World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

International Atomic Energy Agency (IAEA)/WHO guidelines on good practices for quality control of radiopharmaceutical products

Please submit your comments through the online platform, PleaseReview™
https://who.pleasereview.net/Main/Default.aspx?action=loaddocument&reviewid=318
If not registered or included in our mailing list, kindly submit your request with your full name, email address and organization/affiliation to nsp@who.int.
For any technical questions, you may contact **Dr Luther Gwaza**, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (gwazal@who.int), with a copy to **Ms Sinéad Jones** (jonessi@who.int, nsp@who.int).
Comments should be submitted through the online platform on or by **15 June 2025**. Please note that only comments received by this deadline will be considered for the preparation of this document.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.969

International Atomic Energy Agency (IAEA)/WHO good practices for quality control of radiopharmaceutical products

Description of Activity	**Date**
Preparation of first draft working document.	Jul 2024
Review and finalization of the first draft working document with an informal drafting group.	Feb – Mar 2025
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	Apr – Jun 2025
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	Jul 2025
Discussion of the feedback received on the working document in a virtual meeting with an informal drafting group.	Aug – Sept 2025
Preparation of a working document for discussion and possible adoption by the ECSPP	Sept 2025
Presentation to the Fifty-ninth meeting of the ECSPP.	Oct 2025
Any other follow-up action as required.	

International Atomic Energy Agency (IAEA)/WHO good practices for quality control of radiopharmaceutical products

Table of contents

1. Background

1.1. Implementation of a robust quality control system tailored to the unique nature of radiopharmaceuticals requires careful consideration. Radiopharmaceuticals possess inherent characteristics that demand specialized attention, including the narrow testing time window, variability in the types of emitted ionizing radiation, complexities associated with the simultaneous production of radioactive drug substances and final drug products, and the constraints of radiation handling. These factors must be systematically integrated into the design of radiopharmaceutical quality control processes. Concurrently, however, radiopharmaceutical quality control testing must be sufficiently comprehensive and well-integrated into the overall production process, as its function ensures that the radiation administered to the patient provides the intended benefit. These concepts must be incorporated into nuclear medicine professional training and practice. Along with these efforts, this guidance provides recommendations on the minimum requirements for establishing a radiopharmaceutical-specific quality control testing program.

2. Scope

2.1. This guideline is aimed to provide a general overview of the good practices on the quality control of radiopharmaceuticals. This guideline is consistent with *WHO good practices for pharmaceutical quality control laboratory (1)* and the *International Atomic Energy Agency and World Health Organization guidelines on good manufacturing practices for radiopharmaceutical products (2).* The recommendations in this guideline are applicable to the quality control of:

- starting materials;
- finished radiopharmaceutical products; and
- radionuclides.

2.2. The requirements of this guideline apply to quality control testing of radiopharmaceutical products produced from raw starting materials under the practice of in-house production.

2.3. The requirements of this guidance do not cover quality control testing of non-radioactive cold kits prepared under the practice of in-house production. Those requirements are outlined in

IAEA/WHO Good Manufacturing practices for in-house cold kits for radiopharmaceutical preparations (3).

2.4. Compliance with the recommendations provided in these guidelines will help promote international harmonization of quality control laboratory practices for radiopharmaceuticals and will facilitate cooperation among laboratories and mutual recognition of results, also in view of regulatory expectations. The good practice described herein serve as a general guide and it may be adapted to meet individual needs, provided that an equivalent level of quality assurance is achieved.

2.5. This guidance primarily addresses the testing of the physicochemical properties of incoming materials, finished radiopharmaceuticals products, and radionuclides. Microbiology-related quality control testing falls outside its scope. For more information on microbiological quality control, refer to the *WHO Good practices for pharmaceutical microbiology laboratories (4).*

3. Glossary

acceptance criterion for an analytical result. Predefined and documented indicators that determine whether a result falls within or exceeds the limits specified in the corresponding specification.

accuracy. The degree of agreement between the value obtained from an analytical procedure and a conventional true value or an accepted reference value.

"as low as reasonably achievable". A principle of radiation protection aimed at minimizing radiation exposure to the lowest reasonable level. This is achieved through time management, maintaining distance, using shielding, and promoting awareness among stakeholders.

analytical test report. A document that includes a description of the test procedure(s) used, the results of the analysis, discussions, and conclusions.

batch (non-radioactive materials). A defined quantity of material/product prepared in a single process or series of processes to ensure homogeneity.

batch (radiopharmaceutical). A quantity of a radiopharmaceutical product prepared in a single procedure or series of procedure to ensure homogeneity.

calibration. The set of operations performed under specified conditions to establish the relationship between measurements recorded by an instrument or system and the corresponding known values of a reference standard. Acceptable measurement limits should be defined.

certificate of analysis. A document listing the test procedures performed on a sample, the obtained results, and the applied acceptance criteria, indicating whether the sample complies with the specification.

End-of-Synthesis or End-of-Production time. The time recorded when the very last step in radiopharmaceutical batch production (for example, sterile filtration or formulation) is completed.

good manufacturing practices for radiopharmaceuticals. A set of guidelines ensuring that radiopharmaceutical products are consistently produced and controlled according to established quality standards. GMP is part of an overall quality management system to ensure product traceability and consistency.

installation qualification. Testing performed to verify that analytical equipment is installed correctly and operates according to established specifications.

operational qualification. A documented verification process to confirm that analytical equipment functions as intended across all anticipated operating ranges.

out-of-specification result. A test result that falls outside the established specifications or acceptance criteria.

performance qualification. A documented process to verify that analytical equipment operates consistently and produces reproducible results within defined specifications and parameters for its intended analytical application.

precision. The degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision is typically expressed as relative standard deviation and can be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations — different days, different analysts or different equipment) and reproducibility (precision between laboratories).

qualified suppliers. Established and reputable firms, responsible for production and supply standardized starting materials (for example, reagents, reference standards, automated system cassettes, sterilized vials, purification cartridges) commonly used in radiopharmaceutical preparation for clinical use, that have successfully completed a qualification questionnaire provided by the radiopharmaceutical producer confirming presence of adequate quality system.

quality control. A set of analytical tests performed to verify compliance with predetermined quality acceptance criteria for starting materials, radionuclides, and finished radiopharmaceutical products.

quality management system. A structured system that includes an organization's procedures, processes, and resources to ensure that a radiopharmaceutical product or service meets specified quality requirements.

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

reference substance (or standard). A certified, material of uniform composition used in chemical and physical tests, allowing comparison with the product under examination. It must have an appropriate level of purity for its intended use.

specifications. A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the starting material, the radionuclide or the radiopharmaceutical product must conform to, to ensure suitable quality.

step-by-step standard operating procedure. A written, authorized document providing detailed instructions for performing general or specific operations.

system suitability test. A test conducted on analytical instrument using a reference standard or standards prior to radiopharmaceutical product QUALITY CONTROL sample analysis to verify that the analytical instrument functions as intended for the intended analysis

validation of an analytical procedure. A documented process by which a non-pharmacopeial analytical procedure (or method) is demonstrated to be suitable for its intended use.

4. Quality management system

4.1. A quality management system (QMS) should be in place to ensure proper control of radiopharmaceutical products. It should encompass, among other elements, the organizational structure of the quality control laboratory, including job descriptions, procedures, processes, resources, and actions necessary to provide adequate confidence that radiopharmaceutical products are properly controlled and released only if they meet the intended quality standards.

4.2. Risk management principles should be integrated in the establishment, implementation, and management of the quality management system.

4.3. Radiopharmaceuticals constitute a specific class of pharmaceuticals with unique characteristics that should be considered when implementing a quality management system:

- simple distribution chain, where the finished product is often delivered directly from the manufacturer to the nuclear medicine department, which may also serve as the manufacturer;
- small batch size;
- quality control sample representing and entire batch of radiopharmaceutical product;
- limited shelf-life, ranging from minutes to several days;
- decay characteristics of the intended radionuclides; and
- quality control sample representing the entire batch.

4.4. Radiopharmaceuticals with limited shelf-life are often administered prior to completion of all quality control testing. Tests such as sterility, endotoxin content and radionuclidic purity

determination may need to be performed post-release. Hence, the importance of good practices and a solid quality management system are essential to minimize the possible risks to the quality that may not be identified through quality control pre-release testing.

4.5. Quality control of radiopharmaceuticals, particularly those labelled with short half-life radionuclides, is typically performed soon after preparation. Since quality control laboratories are often integrated within the same manufacturing infrastructure, quality control activities generally fall under the broader scope of the overall quality management system.

4.6. In alignment with general QMS principles, documentation summarizing the following information should be established:

- the organizational structure;
- the personnel involved and along with their respective responsibilities and duties, including training;
- a description of the laboratory;
- a list of the available equipment;
- the qualification policy for relevant instruments; and
- the validation policy for analytical methods, if applicable.

4.7. If quality control laboratories operate independently from radiopharmaceutical manufacturers (for example, in countries where regulatory agencies maintain dedicated quality control laboratories for verifying the quality of candidate drugs for marketing authorization), a specific quality management system should be implemented. This system should adhere to the same principles outlined above to ensure consistency and reliability.

4.8. The quality control of radiopharmaceuticals must comply with applicable national radiation safety regulations and be conducted in accordance with the as low as reasonably achievable (ALARA) principles *(5,6)*.

5. Personnel and training

5.1. The Quality Control Unit should have a sufficient number of qualified personnel to effectively carry out its intended operations.

5.2. The laboratory should maintain clearly defined job descriptions for all personnel involved in quality control testing, as well as in the calibration, validation, and verification of equipment.

5.3. The Quality Control Unit and its personnel should operate under the supervision of a responsible person(s) with appropriate qualifications and experience, as required by national regulations.

5.4. The responsible person should oversee batch release and the approval of certificates of analysis to ensure compliance with established quality standards.

5.5. Personnel must possess appropriate qualifications, training, and experience relevant to their specific responsibilities and job descriptions, as determined by the responsible person(s).

5.6. A documented training program should be in place. Training should include the handling of radioactive materials and radiation safety protocols. Personnel should undergo regular training and periodic courses to stay updated on the latest advancements in their field.

5.7. All training activities should be documented, and records should be maintained for future reference.

5.8. All personnel handling radioactive materials must undergo regular monitoring for potential contamination and radiation exposure in accordance with radiation safety regulations.

6. Premises

6.1. Quality control laboratories should be strategically located, properly designed, constructed, adapted, and maintained to accommodate the specific operations to be performed.

6.2. Quality control laboratories should be appropriately segregated from preparation laboratories to prevent cross-contamination and ensure independent testing conditions.

6.3. A dedicated area for handling and storage radioactive samples should be specially designed, properly equipped, and adequately shielded and ventilated based on the decay characteristics of the radionuclides used. Radiation protection measures should be implemented in accordance with ALARA principles to ensure the safety of operators.

6.4. Equipment, or relevant components thereof, used for radioanalytical quality control (for example, radio-high-performance liquid chromatography (HPLC), radio-thin layer chromatography (TLC), gamma spectrometer, dose calibrator) should be properly shielded to maintain low background signal levels for sensitive radioactive detectors and minimize radiation exposure to operators.

6.5. The heating, ventilation and air-conditioning (HVAC) system should be designed to maintain an appropriate temperature and ventilation levels. Unlike manufacturing areas, quality

control laboratories typically do not require classification according to good manufacturing practice rules and grades.

6.6. Radioactive gas emissions should be effectively controlled and continuously monitored in order to minimize the risk of unnecessary radiation exposure to personnel and the surrounding environment. Radiation detectors with alarm systems should be installed to detect potential leaks. Dedicated fume hoods with negative pressure maintenance should be used where necessary (for example, near gas chromatography system outlets, where potentially contaminated vapours may be released during analysis).

6.7. Special precautions should be taken when handling highly toxic or radiotoxic substances. If required, a separate, dedicated unit or containment equipment (for example, isolators) should be used to prevent exposure and contamination. Proper procedures should be in place to ensure operator safety.

6.8. Drains and sinks are allowed in quality control laboratories provided that they are appropriately designed.

6.9. Quality control laboratories should either be equipped with or be in reasonably close proximity to shower facilities which could be used as emergency showers in case of emergencies.

6.10. Suitable containers should be in place to dispose of contaminated materials, such as needles, syringes, etc. The waste containers should be separated according to the decay properties of the radionuclide (alpha, beta, etc.) and half-life, if necessary.

6.11. Access to quality control work areas should be restricted to authorized personnel.

7. Equipment

7.1. The quality laboratory should have the required apparatus, equipment, instruments or instrument system for the correct performance of the tests and related activities *(7)*.

7.2. All equipment maintenance, qualification, and calibration activities should be documented, and records should be maintained for traceability and compliance purposes.

7.3. Computerized systems used for data acquisition and equipment control should be considered an integral part of the equipment or an instrument.

7.4. The dose calibrator should be calibrated and periodically checked using suitable reference standards. If a nationally recognized reference standard is unavailable, alternative sources—

such as dose calibrator manufacturer model-specific recommendations, that have been verified using the radionuclide sources supplied by radionuclide suppliers, or published literature—may be considered when determining the appropriate dial setting.

7.5. The laboratory should have the required test equipment, instruments, and other devices for the correct performance of the tests and/or calibrations, validations, and verifications.

7.6. Quality control laboratories may choose to rely either on electronic or paper-based quality management systems.

7.7. In quality control laboratories that choose to rely on electronic-based QMS systems, computers systems connected to quality control equipment for data collection, processing, recording, reporting, storage, or retrieval, the following measures should be implemented *(8)*:

- Data integrity protection: procedures should be established to ensure data integrity and prevent unauthorized access. Whenever possible, software should include an audit trail feature to track changes.
- Access control: user access to both the operating system and acquisition/control software should be managed through appropriate credentials based on user roles, preventing unauthorized modifications (for example, changes to methods, records, system clock, etc.).
- Change control procedures: a documented system should be in place to monitor and control changes to information stored in computerized systems.
- Electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner to prevent data loss.

7.8. In quality control laboratories that choose to rely on paper-based QMS systems, good written documentation practices standard operating procedures must be established and implemented to ensure integrity and traceability of the generated quality control data.

8. Qualification and calibration

8.1. Quality control laboratory responsible person(s) should be responsible for selecting the analytical instruments and equipment, and their features (for example, type of detector), that are appropriated for the intended use.

8.2. Instruments for quality control should be qualified according to a defined qualification plan, which includes installation qualification, operational qualification, and performance qualification *(7)*.

8.3. The qualification process should demonstrate that quality control instruments are installed, operated, and perform as intended, and are suitable for their intended use.

8.4. A regular calibration schedule should be established. The frequency and methodology of calibration must be documented in written standard operating procedures.

8.5. All equipment, instruments and devices requiring calibration should be clearly labelled, coded, or otherwise identified to indicate calibration status, date of last calibration, and next scheduled recalibration date.

8.6. Measuring equipment (for example, calibrated thermometers, flowmeters) should be calibrated regularly according to a predefined calibration plan established by the laboratory.

8.7. Specific procedures and frequencies of calibration should be established for each type of equipment. For example:

- pH meters should be verified with certified standard buffer solutions before use;
- balances should be checked prior to each use using certified reference weights; In balances equipped with internal adjustment feature, recommendations from the weight balance manufacturer should be followed in regard to weight balance calibration and suitability checks;
- dose calibrators should be verified daily and calibrated periodically using certified calibration sources;
- radiation detectors (for example, HPLC, TLC, gamma spectrometer) should be calibrated and suitability- checked prior to analysis, to ensure they are fit for the intend analysis; and
- other types of detectors (for example, UV detectors, flame ionization detectors) should be calibrated periodically using reference sources (for example, reference substances with known absorbance for UV cells).

8.8. Qualification and calibration documentation should include at least the following:

- identification details of the equipment, instrument, or device;
- manufacturer's information, including model, serial number or other unique identifiers;
- required qualification, verification, and/or calibration procedures;

- dates, results, and copies of reports, verifications, and calibration certificates;
- acceptance criteria and next scheduled qualification, verification, and/or calibration; and
- maintenance history and the future maintenance plan.

8.9. Analysis results should be traceable, where applicable, to a primary reference substance to ensure accuracy and reliability.

8.10. All calibrations and qualification processes should be traceable to certified reference materials and linked to SI units (metrological traceability) to maintain measurement accuracy.

9. Documentation

9.1. Good documentation practices should be followed for all quality control activities *(7)*.

9.2. Documentation should ensure full traceability of radiopharmaceutical quality control processes.

9.3. Quality control documentation is an integral part of the batch record, providing a clear and complete account of the drug product characterization.

9.4. A controlled system of written standard operating procedures should be established to cover all operations performed in a quality control laboratory, including:

- use and maintenance of quality control equipment;
- calibration of quality control equipment;
- management, backup, and archiving of computerized data, if relying on electronic QMS system;
- description of analytical methods used;
- handling of out-of-specification results;
- validation policy for non-pharmacopeial/non-compendial analytical methods;
- quality control testing procedures for specific products or raw materials; and
- for describing the use of suitable reference substances and materials.

9.5. Maintenance and calibration plans should be defined periodically (for example, at the beginning of the year), detailing frequency and type of interventions required.

9.6. The standard operating procedures should be approved, signed and dated by the appropriate responsible personnel, and they should not be modified without proper review, evaluation,

and approval by the designated responsible individual(s). The standard operating procedures should be reviewed periodically to ensure their continued applicability and accuracy.

9.7. All documentation should be retained for an appropriate period based on its content, typically no less than 2 years or as required by local regulations.

9.8. Documentation is an essential component of the QMS. The laboratory should establish and maintain procedures to control, review, and update all quality-related documentation.

9.9. The procedures to control and review documents should ensure that:

- documents are regularly updated and reviewed regularly as required;
- revised documents reference previous versions to maintain traceability;
- old or invalid documents are archived to document procedural evolution, while copies of obsolete documents are securely destroyed; and
- all relevant staff receive training on new and revised standard operating procedures.

9.10. All relevant quality control results for each batch of radiopharmaceuticals should be summarized in approved quality control documentation (for example, COA, quality control batch record, or quality control report). The documentation should contain, at a minimum:

- name and address of the quality control laboratory;
- approved document identification number;
- name and pharmaceutical form of the radiopharmaceutical;
- batch number;
- the name of the manufacturer/provider of the sample, if quality control sample is provided by an external entity;
- batch radioactivity and volume at EOS/EOP time, if necessary either for conduction of quality control analysis or if quality control analysis is also aimed to determine the amount of radioactivity (for example, using gamma spectrometry to determine the amount of radioactivity in 225Ac-radiopharmaceutical products);
- batch Expiration date and time, if determined by quality control testing results;
- results of all tests performed, including a comparison with established acceptance criteria (limits);
- for each test, a conclusion indicating whether the result meets the acceptance criteria;
- relevant comments, observations or information regarding specific test conditions necessary for result interpretation;

- final conclusion on whether the sample meets specifications and may be released or rejected, if applicable; and
- date and signature of the responsible person.

10. Quality control of starting materials

10.1. The material acceptance process—including physical receipt, visual inspection, quality control testing and retesting, segregation requirements, storage conditions, expiration assignment, and labelling—should be conducted in accordance with written and implemented standard operating procedures.

10.2. For materials supplied by qualified suppliers, acceptance may be based on the review and verification of the CoA to ensure conformance with internally established acceptance criteria. No additional testing applied by the quality control laboratory is required.

10.3. If starting materials are prepared in-house, testing criteria and analytical methods must be established and documented to accurately determine their identity and chemical purity.

10.4. For radionuclides supplied by a qualified supplier, acceptance may be based solely on the review of the associated CoA, and no further testing is required.

10.5. For radionuclide generators supplied by a qualified supplier, acceptance may be based on a review of the related CoA, with additional testing performed as per the manufacturer's recommendations.

10.6. For in-house cyclotron-produced radionuclides, which are typically used in continuous processes and not isolated, quality assessment should be performed during production process validation. This assessment should follow internal specifications or conform to a recognized pharmacopoeia monograph.

11. Quality control of finished radiopharmaceutical products

11.1. Finished radiopharmaceutical products are radioactive products that have undergone all stages of preparation, purification, formulation, quality control testing, and packaging in their final container.

11.2. Each batch of a radiopharmaceutical product must undergo testing as specified in the relevant written quality control SOP.

11.3. Due to the inherent radioactive properties of these products, certain quality control tests may be performed post-release. This is typically required for:

- Radio-nuclidic purity testing, which may need to be conducted after the complete decay of the desired radionuclide. This ensures that gamma spectrometry analysis can accurately detect and quantify any potential contaminant radionuclides.
- Under certain circumstances (i.e. radiopharmaceutical products containing radionuclides with radioactive half-life of less than 60 minutes), post-release endotoxin content determination is permitted. The decision to perform this test post-release should be based on a risk assessment unless specified in a pharmacopoeial monograph.

11.4. For radiation safety reasons, final product pH testing may be conducted using pH paper or strips unless the pharmacopoeial monograph has specific requirement for using pH meter.

11.5. Quality control Testing of radiopharmaceuticals containing radionuclides emitting, low energy gamma, mixed energy gamma, beta, and alpha radiation (for example, ^{124}I, ^{177}Lu, ^{161}Tb, or ^{212}Pb, ^{225}Ac) may require additional consideration and controls. At a minimum:

- When measuring radioactivity in a dose calibrator, a dial setting specific to the geometry (i.e. a specific type of vial or vials that contain either the final product or quality control sample) that is used to measure the radioactivity at a specific facility should be established. This can be accomplished through either verification of reference sources, if available, or through conduction of high purity germanium detector gamma spectrometry studies and subsequent cross-calibration.
- When measuring radioactivity of radiopharmaceuticals containing radionuclides with radioactive progeny (for example, ^{225}Ac or ^{212}Pb) in a dose calibrator, the measurements may need to be conducted once the radioactive parent-daughter secular equilibrium is reached.
- HPLC testing of radiopharmaceuticals containing non-gamma emitting parent radionuclides with gamma emitting radioactive progeny (for example, actinium-225), requires fraction collection and counting using a calibrated gamma counter as the direct accurate detection of alpha radiation by the radioactivity detectors currently available is not possible. The frequency of fraction collection must be clearly defined

in written SOP. In addition, HPLC system used for quality control of alpha emitters must be completely segregated and only used for ^{225}Ac products, to avoid cross-contamination with radionuclides with higher energies, that will interfere with accurate measurements.

- High purity germanium detector gamma spectrometers used to measure the radioactivity must be appropriately calibrated for energy, peak shape, and efficiency, using an accurate multi-source reference standard. Suitability testing must be conducted on the gamma spectrometer prior to each analysis. The geometry of the efficiency calibration reference standard must be identical to the geometry of the quality control sample.

12. Reagents and standards

Reagents

12.1. All reagents and chemicals, including solvents and materials used in tests and assays, should be of an appropriate quality and suitable for the intended use *(1)*.

12.2. Reagents should be purchased from qualified suppliers and should be accompanied by the certificate of analysis, and the material safety data sheet, if required.

12.3. For the preparation of reagent solutions in the laboratory:

a) responsibility for reagent preparation should be clearly defined in the job description of the assigned personnel;

b) prescribed procedures should be followed, adhering to pharmacopeial standards or other recognized guidelines where available; and

c) records should be maintained for the preparation and standardization of volumetric solutions.

12.4. All reagent labels should clearly indicate:

a) contents (name and composition);

b) manufacturer's details;

c) date of receipt and date of container opening;

d) concentration, or radioactivity measurement details, if applicable;

e) storage conditions and, if applicable, any specific protection measures (such as protection from heat, light or atmosphere); and

f) expiry date or retest date, with justification where applicable.

12.5. For in-house prepared solutions, labels should specify:

a) name of the solution;

b) date of preparation and initials of technician or analyst;

c) molarity (or concentration), if applicable;

d) expiry date or retest date, as justified; and

e) concentration, or radioactivity measurement details, if applicable.

12.6. Reagents must be stored under appropriate conditions as defined by the manufacturer, including temperature and humidity control. For radioactive solutions, appropriate shielding must also be ensured.

Reference standards

12.7. Reference standards may be used for testing samples of finished radiopharmaceutical products. A typical radiopharmaceutical reference standard is the "cold" (non-radioactive) reference compound of the radiopharmaceutical (for example, [^{19}F]FDG for [^{18}F]FDG), which may be used for identification or quantification purposes (such as constructing a calibration curve). Stability of reference standards in solution needs to be established, unless provided by the supplier of the standards

12.8. For radiopharmaceuticals labelled with elements that lack naturally occurring non-radioactive isotopes (for example, technetium, astatine, or actinium), an appropriate alternative reference standard may be used, such as:

- the precursor compound; or
- a compound labelled with another element that results in a final compound with similar physicochemical properties.

The choice of reference standard should be scientifically justified on a case-by-case basis.

12.9. Reference substances are also used for the calibration of radioactivity detectors, gamma spectrometer detectors, and dose calibrators. These typically consist of calibrated sources containing long-lived radionuclides that emit suitable energies. Such sources may include:

- a single-radionuclide source (for example, cesium-137) for routine dose calibrator checks;
- a multi-nuclide source, containing several radionuclides for high purity germanium detector energy and efficiency calibration; and
- a multi-gamma source, which is a single radionuclide emitting across a broad spectrum of energies, commonly used for gamma spectrometer energy calibration.

The selection of calibration sources should be made case-by-case, depending on the intended analysis and radionuclides involved.

12.10. Other useful reference standards, as previously mentioned, include:

- buffer solutions for pH meter calibration;
- certified reference weights for analytical balance calibration; and
- substances with known absorbance for the calibration of UV detectors.

12.11. Each reference substance and radioactive calibrated source should be traceable via a unique identification number or reference.

12.12. The identification number or reference must be documented in the analytical test report, each time the reference substance is used.

13. Testing and methodology

13.1. The Analytical tests to be performed should be determined based on a thorough evaluation of various factors, including:

- the type of sample being analysed (for example, a finished radiopharmaceutical product, radionuclide, or starting material);
- the respective specifications and quality standards;
- the radioactive half-life;
- the type(s) of radiation being emitted; and
- other relevant physicochemical properties.

Pharmacopoeia monographs may provide an essential reference for selecting certain required tests. Not all tests described in monographs may be mandatory dependent on specific product characteristics (production routes, composition of formulation).

13.2. Basic physicochemical quality control tests for radiopharmaceuticals may be classified as follows:

Tests for identification

The identity of a radiopharmaceutical cannot be verified using conventional direct analytical methods such as Nuclear Magnetic Resonance (NMR) or Mass Spectrometry (MS). This is due to several limitations:

a. the analysis time required is often incompatible with the short half-life of many radionuclides;
b. the need for radiation protection limits the feasibility of such techniques; and
c. the low physical mass of radiopharmaceuticals often provides insufficient sample material for mass-based detection methods.

As a result, radiopharmaceutical identification is typically performed using indirect testing methods that either:

- compare the radiopharmaceutical with a suitable reference standard; or
- utilize the decay properties of the radionuclides for verification.

The identification tests aim to confirm both:

- the identity of the radionuclide (the "radio" component); and
- the identity of the molecular structure binding the radionuclide (the "pharmaceutical" component).

Key identification tests

- Half-Life Determination:
  - Typically performed using dose calibrators, which verify that the time/activity curve of the sample matches the known half-life of the radionuclide.
  - Gamma spectrometers may also be used for half-life determination, although they are primarily employed for energy emission analysis (see below).
- Energy Emission Spectrum Analysis (Gamma Spectrometry):
  - Gamma spectrometers determine the emitted energy spectrum, which provides a unique "fingerprint" for each radionuclide. The test that is required for identity testing of the radionuclide can be found in respective monographs.
- Molecular Structure Identification:
  - Typically verified using high performance liquid chromatography (HPLC) equipped with a dual detector system (a radioactivity detector and a mass-based detector).

- The retention time of the primary peak in the radiochromatogram is compared with the retention time of the UV peak obtained from an authentic non-radioactive reference standard.

Alternative Identification Methods:

Other techniques may be used depending on the nature of the radiopharmaceutical, such as:

- thin-layer chromatography (TLC);
- colorimetric assays;
- electrophoresis;
- particle size determination; and
- radio-immunoreactive fraction determination assay, combined with size-exclusion high performance liquid chromatography (SEC-HPLC).

Impurities tests aim to quantify the percentage and/or amount of impurities present in the final radiopharmaceutical preparation. Impurities in radiopharmaceuticals can be classified into the following categories:

a. Radionuclidic Impurities

- These impurities refer to radioactive contaminants that originate from radionuclides other than the intended radionuclide.
- Detection Method:
  - Typically determined using gamma spectrometry, which identifies emitted energy spectra characteristic of contaminant radionuclides, once the parent radionuclide has decayed.
  - Dose calibrators may also be used in specific cases, such as in the determination of molybdenum-99 breakthrough in the routine control of technetium-99m generators.

b. Radiochemical Impurities

- These impurities refer to chemical forms of the intended radionuclide which are different from the desired radiopharmaceutical compound. Their presence affects radiochemical purity, which is crucial for ensuring proper biodistribution and targeting of the radiopharmaceutical.
- Detection Method:
  - Typically analysed using HPLC equipped with a radiation detector or radio-thin layer chromatography (radio-TLC).

- Alternative methods may be used depending on the specific radiopharmaceutical.
- Filtration tests for human albumin macroaggregates, ensuring the proper particle size distribution.

c. Chemical Impurities

- The nature of non-radioactive impurities varies depending on the specific radiopharmaceutical synthesis route and may include:
  - the non-reacted substrates and products of the decomposition;
  - by-products generated during the radiosynthetic process;
  - metal catalysts;
  - metallic impurities;
  - phase transfer catalysts (for example, Kryptofix® in fluorine-18 chemistry); and
  - residual solvents.
- Detection Method:
  - Analytical methods for chemical impurities vary widely and depend on the nature of the impurity and the radiopharmaceutical formulation.
  - As a result, a detailed discussion of chemical impurity testing methods falls outside the scope of this guideline.

14. Sampling

14.1. Sampling should be representative of the batch from which they are taken. It must be conducted in a manner that prevents contamination, mix-ups, or any other adverse effects on quality *(9)*.

14.2. Sampling procedures should be adapted based on the type of material being analysed. For non-radioactive starting materials, standard sampling procedures and criteria may be followed *(9)*.

14.3. In majority of situations, radiopharmaceuticals are present as a clear and homogeneous solutions packaged in glass vials. Sampling generally involves withdrawing an aliquot of the

solution in a volume sufficient for the intended analysis. In such a scenario, an aliquot is representative of the entire batch and random sampling is not required.

14.4. Quality control of radiopharmaceuticals in solid forms (for example, ^{131}I capsules) may require strategic sampling of material to ensure that the obtained quality control sample results are representative of the entire batch. Factors such as batch size should be taken into account when deciding on the number of samples and randomization of sample collection.

14.5. The container holding radioactive samples should be stored with adequate radiation shielding and should be pre-labelled with essential information, including at a minimum:

- date and time of sampling (if applicable);
- name of the radiopharmaceutical or radionuclide; and
- batch number.

14.6. Sampling of radioactive material should consider ALARA principles. Whenever possible, automated sampling systems located in suitably shielded environments (for example, automated dispensing systems) should be used.

14.7. In cases where batch size is limited (often a single vial), sampling may need to be performed manually by withdrawing an aliquot using a syringe. In such cases, the batch vial should be placed behind a suitable shielding barrier to protect the operator from radiation exposure.

14.8. Samples should be of an adequate volume to allow for the completion of all necessary quality control tests. A single sample may be withdrawn from the finished radiopharmaceutical vial and then distributed into multiple aliquots, each designated for a specific analytical test.

14.9. For radiopharmaceuticals in gaseous form, sampling should be performed using a suitable collection system that ensures proper delivery of the sample to the analytical instrument (for example, a gas chromatograph).

14.10. If necessary, a sample may be diluted with an appropriate diluent to achieve suitable condition for analysis.

14.11. Quality control samples do not need to be retained unless there is a viable and scientifically justified method, and a need, to re-test samples in the future. In practice, because most radiopharmaceutical products are very short lived, due to either short radioactive half-life or continuous auto radiolysis, quality control sample retention for the majority of radiopharmaceutical products is not required.

15. Validation of analytical procedures

15.1. All analytical procedures used for quality control testing of radiopharmaceutical products must be suitable for their intended purpose. However, the analytical methods applied to quality control of radiopharmaceuticals may be divided into two general categories: (1) analytical methods described in relevant pharmacopeia chapter either as stand-alone method or as part of quality control testing of a specific product; or (2) analytical methods not described in any pharmacopeia.

15.2. In general, compendial or pharmacopeial analytical methods described in regionally recognized pharmacopeia chapters do not require additional validation. In limited circumstances, there may be a need to verify that a general compendial method may be suitable for a specific product or material being tested.

15.3. Non-compendial analytical methods applied to quality control testing of non-investigational radiopharmaceuticals do require additional method validation to ensure those methods are suitable for their intended purpose *(10,11,12)*. Validation also establishes acceptance criteria for system suitability tests, which are subsequently performed to verify the analytical procedure before analysis.

15.4. Validation should be conducted according to an approved validation protocol, which outlines the analytical performance characteristics to be evaluated based on the type of analytical procedure.

- For validation of non-radioactive products, validation parameters should align with the regionally recognised standards or guidelines (for example, WHO recommendations, as well as recommendations the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on analytical method validation *(10,11,12)*.
- For radioactive products, validation parameters should align with the regionally recognised standards or guidelines (for example, EANM guidelines on the validation of analytical methods for radiopharmaceuticals) *(13)*. It should be recognized, however, that the published guidelines are only recommendations and should be applied whenever scientifically possible. The ability to establish analytical method validation parameters is ultimately dependent on the specific radioactive material being tested and the type of analytical method being applied. Therefore, the relevant

analytical method validation parameters may need to be decided on a case-by-case basis, if compliance with the published recommendations is not possible.

All validation results must be documented in a manner that ensures traceability.

15.5. Analytical method revalidation is required whenever any changes that render the method no longer fit for the intended purpose occur. These changes may be related to the material being tested (for example, changes in sample analyte concentration or chemical composition) or in the analytical method itself (for example, changes in analytical instruments being used or changes in methods of analysis). The need for revalidation should be decided by a responsible person(s) based on risk-assessment on a case-by-case basis.

15.6. System suitability testing is an essential component of many analytical procedures. The specific system suitability tests required depend on the type of analytical method used.

- These tests should be conducted before quality control sample analysis using appropriate reference standards.
- If the system suitability criteria are met, the instrument is considered fit for its intended analysis.

15.7. Comprehensive Analytical Method Validation is usually not required for quality control methods applied in the testing of novel compounds used in Phase 0 and Phase I clinical trials.

16. Specifications

16.1. For substances or radiopharmaceuticals specification with an official monograph in *The International Pharmacopoeia*, the specifications may be defined based on the respective pharmacopoeial monograph.

16.2. For substances or radiopharmaceuticals that are covered by other recognized pharmacopoeias (for example, European Pharmacopoeia, United States Pharmacopeia) or by publicly available assessed dossiers (for example, for clinical trials or marketing authorization applications), these references may be adopted after a thorough evaluation of the proposed specifications to ensure suitability.

16.3. For substances or radiopharmaceuticals without an existing pharmacopoeial reference (for example, newly developed radiopharmaceuticals or active pharmaceutical ingredients), specifications should be established based on:

- comprehensive knowledge of the substance or radiopharmaceutical;
- validation data collected during radiopharmaceutical development; and

- reference to general monographs, such as *The International Pharmacopoeia*'s general monograph on radiopharmaceuticals (*14,15*), where applicable.

16.4. For finished radiopharmaceutical products, the following testing parameters/characteristics should be considered:

- appearance;
- pH;
- identification and quantification of the non-radioactive (cold) counterpart (for example, via HPLC or another suitable technique), if applicable;
- identification and quantification of impurities, if applicable;
- identification and quantification of excipients, if applicable;
- identification of the radionuclide (for example, via gamma spectrometry, including approximate half-life determination if applicable);
- excipients (for example, guidelines for specific excipients such as ethanol should be followed) (13);
- quantification of unknown peaks seen on the HPLC UV trace (i.e. "chemical purity"), if applicable;
- radiochemical identity;
- radiochemical purity;
- radionuclidic purity: this test does not need to be conducted on every batch or radiopharmaceutical product and may be done periodically, if warranted (for example, for in-house cyclotron produced or in-house radiochemically isolated radionuclides). For radionuclides supplied from qualified suppliers, the radio-nuclidic purity data provided by the radionuclide supplier may be used by the producer, with no additional testing required. For generator produced radionuclides, the radio nuclidic purity testing should follow the recommendations from the generator supplier;
- specific activity at EOS/EOP time, if applicable;
- endotoxin content;
- sterilizing filter integrity testing, if applicable;
- radioactive concentration at EOS/EOP time;
- dissolution time, if applicable (for example, for solid radiopharmaceuticals such as ^{131}I capsules); and

- radio-immunoreactivity, if applicable (for example, radiolabelled monoclonal antibodies).

16.5. Specifications and acceptance criteria must be met throughout the entire shelf-life of the radiopharmaceutical.

16.6. "Out-of-specifications" results must be thoroughly investigated by the responsible person in the quality control laboratory, with support from analysts. The outcome of the investigation should be documented and archived.

16.7. A dedicated standard operating procedure for investigation of out-of-specifications results must be in place. The SOP should outline clear steps, typically including:

- verification of the operations executed by the operators;
- review of specifications and analytical methods;
- check of calculations, if applicable;
- re-evaluation of all results;
- examination of reference standards, if used;
- verification of instrument performance;
- review of instrument calibration status; and
- evaluation of system suitability test results.

16.8. If the OOS result is determined to be caused by a clear and identifiable error during the initial analysis, it may be invalidated, and the testing may be repeated. The batch may still be released, based on re-testing results. The decision to re-test and to subsequently release the batch should be made by the responsible person(s).

16.9. If an OOS result is confirmed, the batch of the starting material, radionuclide, or radiopharmaceutical must be rejected or recalled if it has been supplied to a user.

16.10. In cases where results are inconclusive, re-sampling and/or retesting is permitted if there is clear evidence that the initial results were invalid. This decision should be made by the responsible person(s).

17. Contracts

17.1. Contractors should be evaluated and qualified in accordance with a written procedure. Records of this evaluation process must be maintained. The responsibilities of each party should be clearly defined in a written agreement *(1).*

17.2. A written contract must be established, clearly outlining:

- the duties and responsibilities of each party;
- the scope of the contracted work (for example, sterility testing);
- any technical arrangements related to the contract; and
- audits of the contractor should be conducted as necessary *(1).*

17.3. The contracted organization is not permitted to subcontract any work entrusted to it without prior evaluation and approval by the laboratory.

17.4. The laboratory should:

- maintain a register of all subcontractors used; and
- keep records of the competence assessments of subcontractors.

17.5. The laboratory retains full responsibility for all reported results, including those generated by subcontracted organizations.

18. Safety

Personnel safety

18.1. Safety in the quality control laboratory for radiopharmaceuticals is often underestimated, yet it should be a top priority. Although the radioactivity levels handled in these laboratories are relatively low, most manipulations are performed manually, increasing the risk of radiation exposure and contamination. Therefore, strict safety measures must be in place to minimize unnecessary worker exposure and contamination risks *(2).*

18.2. All personnel working in the quality control laboratory must wear personal dosimetry devices and appropriate personal protective equipment (PPE) at all times *(5,6)*.

18.3. Special precautions must be taken when handling alpha-emitting radionuclides, due to their high emission energy and short penetration range. While they pose a lower risk of external radiation exposure, they are difficult to detect, and ingestion or inhalation can result in serious radiation hazards. Extra surface contamination control measures should be implemented to minimize the risk of ingestion or inhalation.

18.4. General and specific safety instructions, reflecting identified risk, should be made available to all staff members and regularly updated as needed. Training materials may include:

- written guidelines;

- poster displays;
- audiovisual materials; and
- safety seminars and workshops *(1)*.

Environmental safety

18.5. The handling of quality control samples should be conducted in a shielded fume hood or, at minimum, behind a suitable shielded protective barrier. The thickness of the shielding must be determined based on the type and activity of the radionuclide being handled. Additionally, quality control equipment should be shielded when necessary (for example, HPLC column and waste HPLC eluent bottle).

18.6. Radioactive waste generated during quality control activities must be stored in suitable shielded containers until radioactive decay has sufficiently reduced its activity to safe levels.

18.7. Standard chemical safety requirements applicable to laboratories handling flammable, corrosive, toxic chemicals, and gases must also be observed in radiopharmaceutical quality control laboratories.

General rules for safe laboratory practices

18.8. All personnel must adhere to national regulations and standard operating procedures to ensure safe working conditions. These include:

- Safety data sheets should be available to staff before conducting any testing.
- All staff should be trained in the proper use of fire extinguishers and on the safe handling of glassware, corrosive reagents, and solvents.
- Personnel should wear laboratory coats or other protective clothing, including eye protection.
- All chemical containers must be clearly labelled with hazard warning signages such as:
    - "Poison";
    - "Flammable"; and/or
    - "Radioactive" (where applicable).
- First-aid kits should be available, and staff should be trained in:
    - first-aid techniques;

- emergency medical response; and
- use of antidotes for chemical exposures.

- The appropriate protective clothing should be available, including:
  - eye protection (safety goggles); and
  - face masks and gloves.
- Safety showers should be installed and maintained.
- Poisonous or hazardous substances must be identified and clearly labelled. However, staff should be reminded not to assume that other chemicals and biological materials are inherently safe.

Abbreviations

ALARA: as low as reasonably achievable
HPLC: high performance liquid chromatography
MS: mass spectrometry
NMR: nuclear magnetic resonance
TLC: thin layer chromatography
CoA : Certificate of Analysis

References

1. WHO good practices for pharmaceutical quality control laboratories. WHO Technical Report Series, No. 957, Annex 1. Geneva: World Health Organization; 2010; (https://www.who.int/publications/m/item/trs957-annex1).
2. International Atomic Energy Agency (IAEA) and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 2 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/m/item/trs-1025-annex-2-gmp-radiopharmaceutical-products.
3. IAEA/WHO Good Manufacturing practices for in-house cold kits for radiopharmaceutical preparations.

4. WHO good practices for pharmaceutical microbiology. WHO Technical Report Series, No. 961, Annex 2. Geneva: World Health Organization; 2011; (https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs961-annex2-goodpractices-pharmaceutical-microbiology-laboratories.pdf?sfvrsn=ebd1845e_0).

5. IAEA safety standards for protecting people and the environment. Radiation protection and safety of radiation sources: international basic safety standards. Jointly sponsored by EC, FAO, IAEA, ILO, OECD/NEA, PAHO, UNEP, WHO. (Safety Requirements No. GSR. Part 3). Vienna: International Atomic Energy Agency; 2014; (https://www-pub.iaea.org/mtcd/publications/pdf/pub1578_web-57265295.pdf).

6. Radiation Protection and Safety in Medicinal Uses of Ionizing Radiation. (Specific Safety Guide No. SSG-46). Vienna. Jointly sponsored by IAEA, ILO, PAHO and WHO; 2018; (https://www-ns.iaea.org/standards/).

7. Quality control in the production of radiopharmaceuticals. IAEA TECDOC 1856. Vienna: International Atomic Energy Agency; 2018; (https://www-pub.iaea.org/MTCD/Publications/PDF/TE-1856web.pdf).

8. Guidance on good data and record management practices. WHO Technical Report Series No. 996, Annex 5. Geneva: World Health Organization; 2016; (https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/trs966-annex05-fr-who-record-management-practices.pdf?sfvrsn=6218a4e6_4&download=true).

9. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Technical Report Series, No. 929, Annex 4. Geneva: World Health Organization; 2005; (https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs929-annex4-guidelinessamplingpharmproducts.pdf?sfvrsn=f6273f30_2).

10. Supplementary guidelines in good manufacturing practice: Validation. Analytical method validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fortieth report. WHO Technical Report Series, No. 937, Annex 4. Geneva: World Health Organization; 2006; (https://iris.who.int/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf).

11. ICH Q2 (R2): Validation of analytical procedures. In: ICH Harmonised Guideline. Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2023; (https://www.ich.org/page/quality-guidelines).

12. WHO good practices for pharmaceutical quality control; (https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/current-projects/qas21.882_who-good-practices-for-pharmaceutical-quality-control-laboratories.pdf?sfvrsn=a277b05c_1).

13. Gillings N, Todde S, Behe M, Decristoforo C, Elsinga P, Ferrari V, Hjelstuen O, Peitl PK, Koziorowski J, Laverman P, Mindt TL, Ocak M, Patt M. EANM guideline on the validation of analytical methods for radiopharmaceuticals. EJNMMI Radiopharm Chem. 2020 Feb 12;5(1):7. doi: 10.1186/s41181-019-0086-z. PMID: 32052212; PMCID: PMC7016057.

14. Guide for the elaboration of monographs on radiopharmaceutical preparations. Pharmacopoeia E. Strasbourg: European Directorate for the Quality of Medicines & Healthcare; 2024; (https://www.edqm.eu/en/d/66901).

15. General Monograph. In: WHO Department of Essential Medicines and Health Products. Tenth Edition of the International Pharmacopoeia. 4.25. Geneva: World Health Organization; 2022; (https://digicollections.net/phint/2022/index.html#d/b.6.3.1).

16. Questions and Answers on Ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use'. (CPMP/463/00). In: Committee for Human Medicinal Products. London: European Medicines Agency; 2014; (https://www.ema.europa.eu/en/ethanol).

***