

Annex 2

International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products

Acknowledgements

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1. Scope

This guideline provides a general overview of the minimum good manufacturing practices (GMP) requirements for radiopharmaceutical products. The main principles of GMP are described in detail in the WHO guidelines related to pharmaceutical products (1, 2), as well as in those for sterile pharmaceutical products (3).

The procedures necessary to manufacture, prepare and control radiopharmaceutical products are in large part determined by the nature of these products, the methods of manufacture and their intended use. The recommendations in this guideline are applicable to:

- the production, preparation or compounding of radiopharmaceuticals in hospital radiopharmacies, including diagnostic and therapeutic products;
- the production or compounding of radiopharmaceuticals in centralized radiopharmacies;
- the production or compounding of radiopharmaceuticals in nuclear centres and institutes;
- the production of radiopharmaceuticals by industrial manufacturers; and
- the production of cyclotron-based radiopharmaceuticals.

The scope of this guidance does not include:

- radiopharmaceutical dispensing (i.e. the drawing of a patient's specific unit dose from a bulk vial of a radiopharmaceutical product);
- regulatory authority-approved radiopharmaceutical preparation (i.e. the use of approved kits and approved generators in order to produce a radiopharmaceutical product as per instructions of the marketing authorization holder);
- handling of ready-to-administer radiopharmaceutical products (e.g. receipt, storage, assay, etc.);
- production or compounding of non-radioactive compounds, including cold kits; or
- production of investigational radiopharmaceutical products.

2. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

“as low as reasonably achievable”. ALARA is an acronym standing for “as low as reasonably achievable”, used to define the principle of underlying optimization of radiation protection. This is practised based on the principles of time, distance and shielding, as well as an emphasis on creating adequate awareness among all stakeholders.

dispensing. The generation of a patient-specific unit dose, which involves physical withdrawal of the radiopharmaceutical from the bulk single-use or multidose vial into a syringe; dilution with an appropriate diluent as necessary; measurement of the radioactivity content; and labelling of the syringe.

good manufacturing practices for radiopharmaceutical products. Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use, and designed to consistently yield the radiopharmaceutical product. GMP fall under the umbrella of the overall quality management system (QMS).

manufacturing or production. Within the scope of this guidance, these terms refer to all the operations performed leading up to the finished radiopharmaceutical product, including the purchase of starting materials, production, quality control, release and storage of radiopharmaceuticals.

preparation or kit-reconstitution. Within the scope of this guidance, preparation or kit-reconstitution refers to all the procedures carried out as per instructions from a marketing authorization holder, which involves the addition of radionuclide solution approved by regulatory authorities to an approved cold kit.

primary packaging. Any packaging material that comes into direct contact with the finished radiopharmaceutical product (i.e. an immediate container, such as a vial or a syringe).

quality control. A set of analytical tests designed to demonstrate compliance of the quality of starting materials, intermediates and final radiopharmaceutical products with predetermined specifications for quality acceptance.

quality management system. An appropriate system encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will satisfy the given requirements for quality.

radiopharmaceutical compounding. This term refers to producing radiopharmaceuticals with no marketing authorization but pursuant to the order for a specific patient or patients from a physician certified/qualified for practice of nuclear medicine. In various regions of the world, this practice may also be referred to as “in-house preparation”, “in-house-manufacturing” or “hospital preparation”.

radiopharmaceutical product. Any pharmaceutical product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medicinal purposes.

secondary packaging. The shielded container housing the primary packaging.

3. Quality management system

- 3.1 There should be a quality management system (QMS) that covers the organizational structure, job descriptions, procedures, processes, resources and actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will consistently yield a product of intended quality.
- 3.2 Principles of risk management should be applied in the establishment, implementation and management of the QMS and GMP.
- 3.3 Risk assessment should include a thorough identification and evaluation of all possible risks associated with the manufacturing process, and controls should be identified in order to minimize those risks to an acceptable level.
- 3.4 Risk assessment and risk controls should be commensurate with the complexity of the risk identified. Because radiopharmaceuticals are significantly different from “traditional” medicines, in both their characteristics and the production process, the GMP requirements applicable to the manufacture of “traditional” pharmaceuticals may often be different from those applied to the manufacture of radiopharmaceutical products.
- 3.5 Radiopharmaceutical-specific characteristics generally include the following:

- a simple distribution chain, with direct delivery of the finished product from the manufacturer to the nuclear medicine department;
- a small batch size;
- a limited shelf-life of minutes to several days; and
- a quality control (QC) sample representing the entire batch.

In addition:

- diagnostic radiopharmaceuticals often have a low potential to exert pharmacological or toxic effects, owing to the micro-dose levels administered; and
- radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility and determination of endotoxin content and radionuclidic purity may need to be performed post-release. Hence, the application of GMP is essential in order to minimize possible risks to the quality that may not be identified through QC pre-release testing.

3.6 The risk assessment should cover the unique nature of these agents, with controls that are tailored to the actual production process, the nature of the radiopharmaceutical itself, the level of risk associated and the clinical indication. The preparation and control of these agents should be in compliance with applicable national radiation safety regulations and be based on the principles of ALARA (4, 5) (see [Glossary](#))

4. Qualification and validation

- 4.1 Qualification of instruments and equipment and validation of procedures should be done.
- 4.2 Validation and qualification activities should be planned, organized and documented.
- 4.3 Qualification of premises, utilities, equipment and instruments should demonstrate that they have been designed, installed, operated and performed (as applicable) in accordance with the requirements of GMP and that they are appropriate for their intended use.
- 4.4 The extent of qualification and validation activities should be in accordance with a risk-based approach considering the complexity and critical aspects of the intended radiopharmaceutical production.
- 4.5 A schedule of planned preventive maintenance should be established. Procedures and records should be maintained.

- 4.6 There should be a schedule for regular calibration and verification. Procedures and records should be maintained.
- 4.7 Process validation should be carried out after all other qualification and validation have been successfully completed.
- 4.8 Process validation should be done by including an adequate number of batch preparations, or batches of preparations, of the intended radiopharmaceutical(s), following the same procedures, covering the intended range of batch size and with the same production and quality specifications as typically intended routine batches. The number of batches and the range of batch size should be predetermined as part of a risk assessment performed prior to process validation.
- 4.9 Cleaning validation should be especially focused on surfaces that come into direct contact with the operators or with starting materials, intermediates and finished products.
- 4.10 Non-pharmacopoeia analytical procedures should be validated. Compendial analytical procedures should be verified for their suitability under actual conditions. This should be documented and records maintained.
- 4.11 General principles on validation of analytical procedures may be followed (6, 7); however, the unique nature of radioactivity should be considered and specific adaptations should be made, where required (7).
- 4.12 Revalidation of certain processes (e.g. aseptic process simulation) should be performed on a periodic basis, in accordance with a written procedure. Requalification of equipment should be considered when appropriate, for example, in case of significant changes and/or of deviations.
- 4.13 Validation and qualification activities and results obtained, including the responsibilities of personnel, should all be documented. Records should be maintained.
- 4.14 Processes and procedures should be validated, as appropriate.

5. Product complaints

- 5.1 There should be a written procedure for handling and investigating product complaints.
- 5.2 The procedure should describe the actions to be taken in case of a complaint.

6. Product recall

- 6.1 There should be a written procedure to recall a radiopharmaceutical product, when required.
- 6.2 Since the return of radioactive products is generally not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with national and, where applicable, international transport regulations (8).

7. Outsourced activities

- 7.1 Contractors should be evaluated and qualified in accordance with a written procedure. Records should be maintained. The responsibilities of each party should be clearly described in a written agreement.

8. Personnel and training

- 8.1 The manufacturing establishment should have an adequate number of personnel to carry out the intended operations.
- 8.2 The responsibilities placed on any individual should not be so extensive as to present an increased risk to the quality of the product.
- 8.3 The manufacturing establishment and its personnel should be under the supervision of a responsible person(s) who has the appropriate qualifications and experience as required by national legislation.
- 8.4 Personnel should have appropriate qualifications, training and experience related to their responsibilities and job description.
- 8.5 Personnel should receive relevant training in GMP, procedural training and training related to the preparation and control of radiopharmaceutical products.
- 8.6 A written training programme should be followed. Topics should also include the handling of radioactive materials and safety. Personnel should take periodic courses and receive training to keep abreast of the latest developments in their fields.
- 8.7 Training and assessment following training should be documented. Records should be maintained.

- 8.8 All personnel handling radioactive materials should be monitored for possible contamination and radiation exposure.
- 8.9 Personnel working in clean areas should observe good personal hygiene. They should report any personal medical condition that may adversely affect products.

9. Premises

- 9.1 Facilities should be located, designed, constructed, adapted and maintained, in order to suit the operations to be carried out. The laboratories for the handling of radioactive materials should be appropriately designed. Consideration should be given to radiation protection, ALARA compliance, a high level of cleanliness and the appropriate controls to minimize possible microbial contamination.
- 9.2 Lighting, heating, ventilation and air-conditioning (HVAC) systems should be designed to maintain an appropriate temperature and relative humidity where required, in order to ensure the appropriate equipment performance, material storage, safety and comfort of personnel.
- 9.3 Facilities should be correctly maintained. Special precautions should be exercised, in order to ensure that facility repairs and maintenance operations do not compromise product quality. There should be adequate space for the operations to be carried out allowing for efficient workflow, effective communication and overall supervision. Facilities should also be designed in a manner that minimizes the risk of entry of insects, pests and vermin.
- 9.4 Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks. They should not shed particles and should allow for easy cleaning and decontamination.
- 9.5 Drains should be avoided wherever possible, and should not be present in clean rooms. Where drains are required, these should be appropriately designed.
- 9.6 Sinks should be excluded from clean areas.
- 9.7 Pipes and valves should be appropriately marked, designed and located, in order to facilitate cleaning and decontamination. Vent filters should be appropriately controlled.

- 9.8 Technical area (e.g. rooms to access the rear of hot cells) access points should be configured in a way to minimize the entrance of maintenance and technical personnel to the production (clean) areas.
- 9.9 The HVAC system and pressure cascade design for the different areas should be appropriately designed and maintained, in order to minimize the risk of product contamination and to protect personnel from the risks of radiation exposure. The pressure differentials should be controlled, monitored and recorded. Appropriate controls should be put in place to promote the containment of radioactive gases and vapours.
- 9.10 Radioactive gas emissions should be effectively controlled and monitored, in order to minimize the risk of unnecessary radiation exposure to personnel and the surrounding environment. Alarm systems should be in place.
- 9.11 Radioactive gas should be removed through separate air-handling units fitted with the appropriate filters before being exhausted. These should be regularly checked for performance. The recirculation of radioactive contaminated air should not be allowed.
- 9.12 All operations such as the handling, storage and distribution of materials and products, as well as waste disposal, should be performed in compliance with national regulations and guidance.
- 9.13 A dedicated area with the appropriate equipment should be used for the manufacture of any radiopharmaceutical product involving human blood or plasma.
- 9.14 QC laboratories should be separated from production areas.

10. Equipment

- 10.1 Equipment should be appropriately qualified for its intended use. This includes user requirement specifications, design qualification (if applicable), installation qualification, operational qualification and performance qualification. Equipment and devices, as appropriate, should be calibrated and maintained. Consideration should be given to reducing the risk of product contamination, minimizing the risk of staff radiation exposure and optimizing ergonomics, in order to facilitate the operation, maintenance and cleaning of equipment. Records should be retained (9).
- 10.2 Equipment maintenance, qualification and calibration operations should be recorded and the records maintained.

- 10.3 Computerized systems, such as those controlling equipment, should be included in validation.
- 10.4 The dose calibrator (also known as the activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose-calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.

11. Starting materials

- 11.1 Starting materials of appropriate quality should be used for radiopharmaceutical production. Written procedures for material acceptance should be established for starting materials to be subsequently used in radiopharmaceutical production.
- 11.2 Specifications for starting materials should be established. Specifications should include, for example, the identity, purity or certification of origin (if applicable) and any other parameters or characteristics required in order to make the material suitable for its intended use.
- 11.3 Starting materials should be accepted by performing in-house testing. Where this is not possible, and in lieu of testing, a review of the certificate of analysis supplied by the reliable material manufacturer to confirm compliance with the specification may be acceptable.
- 11.4 The status of materials should be clear. This includes: (i) accepted materials; (ii) quarantined materials; and (iii) rejected materials.
- 11.5 Rejected materials should be securely stored in an area that is separate from other materials.
- 11.6 Waste materials should be disposed of in accordance with the national requirements.

12. Documentation

- 12.1 Good documentation practices should be followed.
- 12.2 Documents should ensure the traceability of radiopharmaceutical production (including the processes and the product).
- 12.3 The processing records of regular production batches must provide a clear and complete account of the manufacturing history of each batch of a radiopharmaceutical product, showing that it has been manufactured,

tested, dispensed into containers and delivered in accordance with the applicable standard operating procedures (SOPs).

- 12.4 A controlled system of written SOPs must be created, in order to cover the requirements for major aspects of radiopharmaceutical manufacturing. The SOPs should be approved, signed and dated by the appropriate responsible person(s). No approved SOP document should be changed without an appropriate review, evaluation and approval by the responsible person(s). The SOPs should be reviewed periodically, in order to ensure applicability.
- 12.5 Documentation should be retained for a period appropriate to the nature of the document content.

13. Good practices in production

- 13.1 Access to restricted areas should be by authorized and trained personnel only.
- 13.2 Only the minimum number of personnel required should be present in clean areas.
- 13.3 Processes should be designed to minimize the risk of contamination, cross-contaminations and mix-ups. The following measures may be adopted to minimize these risks:
 - processing and filling in segregated areas;
 - avoiding the manufacture of different products at the same time, either in the same dedicated space or by the same personnel;
 - performing decontamination and visual pre-checks of the manufacturing area; and
 - using manufacturing “closed systems”, whenever possible.
- 13.4 The critical aseptic operations, such as final product vial assembly, vial filling or sterility testing, should be carried out under aseptic conditions of a clean area of grade A in grade B background (10).
- 13.5 Both raw materials and final radiopharmaceutical products should be stored under appropriate controlled conditions.
- 13.6 The stability and shelf-life of the finished product should be defined in a written protocol in agreement with the competent authority.
- 13.7 The expiration dates and times for radiopharmaceutical products should be based upon the results of an adequate number of stability studies.

14. Good practices in quality control

- 14.1 A radiopharmaceutical's final product acceptance criteria, including criteria for release, should be established and documented in a written SOP.
- 14.2 Sampling procedures should consider the nature and characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content), in order to make sure that the samples are representative of the radiopharmaceutical batch.
- 14.3 The QC procedures should be described in written SOPs.
- 14.4 QC samples should be prepared, handled and stored in a way to ensure adequate identification and segregation of the test samples, to avoid mix-ups and cross-contamination.
- 14.5 A final radiopharmaceutical product that fails to meet the acceptance criteria should be rejected and segregated. Such events should be investigated and the investigation outcome and proposed actions documented.
- 14.6 The release of a batch should be performed by a responsible person. Under certain circumstances (e.g. radiopharmaceuticals with an extremely short radioactive half-life and/or shelf-life), a final radiopharmaceutical drug product may need to be released and delivered prior to completion of all final drug product characterization testing. Under these circumstances, a SOP that clearly describes the required release process should be established and documented.
- 14.7 Batch release by the manufacturer should be carried out by a responsible person who is independent of the person carrying out the production and QC.

15. Labelling

- 15.1 Finished radiopharmaceutical products should be clearly labelled.
- 15.2 Whenever possible, a portion of the primary packaging container should be left uncovered, in order to allow for inspection of the contents.
- 15.3 The content of the labels for radiopharmaceutical products should comply with national legislation and international agreements, where applicable.
- 15.4 In the absence of regulatory authority requirements, the following information should be listed on the primary packaging container label:

- the name of the product and batch number;
- the name of the manufacturer;
- the amount of activity in SI units;
- for liquid radiopharmaceuticals, the total activity or the radioactive concentration per millilitre at the calibration date and time, and the volume of liquid;
- for capsules, the radioactivity of each capsule at the calibration date and time, and the number of capsules in the container;
- where relevant, the international symbol for radioactivity;
- the expiration date and time; and
- cautionary statements, e.g. “Caution: radioactive material”.

Note: reporting information about an activity on a primary label may not always be possible, for reasons of radiation protection. In this case, the information may be reported on the secondary packaging label.

15.5 In the absence of regulatory authority requirements, the following information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:

- the qualitative composition;
- excipient information;
- the route of administration;
- any special storage instructions; and
- the address of the manufacturer.

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Additional reading

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