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

(February 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) by 28 February 2019.

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<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for updating of the GMP for radiopharmaceuticals identified by IAEA and its experts.</td>
<td>Early 2018</td>
</tr>
<tr>
<td>IAEA consultation meeting on Harmonization of Health Regulations related to the Production of Radiopharmaceuticals, IAEA Headquarters, Vienna, Austria.</td>
<td>5-9 November 2018</td>
</tr>
<tr>
<td>Editing by WHO, circulation by mail to the participants of the IAEA meeting (5–9 November 2018) for final feedback and agreement.</td>
<td>December 2018</td>
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<tr>
<td>Circulation to IAEA for final review and editing.</td>
<td>January 2019</td>
</tr>
<tr>
<td>Circulate widely for public consultation using the IAEA and the WHO mailing list and public web posting.</td>
<td>January–March 2019</td>
</tr>
<tr>
<td>Collect and collate the comments received during the global consultative process in IAEA and WHO using a common format.</td>
<td>April 2019</td>
</tr>
<tr>
<td>Revision of working document based on feedback received during a consultation organized by IAEA in 2019.</td>
<td>TBD</td>
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<tr>
<td>Re-circulate widely for public consultation, review of comments by IAEA specialists and staff and communication of the final outcome to WHO.</td>
<td>TBD</td>
</tr>
<tr>
<td>Present to the IAEA’s International Symposium on Trends in Radiopharmaceuticals (ISTR -2019) to be held at the IAEA headquarters in Vienna, Austria, Oct 28 -Nov 1, 2019.</td>
<td>28 October – 1 November 2019</td>
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<tr>
<td>Present the outcome to the 54th WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
<td>14-18 October 2019</td>
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</tbody>
</table>
1. SCOPE OF THESE GUIDELINES

These guidelines are intended to provide a general overview of the Good Manufacturing Practice (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 regulatory 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 this guideline are applicable to the following scenarios:

- The production of radiopharmaceuticals in hospital radiopharmacies, including diagnostic and therapeutic products.
- The production of radiopharmaceuticals in centralized radiopharmacies.
- The production 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:

- Approved radiopharmaceutical preparation and dispensing. (e.g. receipt, handling, storage, and use of kits, generators, and ready-to-use doses; drawing of a patient specific unit dose from a bulk vial of a radiopharmaceutical). In these cases, the instructions from the marketing authorization holder should be followed.

- In-house preparation or compounding of non-radioactive compounds, including cold kits.

- In-house preparation of investigational radiopharmaceuticals.

2. DEFINITION OF TERMS

“Manufacturing” or “production”: within the scope of this guidance, these terms mean all the operations that bring to the finished radiopharmaceutical product, including the purchase of starting materials, production, quality control, release, and storage of radiopharmaceuticals.

“Dispensing”: the generation of a patient-specific unit dose which involves the physical withdrawal of the approved radiopharmaceutical from the bulk single-use or multi dose vial into a syringe, diluting the patient-specific unit dose with appropriate diluent as necessary, and labelling the syringe.

“Preparation” the act of adding an approved radionuclide solution and kit components to an approved kit, as per manufacturer instructions.

“In-house preparation” or “hospital preparation” or “radiopharmaceutical compounding”: these terms refer to the making of radiopharmaceuticals with no marketing authorization, but pursuant to a physician order for a specific patient or patients.
“Primary Packaging”: any packaging material that comes into direct contact with the radiopharmaceutical finished product (i.e. immediate container such as a vial or a syringe).

“Secondary Packaging”: the shielded container housing the primary packaging.

“Quality Control” (QC): a set of analytical tests designed to demonstrate compliance of the radiopharmaceutical final product quality with pre-determined quality acceptance specifications.

“Quality Management System” (QMS): a set of procedures and processes utilized by radiopharmaceutical manufacturers to ensure reliable and consistent production of radiopharmaceutical final products that are of the quality required for their intended use.

“Radiopharmaceutical Good Manufacturing Practices” (GMP): a set of practices, using a traceable process, which ensures that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for the intended use and designed to consistently yield the radiopharmaceutical product.

3. QUALITY MANAGEMENT SYSTEM

3.1 One of the main goals of any manufacturing process is to consistently yield a product of intended quality. Quality Management System (QMS) is a compilation of procedures, processes and equipment used by radiopharmaceutical manufacturers to achieve this goal.

3.2 The utilization of 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).
While the terms QMS and GMP also apply to the manufacture of “traditional” pharmaceuticals, the actual controls needed to satisfy these manufacturing process requirements for radiopharmaceuticals are quite different from the requirements for “traditional” pharmaceutical manufacturing and should be based on a well-defined and appropriate risk assessment (for details, see below).

3.4 Risk assessment and risk management are the key concepts utilized when trying to establish 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 and consider 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 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: very simple distribution chain, with direct delivery of the finished product from the manufacturer to the end user, small batch size, very limited shelf-life of minutes to several days, QC sample representing the entire batch; moreover, diagnostic radiopharmaceuticals often possess very low potential for pharmacologic effect and toxicity due to micro-dose level administered mass. On the other hand, radiopharmaceuticals are often administered prior to completion of all QC testing. For example, tests such as sterility, endotoxin content determination, and radionuclidic purity, may need to be performed post-release. Hence, the reliance on GMP is essential to minimize the possible risks to the quality, that may not be identified through QC pre-release testing.
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. The recommendations provided in this guidance are based on this reasoning.

4. **QUALIFICATION AND VALIDATION**

4.1 Validation and qualification activities are aimed 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 the premises, supporting utilities, production and QC equipment, should demonstrate that they have been designed (if applicable), installed, operated and performing in accordance with the requirements for GMP and are aimed to improve reliability and to reduce deviations and out of specification to a minimum extent.

4.4 Planning of qualification and validation activities should consider the complexity and critical aspects of the intended radiopharmaceutical production.

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

4.6 Process validation should include three consecutive productions of the intended radiopharmaceutical(s), prepared following the same procedures, with the same batch size, and with the same production, quality specifications and acceptance criteria as of typical intended routine batches.
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 only be validated in case they are not described in any recognized source (e.g. pharmacopoeia, manufacturer specification, etc.).

4.9 General principles on validation of analytical methods may be found following suitable guidelines (4,5); however, the unique nature of radioactivity should be considered, and specific adaptations should be made.

4.10 Re-validation/re-qualification should be performed only in case of significant changes and/or of deviations that prompt for a loss of validated/qualified status.

4.11 Validation/qualification activities must be documented, responsibilities clearly defined, and the resultant data collected 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 procedure for handling and investigating product complaints.

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

6. **PRODUCT RECALL**

6.1 There should be a written procedure 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.

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 standard operating procedures (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 documented, and the current approved training records should be kept.
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 must be designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility.

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

9.3 Facilities should be in a good state of repair. Special precautions should be exercised to ensure that facility repair or maintenance operations do not compromise product quality. Premises should provide sufficient space for the operations to be carried out, allowing an efficient flow of work 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 validation of cleaning and decontamination.

9.8 Technical area (e.g. rooms to access the rear of hot cells) access points should be designed 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, to minimize the risk of unnecessary radiation exposure to personnel as well as the surrounding environment.

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

9.12 Facilities should be designed to allow for radiation handling and waste disposal to be performed in compliance with national regulations and guidance.

9.13 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 a 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 such as minimizing the risk of product contamination, minimizing the risk of staff radiation exposure, and optimised ergonomics should be considered during equipment design, to facilitate their operation, maintenance, and cleaning.

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 involved during the process of equipment qualification.

10.5 A list of critical equipment must be generated and maintained for the purposes of controlling the equipment qualification programme.

10.6 Equipment preventative maintenance, qualification, and calibration should be carried out periodically and as per written schedule.

10.7 The dose calibrator (also known as activity meter) should be qualified using suitable reference standards, if available. If such a reference standard recognized by a national authority is not available, dose calibrator manufacturer recommendations or published literature may be used.

11. **STARTING MATERIALS**

11.1 Good quality starting materials must be used when preparing radiopharmaceuticals.
11.2 Written procedures must be established for starting materials to be subsequently used in radiopharmaceutical production.

11.3 Product specific 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 intended use.

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

11.5 Incoming materials should be segregated into three separate categories: (1) accepted materials, (2) quarantined material, and (3) rejected materials.

11.6 Rejected materials must be clearly tagged with a rejected label and stored separately from the rest of materials.

11.7 Generated non-radioactive 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 traceability of the radiopharmaceutical productions.

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 written procedures.
12.4 A controlled system of written SOPs must be created to cover the requirements for major aspects of radiopharmaceutical manufacturing. The SOP’s 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 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 pre-synthesis manufacturing area decontamination and visual checks.

(d) Using “closed systems” of manufacture, 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 HEPA filtered laminar air flow (6).

13.5 Storage of both raw materials and final radiopharmaceutical products should be carried out under 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 the 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), if reference samples are representative of the batch of radiopharmaceutical.

14.3 Samples for quality controls should be properly labelled and stored to avoid mix-ups.

14.4 The QC procedures should be described in a written SOP.

14.5 QC samples should be prepared, handled and stored in a way to ensure the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination.

14.6 Radiopharmaceutical final products failing to meet the acceptance criteria should be rejected and segregated. Such events should be investigated, and the investigation and outcome should be documented.

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

14.8 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.
14.9 In the “in-house preparation”, “hospital preparation” or “radiopharmaceutical compounding”, the QMS person or persons may be involved in all aspects of radiopharmaceutical manufacture.

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 in the container, or the radioactive concentration per millilitre, at calibration date and, if necessary, time, and the volume of liquid in the container;

(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; and

(i) caution: radioactive material.

Please note that reporting information about activity on 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:

(a) any information listed on the primary packaging container PLUS;

(b) the qualitative and quantitative composition;

(c) excipient information;

(d) the route of administration;

(e) any special storage instructions; and

(f) the address of the manufacturer.
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5. Guide for elaboration of monographs on radiopharmaceutical preparations, EDQM, 2018
6. EN ISO 14644.


Additional Reading


15. *Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of Fluorodeoxyglucose (FDG)*

Details: STI/PUB/1515; (ISBN:978-92-0-117310-2); 2012


16. *Technetium-99m Radiopharmaceuticals: Status and Trends*

Details: STI/PUB/1405; (ISBN:978-92-0-103509-7); 2010


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