World Health Organization

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA)/WHO GUIDELINES ON GOOD MANUFACTURING PRACTICES FOR RADIOPHARMACEUTICAL PRODUCTS

(July 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by **20 September 2019**.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the "Current projects" link. If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

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INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA)/WHO GUIDELINES ON GOOD MANUFACTURING PRACTICES FOR RADIOPHARMACEUTICAL PRODUCTS

Need for updating of the GMP for radiopharmaceuticals identified by IAEA and its experts.	Early 2018
IAEA consultation meeting on Harmonization of Health Regulations related to the Production of Radiopharmaceuticals, IAEA Headquarters, Vienna, Austria.	5-9 November 2018
Editing by WHO, circulation by mail to the participants of the IAEA meeting (5–9 November 2018) for final feedback and agreement.	December 2018
Circulation to IAEA for final review and editing.	January 2019
Circulate widely for public consultation using the IAEA and the WHO mailing list and public web posting.	January–March 2019
Collect and collate the comments received during the global consultative process in IAEA and WHO using a common format.	April 2019
Revision of working document based on feedback received during a consultation organized by IAEA in 2019.	10-12 July 2019
Re-circulate widely for public consultation, review of comments by IAEA specialists and staff and communication of the final outcome to WHO.	20 September 2019
Present the outcome to the Fifty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations.	14-18 October 2019
Present to the IAEA's International Symposium on Trends in Radiopharmaceuticals (ISTR -2019) held at the IAEA headquarters in Vienna, Austria.	28 October – 1 November 2019
Any further action, if needed	

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1. SCOPE OF THESE GUIDELINES

These guidelines are intended to provide a general overview of the minimum Good Manufacturing Practices (GMP) requirements for radiopharmaceuticals. The main principles of GMP are described in detail in the chapters for pharmaceutical products (*1*,*2*) as well as those for sterile pharmaceutical

products (*3*). Unless otherwise specified, the GMP requirements for radiopharmaceuticals described in this guidance should take precedence over the GMP requirements for pharmaceutical products.

The procedures necessary to manufacture 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 these guidelines are applicable to the following scenarios:

- The production 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.
- The production of cyclotron-based positron emission tomography (PET) radiopharmaceuticals.

The scope of this guidance does not include the following:

- Radiopharmaceutical dispensing (i.e. the drawing of a patient specific unit dose from a bulk vial of a radiopharmaceutical).
- 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.
- Production of investigational radiopharmaceuticals.

2. DEFINITION OF TERMS

"As Low As Reasonably Achievable" (ALARA)

A set of practices designed to ensure the minimum necessary worker radiation exposure. These practices are based on the principles of time, distance, shielding and awareness.

Dispensing

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

Good Manufacturing Practices for radiopharmaceuticals

A set of practices, using a traceable process, which ensures 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. Good Manufacturing Practices fall under the umbrella of the overall Quality Management System.

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 (QC), 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 marketing authorization holder which involves 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 radiopharmaceutical finished 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 radiopharmaceutical final products with pre-determined quality acceptance specifications.

Quality Management System

An appropriate system encompassing the organizational structure, procedures, processes and 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 a physician's order for a specific patient or patients. 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 which, 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 One of the main goals of any manufacturing process is to consistently yield a product of intended quality. The Quality Management System (QMS) is 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.

3.2 QMS is part of the manufacturer's overall commitment to establish manufacturing process controls that comply with applicable regulations and consistently yield a product of acceptable quality. These manufacturing process controls are also known as Good Manufacturing Practices (GMP).

3.3 While the terms QMS and GMP also apply to the manufacture of "traditional" pharmaceuticals, the actual requirements of controls for radiopharmaceutical manufacturing are quite different from the requirements for "traditional" pharmaceutical manufacturing and should be based on a well-defined and appropriate risk assessment.

3.4 Risk assessment and risk management are the key concepts applied when establishing manufacturing process controls intended to minimize the risk of unnecessary patient harm, resultant from the suboptimal quality of the product. Risk assessment involves a thorough evaluation and identification of all possible risks associated with the manufacturing process and risk management involves implementing measures to minimize those risks.

3.5 Risk management measures should be based on consideration of the complexity of the intended process. Because radiopharmaceuticals are significantly different from "traditional" medicines, both in their characteristics and the production process, the GMP requirements applicable to the manufacture of "traditional" pharmaceuticals cannot be applied in their entirety to the manufacture of all classes of radiopharmaceuticals.

3.6 Radiopharmaceutical specific characteristics generally include the following:

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

- diagnostic radiopharmaceuticals often possess low potential to exert pharmacological or toxic effects due to the micro-dose levels administered.
- Radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility, endotoxin content determination and radionuclidic purity, may need to be performed post-release. Hence, the importance of the application of GMP is essential to minimize the possible risks to the quality that may not be identified through QC pre-release testing. Qualification of instruments/equipment and validation of methods/processes are essential to prove that the critical aspects of their operation are controlled.

3.7 The unique nature of these agents requires specialized risk management that is tailored to the actual production process, the nature of the radiopharmaceutical itself, the level of risk associated and the clinical indication. As always, the radioactive nature of these agents requires compliance with "as low as reasonably achievable (ALARA) principles" (*4,5*). The recommendations provided in this guidance are based on such reasoning.

4. QUALIFICATION AND VALIDATION

4.1 Qualification of instruments/equipment and validation of methods/procedures are essential to prove that the critical aspects of their operation are controlled.

4.2 Validation and qualification activities should be planned in an orderly manner and documented.

4.3 Qualification of premises, supporting utilities, production and QC equipment should demonstrate that they have been designed (if applicable), installed, operated and perform in accordance with the requirements of GMP and are fit-for-purpose.

4.4 The planning of qualification and validation activities should consider the complexity and critical aspects of the intended radiopharmaceutical production. A schedule of planned preventive maintenance should be established for instruments/equipment as well as regular

verifications and/or calibrations as appropriate. These commitments must be documented in a written and approved standard operating procedure (SOP).

4.5 Process validation should be carried out after all other qualification and validation have been successfully completed.

4.6 Process validation should include an adequate number of productions of the intended radiopharmaceutical(s), prepared following the same procedures, covering the intended batch size range and with the same production, quality specifications and acceptance criteria as of typical intended routine batches. The number of batches and the batch size range should be pre-determined as part of a risk assessment performed prior to process validation.

4.7 Cleaning validation should be especially focused on critical production areas, such as working surfaces, and in general surfaces which come into direct contact with the operators or with starting materials, intermediates and finished products.

4.8 Analytical methods should be validated in case they are not described in any recognized source (e.g. a pharmacopoeia). Compendial analytical methods, already described in a recognized source, are not required to be validated; however, method suitability under actual conditions of use should be performed and documented.

4.9 General principles on validation of analytical methods may be found following suitable guidelines (*6,7*); however, the unique nature of radioactivity should be considered, and specific adaptations should be made, if justified.

4.10 Re-validation of critical processes (e.g. media fill studies) should be performed on a periodic basis. These commitments must be documented in a written and approved SOP. Re-validation of any process or requalification of equipment may be warranted under

certain circumstances (e.g. in case of significant changes and/or of deviations which may affect the quality of the product).

4.11 Validation/qualification activities, including clearly defined responsibilities and the resultant data, should be documented and archived.

4.12 Processes and procedures should ultimately be established based on the results of the validation performed.

5. PRODUCT COMPLAINTS

5.1 There should be a written SOP for handling and investigating product complaints.

5.2 The SOP should also describe the actions to be taken in case of complaints.

6. PRODUCT RECALL

6.1 There should be a SOP for product recall.

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 international and national transport regulations (*8*).

7. CONTRACT PRODUCTION, ANALYSIS AND OTHER ACTIVITIES

7.1 Sub-contractors should be qualified as per internal written approved procedure. The respective responsibilities of each party must be clearly defined.

8. PERSONNEL AND TRAINING

8.1 The manufacturing establishment should have adequate personnel to carry out the intended operations. The responsibility placed on any one of the personnel should not be so extensive as to present an increased risk to the quality. The manufacturing establishment and its personnel should be under the supervision of a responsible person(s) who possesses qualifications and practical experience or as required by national legislation.

8.2 Supporting personnel should have the necessary training and experience appropriate to their function.

8.3 Personnel should be trained on SOPs related to radiopharmaceutical manufacture, approved by the responsible person.

8.4 To ensure the safe manufacture of radiopharmaceuticals, personnel should also be trained in GMP, the safe handling of radioactive materials and radiation safety procedures. Personnel should take periodic courses and receive training to keep abreast of the latest developments in their fields.

8.5 Training should be planned and documented, and the training records should be retained in a personnel file

8.6 All personnel handling radioactivity should be monitored for possible contamination and/or irradiation exposure.

8.7 Personnel working in clean areas should maintain good personal hygiene. Personnel are required to report to the immediate supervisor any condition that may potentially adversely affect the product.

9. PREMISES

9.1 As a general principle, facilities must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials should be designed to take into consideration aspects of radiation protection and ALARA compliance, in addition to cleanliness and controls to minimize microbial contamination.

9.2 Lighting, heating, ventilation and air-conditioning systems should be designed to maintain an appropriate temperature and relative humidity in order to ensure the proper equipment function, material storage conditions and safety and comfort of personnel.

9.3 Facilities should be maintained in a good state of operation. Special precautions should be exercised to ensure that facility repair or maintenance operations do not compromise product quality. Premises should provide adequate space for the operations to be carried out, allowing an efficient workflow and effective communication and supervision. Facilities should be designed to have controls to prevent 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 matter and should permit easy cleaning and decontamination.

9.5 Drains should be avoided wherever possible and, unless essential, should be excluded from clean areas.

9.6 Sinks should be excluded from clean areas.

9.7 Pipework, valves and vent filters should be properly designed to facilitate cleaning and decontamination.

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 the maintenance/technical personnel to the production/clean areas.

9.9 The pressure regime and ventilation system for the different facility areas should be carefully established to both minimize the risk of product contamination and to protect the personnel from unnecessary radiation exposure. The pressure differentials should be monitored.

9.10 Radioactive gas emissions should be effectively monitored, including alarms, in order to minimize the risk of unnecessary radiation exposure to personnel as well as to the surrounding environment.

9.11 Radioactive gas exhausts should be removed via a separate air handling unit through appropriate filters that are regularly checked for performance.

9.12 All operations of radioactivity handling, storage and waste disposal should be performed in compliance with national regulations and guidance.

9.13 A dedicated area and equipment should be used for the manufacture of any radiopharmaceutical product involving human blood or plasma.

9.14 A manufacturer's QC laboratory should be in a separate dedicated area.

10. EQUIPMENT

10.1 Equipment used should be qualified for the intended purpose through appropriate design, specifications, installation, calibration, operation, and maintenance. Critical factors, including minimizing the risk of product contamination, minimizing the risk of staff radiation exposure and optimised ergonomics, should be considered during equipment

design (design qualification) in order to facilitate their operation, maintenance and cleaning. Subsequently, before use, equipment should be qualified for the intended purpose by performing installation qualification, operational qualification and performance qualification, records of which are to be retained (*9*).

10.2 Equipment used for radiopharmaceutical manufacture and QC should be periodically calibrated and maintained.

10.3 Equipment maintenance, qualification, and calibration operations should be recorded and archived in proper log-books.

10.4 Equipment controlling software may be considered as part of the equipment and, therefore, may be included in the process of equipment qualification.

10.5 SOP's should be established for the operation, calibration, and planned preventative maintenance (PPM) of the equipment

10.6 The dose calibrator (also known as 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 material acceptance SOPs must be established for starting materials to be subsequently used in radiopharmaceutical production.

11.2 Specifications for every starting material must be established. Examples of such specifications may include identity, purity or certification of origin (if applicable) and any other parameter or characteristic that makes the material suitable for the intended use.

11.3 Starting materials could be accepted by either performing in-house testing or a review of the Certificate of Analysis (CoA) supplied by the reliable material manufacturer to confirm compliance with the internal acceptance specification.

11.4 Materials should be segregated into three separate categories: (1) accepted materials, (2) quarantined material, and (3) rejected materials and labelled accordingly.

11.5 Rejected materials must be securely stored in an area separate from the rest of the materials.

11.6 Waste materials should be disposed of in accordance with the national requirements.

12. DOCUMENTATION

12.1 Good documentation practices should be used.

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, showing that it has been manufactured, tested, dispensed into containers and delivered in accordance with the applicable SOPs.

12.4 A controlled system of written SOPs must be created 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 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:

(a) processing and filling in segregated areas;
(b) avoiding the manufacture of different products at the same time, in the same dedicated space or by the same personnel;
(c) performing manufacturing area decontamination and visual pre-checks;
(d) 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 in areas under high efficiency particulate air (HEPA) filtered laminar air flow (*10*).

13.5 Both raw materials and final radiopharmaceutical products should be stored under appropriate controlled conditions.

13.6 An evaluation program aimed to define the stability of the finished products should be established.

13.7 The expiration dates and times for radiopharmaceuticals should be based on the results of an adequate number of stability studies.

14. GOOD PRACTICES IN QUALITY CONTROL

14.1 Radiopharmaceuticals 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 the characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content) to make sure that the samples are representative of the batch of radiopharmaceutical.

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 the adequate identification and segregation of the test samples to avoid mix-ups and cross-contamination.

14.5 Radiopharmaceutical final products failing to meet the acceptance criteria should be rejected and segregated. Such events should be investigated; and the investigation outcome and proposed actions should be documented.

14.6 The release of a batch should be performed by a responsible person.

14.7 In the manufacturer setting, batch release should be carried out by the responsible person or Persons separate from the person or persons carrying out production and QC.

15. LABELLING

15.1 Radiopharmaceutical final products should be clearly identified by labels.

15.2 Whenever possible, a portion of the primary packaging container should be left uncovered to allow for the inspection of contents.

15.3 The content of the labels for radiopharmaceutical products must comply with the relevant national regulations and international agreements.

15.4 In the absence of regulatory authority requirements, the following information may be listed on the primary packaging container label:

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

Please note that reporting information about activity on a primary label may not always be possible due to radiation protection reasons; in this case, they may be reported on the secondary packaging label only.

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:

(a) the qualitative and quantitative composition;

(b) excipient information;
(c) the route of administration;
(d) any special storage instructions; and
(e) the address of the manufacturer.

Acronyms

ALARA	"As Low As Reasonably Achievable"
CoA	Certificate of Analysis
GMP	good manufacturing practices
HEPA	high efficiency particulate air
PET	positron emission tomography
PPM	planned preventative maintenance
QC	quality control
QMS	quality management system
SOP	standard operating procedure

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