions

World Health Organization (WHO) *Annex 3: Guidelines on Good Manufacturing Practices for Radiopharmaceutical Products*
who.int/medicines/areas/quality_safety/quality_assurance/GMPRadiopharmaceuticalProductsTRS908Annex3.pdf

United States Food and Drug Administration Guidance*: PET Drug Products – Current Good Manufacturing Practice (cGMP)*
fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf

Pharmaceutical Inspection Cooperation Scheme (PIC/S) *Guide for Good Manufacturing Practice for Medicinal Products – Annex 3 – Manufacture of Radiopharmaceutical*s
picscheme.org/en/publications?tri=gmp

United States Pharmacopeia in particular ⟨823⟩ *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses*

European Commission *Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use: Annex 3: Manufacture of Radiopharmaceuticals*
ec.europa.eu/health/files/eudralex/vol-4/2008_09_annex3_en.pdf