

GUIDELINES ON CURRENT GOOD RADIOPHARMACY PRACTICE (cGRPP) IN THE PREPARATION OF RADIOPHARMACEUTICALS

General

Preparation of radiopharmaceuticals for injection involves adherence to regulations on radiation protection as well as to appropriate rules of working under aseptic conditions, which are covered by these guidelines on Good Radiopharmacy Practice (GRPP). The handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation emitted and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, and to waste disposal. A continuous assessment of the effectiveness of the Quality Assurance system is essential to prove that the procedures applied in the Radiopharmacy Department lead to the expected quality.

Clinical trials with new radiopharmaceuticals should follow these regulations on cGRPP as well as the Guideline on Good Clinical Practice.

As there is a considerable difference in complexity in preparing “classical” radiopharmaceuticals in “kit” procedures and producing radiopharmaceuticals by distinct chemical procedures (Positron Emission Tomography (PET) Radiopharmaceuticals, in house prepared radiopharmaceuticals including in house prepared kits*) these guidelines have been divided in two parts (A and B) respecting these differences.

**For simplicity in the text these will collectively be covered by the term PET radiopharmaceuticals*

Part A. Guidelines on Current Good Radiopharmacy Practices (cGRPP) for kit-based Radiopharmaceuticals in Nuclear Medicine

Chapter 1. Personnel and Resources

In place has to be enough personnel with the necessary education, background, training, and experience and the resources, including equipment and facilities, to enable them to perform their functions.

General

Only trained people should be responsible for and participate in the preparation and quality control of radiopharmaceuticals. All operations should be carried out under control of a responsible person. Personnel involved in release of the prepared radiopharmaceuticals should be appropriately trained in quality systems, GRPP and regulatory requirements specific to this type of products.¹

All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are handled should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

Training should be provided for all staff working in radiopharmacy departments in the aspects of Quality Assurance in which they are involved. This includes: preparation, release, quality control and analytical techniques, cleaning, transport, calibration of equipment (especially for the measurement of radioactivity), working practices in the radiopharmacy, preparation of the individual doses, documentation, hygiene and pharmaceutical microbiology, microbiological monitoring. A description of the training and records of completion should be kept.

The responsibilities should be outlined in job descriptions.

Aseptic techniques

Personnel should appropriately apply aseptic techniques throughout the handling of radiopharmaceuticals for injection, including the radiolabelling of kits. This implies the use of special clothing, sterile gloves, sterile vials, sterile syringes, sterile needles and sterile diluents, and that the work is done in a well-planned and expedient way.

Radiation protection

Control of personnel radiation exposure is performed with approved personal dosimeters, which are regularly checked and their readings recorded. This control may be supplemented with electronic dosimeters, finger dosimeters etc. After work, both personnel and work places must be checked for radioactive contamination with suitable monitors. Any contamination must be removed immediately or must be contained and access to the contaminated area must be denied until the radioactivity has decayed to an appropriate dose level.

Chapter 2. Quality assurance

There has to be a quality assurance unit that can oversee preparation operations to ensure that a radiopharmaceutical of sufficient quality is prepared.

¹ *The EANM syllabus on radiopharmacy covers the main aspects of the knowledge required for the responsible person.*

Chapter 3. Equipment and facilities

General

Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. The equipment used should be reserved exclusively for radiopharmaceuticals. The radiopharmacy has to be organized in such a way as to minimize the risk of cross contamination and mix-up. Only the necessary equipment should be located there. Access to the controlled areas should be via a gowning area and should be restricted to authorized personnel. Guests and technical staff should follow appropriate rules for access, which should be described in a special instruction. After repairs the premises have to be cleaned and decontaminated appropriately.

The technetium-99m generator and the working area for the preparation of technetium-99m labelled radiopharmaceuticals should be located in a controlled area. The room must be approved for work with open radioactive sources. The solutions of ^{99m}Tc eluate and the ready preparations have to be stored in well-shielded conditions.

Appropriate measures should be taken to avoid the spread of radioactivity from the controlled areas and to protect the controlled areas from particular and bacterial contamination

The storage and handling of any kind of biological material should be avoided in the same place. An exception can be made for the preparation of radiopharmaceuticals from patient origin, e.g. the preparation of labelled blood components. However, where available, a separate room or Grade A workstation should be used for labelling of patient's autologous cells.

Technetium-99m generator and dose calibrator location

In order to minimize the radiation risk to the personnel the generator must be adequately shielded. The lead surfaces of the shielding must be covered. The needle(s) of the generator must be covered between elutions, using the special vials or caps delivered with the generator. This precaution should be applied according to the supplier's instructions.

The generator should be placed in a Grade A environment.

The dose calibrator(s) should be properly shielded from background activity influence.

Preparation area

For sterile radiopharmaceuticals the working area where products are prepared should comply with appropriate environmental requirements. This may be achieved by the provision of a workstation with a laminar flow of HEPA-filtered Grade A air or a total containment workstation. The workstations should be in an environment conforming to at least Grade D. This can also be ascertained by surrounding the laminar flow workstation by a curtain of filtered Grade A air.

The aseptic workstation should be sanitised at appropriate intervals.

Monitoring

Workstations and their environment should regularly be monitored with respect to microbiological quality.

Maintenance and Cleaning

All surfaces (walls, floor, tables and furniture) must be made out of materials easy to clean and disinfect and to decontaminate in case of a radioactive spill. Sinks used should be outside the preparation area.

Facilities and equipment

Equipment must be qualified.

Daily checks must be performed on radionuclide dose calibrators. Background activity should be checked every time the dose calibrator is used. Any increase of the background readings should be investigated

A check of constancy using a long-lived radioactive source with a valid calibration certificate should be performed before use for each setting on any day.

Regular calibration of radionuclides, in the appropriate containers (vial, syringe), with the sample volumes and position in the calibrator used should be undertaken with radionuclides traceable to national or international standards.

A linearity check of the dose calibrator-response over the complete range of activities measured should be undertaken at least annually.

Devices used for radiochemical purity determination such as a dose calibrator, gamma counter, gamma camera, thin layer chromatography scanner, high performance liquid chromatography radioactivity detector and autoradiography apparatus, require determination of background activity each time when used for measurements and regularly verification of detection linearity and accuracy of measurement.

Other equipment used for preparation of radiopharmaceuticals such as water baths, thermometers, heating plates etc. have to be checked for correctness of the settings.

A system of planned preventive maintenance and calibration should be operated to ensure that all facilities and equipment used in the preparation of radiopharmaceuticals are regularly maintained and calibrated where appropriate. Records and logs should be kept for all equipment irrespective of whether maintenance and calibration is performed in house or by external contractors.

Chapter 4. Documentation

A system of documentation must be in operation at the Department allowing the traceability of each preparation, starting from the prescription to the administration of the individual patient doses.

The instructions and Standard Operating Procedures (SOPs) should be written and independently approved for each procedure or activity associated with the operations of the department. SOPs should be reviewed and re-issued at least every two years.

A specification should be available for each component used as well as for the finished radiopharmaceutical.

Records should be kept for the legally required period of time of:

- Purchase and check on arrival of all ingredients and expipients
- Purchase and check on arrival of radioactive products
- Generator elution: activity (date, time), molybdenum-99 breakthrough and, if tested, aluminum ion breakthrough
- Product preparation: batch numbers, activity and volume added, results of quality control and release
- Laboratory cleaning and maintenance
- Equipment calibration and maintenance
- Training of personnel
- Transport of radioactive materials
- Radioactive contamination monitoring and radioactive waste disposal
- Product defects and events of non-conformity to SOPs
- Prescription of patient doses.
- Microbiological monitoring

Chapter 5. Preparation and Process Controls

All goods received should be checked against the order for correctness of delivery. Records of batch numbers and quantities received should be kept. In addition a visual inspection should be carried out prior to acceptance. Products or kits with Marketing Authorization should be used wherever possible. Materials should only be used within the declared shelf life.

The preparation of radiopharmaceuticals should be organized in a way preventing cross-contamination of the product. Process validation, in process controls and monitoring of process parameters and environment are particularly important in cases where it is necessary to take the decision to release or reject a batch or a product before all tests are completed.

The specific information about the handling of the technetium-99m generator, including instructions for generator elution, checking of the elution yield and other tests of generator quality is given in the package insert supplied with the generator. Similarly, the package insert of the labelling kits gives detailed information about the procedure of kit labelling. Manufacturer instructions are based on the experience acquired with the particular generator or kit. The package insert is approved by national authorities. It is a pre-requisite for a correct handling of a technetium-99m generator and the labelling of kits that the package insert be carefully read and followed. Any deviations from the procedures in the package insert have to be validated and approved.

All rubber stoppers, including those on the eluate vials, must be wiped with a disinfecting agent immediately before puncture. The solution of the disinfecting agent should be allowed to evaporate completely before puncture, as the introduction of this agent may influence kit performance. The elution shield and the shields for vials and syringes must be checked for contamination and cleaned inside and outside before use, preferably with 70% ethanol or isopropyl alcohol.

The aseptic process has to be validated. New personnel have to be qualified by media fills and all personnel requalified at regular intervals.

Transport of eluates and preparations inside the department must take place within shields, e.g. the elution shield, syringe shield.

In order to minimize the personnel exposure to radiation, proper shielding is needed as well as proper planning of the handling of the radioactive products. The elution shield delivered with a technetium-99m generator should always be used and technetium-99m solutions stored in suitable shielding. Tongs or tweezers should always be used when the technetium-99m solutions are handled outside the lead shielding, e.g. when measuring activity in the dose calibrator.

All containers for radiopharmaceutical preparations (including syringes) must be identified by: name of the preparation, date and time of preparation, amount of radioactivity, volume, expiration time, international symbol of radioactivity; the amount of radioactivity and the volume may be written on the label on the lead shielding.

Chapter 6. Quality control

The specifications and quality control testing procedures for most of the currently used radiopharmaceuticals are given in the European Pharmacopoeia or other Pharmacopoeia (BP, USP etc.). It is accepted that full testing of products to pharmacopoeia methods in the Radiopharmacy Department before release is often not possible.

There should be a written procedure detailing all Preparation and Quality Control data that should be considered before the preparation is dispatched. A procedure should also describe the measures to be taken by the responsible person if unsatisfactory test results are obtained.

Parameters to be assessed on every product prior to release

- The label has to be checked for correctness and completeness
- Total radioactivity. Since the radioactivity content determines the radiation dose to the patient, each patient dose should have an independent check of its total radioactivity prior to administration. The activity of each patient dose must be carefully measured and documented.
- Appearance and freedom from gross particulate contamination

Quality control parameters of the eluates of technetium-99m generators

- Molybdenum-99 breakthrough on the first eluate from each technetium-99m generator
- Elution activity must be measured on each eluate.
- Aluminum ion breakthrough should be checked on any eluate used to prepare products that are adversely affected by the presence of aluminum ions.

Labelling kits are prepared at a manufacturers facility and released for sale after all prescribed quality control tests are completed. Therefore, the composition, chemical purity, apyrogenicity, sterility and particle size (where applicable) are guaranteed by the producer. The instructions for use accompanying the kit should strictly be followed when the labelling procedure is performed. Any deviation from these instructions has to be validated. Verification of the effectiveness of the applied labelling procedure is done by checking the final activity (at a stated time), the labelling yield and/or radiochemical purity of the preparation as well as particulate contamination. Parameters such as particle size (if applicable), sterility, pH, and isotonicity should be controlled at regular time intervals as well.

Quality control parameters of kits for labelling with technetium-99m and resulting radiolabelled preparations

- Integrity upon receipt
- Radiochemical purity (RCP) testing of products prepared from licensed labelling kits should be performed on each preparation.
- Unlicensed radiopharmaceuticals, whether purchased as finished products, prepared form unlicensed kits or prepared according to in-house formulae, should be fully tested on each occasion.
- Sterility should be controlled on a random sampling following decay of radioactivity.
- The particle size of particulate radiopharmaceuticals used for lung perfusion imaging or particle sizing of colloidal radiopharmaceuticals may be valuable in ensuring consistent pharmacokinetics of the product. This involves light microscopic methods or membrane filtration.
- The preparation of radiopharmaceuticals and their quality control should, if possible, be performed in separate rooms.
- Measurement of pH using narrow range pH paper may be undertaken on technetium-99m generator eluates and on products known to have a non-physiological pH or products for which the pH has to be adjusted during the labelling procedure.

Sterility and bacterial endotoxins testing

The purpose of sterility testing is to ensure that the procedures used in the radiopharmacy result in sterile products. The frequency of testing depends on the experience of the Department. The aseptic preparation and dispensing procedures should regularly be checked,

especially if new personnel are involved. Usually, the samples for sterility testing are stored for sufficient radioactivity decay and then sent for sterility testing by an external, validated laboratory. Internal sterility testing is only recommended if according to the European Pharmacopoeia, dedicated rooms and equipment are available.

Pyrogen or bacterial endotoxin testing of radiopharmaceuticals is not routinely carried out. The Limulus amoebocyte lysate (LAL) test may be usefully employed as part of the validation of new systems or changes in working practice. When one or more column purifications are involved in the preparation of a radiopharmaceutical, a bacterial endotoxin test must be performed on the final preparation. The procedure should be validated before introduction in routine use and preparations may be released for use before completion of the bacterial endotoxin test.

Environmental monitoring is crucial to maintain aseptic conditions. Microbiological testing of the aseptic workstation should be performed periodically. Methods can include using swabs or contact plates for surfaces, and settling plates or dynamic air samplers for air quality.

Preparations from autologous patients' material

Strict requirements regarding aseptic handling of patient autologous material have to be followed. All starting materials should be identified. For any reagent, material or solution specifically intended for human use it has to be tested and documented that its specifications meet the required standards. Only materials and reagents certified for human use must be used.

Preparation of labelled cells must be performed one after the other or by different people in different locations.

The following checks should be performed:

- Calculation of the labelling yield of every preparation
- Control of radiochemical purity (as far as possible) on every preparation before administration
- Control of patient identity prior to administration
- Control of cell viability, morphology or function, depending on the cell type, on the first three preparations (same reagents and personnel).

Kits prepared in house:

More elaborate Good Radiopharmacy Practice requirements have to be followed when kits are prepared in house (follow Part B of these Guidelines).

Chapter 7. Finished Radiopharmaceutical Controls and Acceptance Criteria

The Responsible person should take a formal, recorded decision of approval before a product is released.

The Responsible person should not normally be the person who prepared the product, although there may be no alternative.

The Responsible person should be suitably trained and have documented evidence of competence.

There should be a written procedure for dealing with products failing to meet the required standard. Such events should be investigated, and measures taken to prevent future events and this process must be documented.

There should be a written release procedure.

Release can only be effected if:

- The product complies with the specifications
- The product has been prepared according to Good Radiopharmacy Practice

There should be a written procedure for the recall of defective products and a log of errors / near misses should be maintained.

Chapter 8. Dispensing

- (a) Dispensing of patient doses should be individual and nominative, considering the radiopharmaceutical prescription.
- (b) All syringes must be identified (at least by: patient's name, preparation's name, amount of radioactivity at a stated time, international symbol of radioactivity).

Chapter 9. Distribution

These guidelines are not conceived to cover the delivery of radiopharmaceuticals outside of the nuclear medicine department.

If such delivery would be considered, the guidelines described in Part B should be followed.

Chapter 10. Complaint Handling

- (a) Written procedures should be followed for the receipt and handling of complaints regarding a radiopharmaceutical.
- (b) Such procedures should include provisions for review by the quality assurance unit of the complaints and of the investigation conducted to determine the cause of the failure.
- (c) A written record of each complaint should be maintained in a file designated for radiopharmaceutical complaints. The record should include the name and concentration of the radiopharmaceutical, its batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It should also include the findings of any investigation and follow-up, or a reason why no investigation was conducted and the name of the person who determined this.
- (d) A radiopharmaceutical that is returned because of a complaint may not be reprocessed and should be destroyed
- (e) Problems with Radiopharmaceuticals should be reported to the manufacturer, the regulatory agency and the EANM Radiopharmacy Committee Reporting Scheme

Chapter 11. Self inspection

The Quality Assurance System established at the Radiopharmacy Department should be verified by internal inspections. Internal inspections of the premises should be done at least once a year.

New personnel should be assessed after their training and initial period of independent work. Thereafter assessment will be on a random basis.

Chapter 12. Records

(a) All records should be maintained at the radiopharmaceutical laboratory or another location that is accessible to responsible officials and to government employees designated to perform inspections (inspectors). Such records, including those not stored at the inspected establishment, should be legible, stored to prevent deterioration or loss, and readily available for review and copying by inspectors.

(b) All records and documentation referred to in this guideline should be kept for the legally required period of time from the date of release of the radiopharmaceutical.

PART B. Guidelines on Current Good Radiopharmacy Practices (cGRPP) for Positron Emission Tomography (PET) and other Locally Prepared Radiopharmaceuticals*

Chapter 1. Personnel and Resources

In place has to be enough personnel with the necessary education, background, training, and experience and the resources, including equipment and facilities, to enable them to perform their functions.

General

Only trained people should be responsible for and participate in the preparation and quality control of radiopharmaceuticals. All operations should be carried out under control of a responsible person. Personnel involved in release of the prepared radiopharmaceuticals should be appropriately trained in quality systems, GRPP and regulatory requirements specific to this type of products.²

All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are handled should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

Training should be provided for all staff working in radiopharmacy departments in the aspects of Quality Assurance in which they are involved. This includes: preparation, release, quality control and analytical techniques, cleaning, transport, calibration of equipment (especially for the measurement of radioactivity), working practices in the radiopharmacy, preparation of the individual doses, documentation, hygiene and pharmaceutical microbiology, microbiological monitoring. A description of the training and records of completion should be kept.

The responsibilities should be outlined in job descriptions.

Aseptic techniques

Personnel should appropriately apply aseptic techniques throughout the handling of radiopharmaceuticals for injection, including the radiolabelling of kits. This implies the use of special clothing (masks, sterile gloves), sterile vials, sterile syringes, sterile needles and sterile diluents, and that the work is done in a well-planned and expedient way.

Radiation protection

Control of personnel radiation exposure is performed with approved personnel dosimeters, which are regularly checked and their readings recorded. This control may be supplemented with electronic dosimeters, finger dosimeters etc. After work, both personnel and work places must be checked for radioactive contamination with suitable monitors. Any contamination must be removed immediately or must be contained and access to the contaminated area must be denied until the radioactivity has decayed to an appropriate dose level.

** These guidelines are meant to cover the in house preparation of radiopharmaceuticals, which are not kit procedures and also the in house preparation of kits. For simplicity in the text they will collectively be covered by the term PET radiopharmaceuticals*

² *The EANM syllabus on radiopharmacy covers the main aspects of the knowledge required for the responsible person.*

Chapter 2. Quality Assurance

(a) There has to be a quality assurance unit that can oversee preparation operations to ensure that a PET radiopharmaceutical of sufficient quality is prepared.

(b) The quality assurance unit should have the authority to examine and approve or reject components, containers, closures, in-process materials, packaging materials, labelling, and finished product to ensure compliance with procedures and specifications affecting the identity, concentration, quality and purity of a PET radiopharmaceutical.

(c) The quality assurance unit should also be able to approve or reject procedures or specifications and any changes to a specification, method, process or procedure that affect the identity, concentration, quality or purity of a PET radiopharmaceutical before they are implemented. It should also assess the need for revalidation after a change has been made.

(d) The quality assurance unit should also have authority to review preparation records to determine whether errors have occurred. If errors have occurred, or a production batch or its components fail to meet any of its specifications, the quality assurance unit should ensure that the errors or failures have been fully investigated and corrective action taken.

(e) To ensure that the responsibilities of the quality assurance unit are known to all involved in PET radiopharmaceutical preparation, the responsibilities of the unit and the procedures they will follow should be in writing.

Chapter 3.--Equipment and Facilities

(a) Facilities should be adequate to assure the orderly handling of materials and equipment, the prevention of mix-ups and the prevention of contamination of equipment or product by substances, personnel or environmental conditions that could reasonably be expected to have an adverse effect on product quality. In small PET centres, the same area or room can be used for multiple purposes. For example, the preparation (e.g., radiochemical synthesis), laboratory operation (e.g., release testing), and storage of approved components, including containers and closures, can be located in the same room.

(b) The aseptic work area should be suitable for the preparation of a sterile PET radiopharmaceutical. Air quality in the aseptic processing area should be adequately controlled to limit the presence of microorganisms and particulate matter. Critical activities in the preparation and testing of a PET radiopharmaceutical that expose the PET radiopharmaceutical or the sterile surface of the container/closure system to the environment should be conducted within an aseptic workstation with a rating of Grade A (e.g., a LAFW or isolator). The Grade A rated workstation may be placed in a Grade C environment, which may be in a Grade D environment without further locks and changes of clothing, provided a strict working regime is maintained.

Examples of such activities include (1) the aseptic assembly of sterile components (syringe, needle, filter and vial) for sterile filtration of the PET radiopharmaceutical, (2) sampling of the sterility samples, and (3) sterility testing of the finished PET radiopharmaceutical.

Working regime:

- The aseptic workstation should be sanitised at appropriate intervals.
- Microbiological monitoring should be performed on workstation and personnel during respectively immediately after aseptic activities.
- Timing of sterile component assemblies should be organised in such a way that during that time no additional personnel enters the room.
- Items within a laminar airflow aseptic workstation should be kept to a minimum and should not interrupt the airflow to a major extent.
- Operators should wear designated lab coats and sterile arm protection and sterile gloves when conducting an aseptic manipulation within the aseptic workstation. Nose and mouth protection should be worn when doing aseptic handling outside isolators.
- The surface of non-sterile items (e.g., test tube rack, and the over-wrap for sterile syringes, and filters) should be sanitised immediately before being placed in the aseptic workstation.

(c) All equipment that influences the quality and purity of a PET radiopharmaceutical, or gives erroneous or invalid test results when improperly used or maintained, should be clean, suitable for its intended purposes, properly installed, maintained and capable of repeatedly producing valid results. These activities should be documented.

(d) Equipment should be constructed so that surfaces that contact components, in-process materials or radiopharmaceuticals are not reactive, additive, or absorptive so as to alter the quality of the radiopharmaceutical.

(e) New equipment should be qualified.

(f) Procedures for cleaning and calibration of preparation equipment have to be validated.

(g) Cleaning, calibration and maintenance should be performed at adequate intervals and properly documented.

Chapter 4. Documentation

(a) Written procedures should be established, maintained and followed describing the receipt, storage in quarantine, log-in, identification, storage, handling, testing of a representative sample, approval and rejection of components and radiopharmaceutical containers and closures.

(b) Appropriate written specifications should be established for the identity, concentration, quality, and purity of components and radiopharmaceutical containers and closures.

(c) Upon receipt, each lot of components, containers and closures should be identified and examined to determine whether it complies with specifications. Any lot that does not meet its

specifications, including any expiration date if applicable, or that has not yet been released should not be used in PET radiopharmaceutical preparation.

A representative sample of each lot of each component, and each container and closure, should be tested for conformity to its written specifications. Instead of such testing a certificate of analysis may be accepted from the supplier provided the reliability of the supplier's test results is established. The PET centre should perform an identity test on each lot of the active components, and should conduct at least a visual identification of each lot of containers and closures.

(d) Components and containers and closures should be handled and stored in a manner that prevents contamination, mix-ups, or deterioration and ensures that these are suitable for their intended use.

(e) A record should be kept for each shipment of each lot of components, containers, and closures that includes the identity and quantity of each shipment, the supplier's name and lot number, the date of receipt, the results of any testing performed, the disposition of rejected material and the expiration date.

Chapter 5. Production and Process Controls

(a) Production and process controls should ensure the consistent preparation of a PET radiopharmaceutical that meets the quality standards.

(b) Production and process controls should include written production and process control procedures, master and batch production and control records, and validation of the production process and controls.

(c) Written production and process control procedures should include a master production and control record that documents all steps in the production process. The procedures should also ensure and document that key process parameters are controlled and deviations from the procedures are documented and justified. Master production and control records should include:

- (1) The name, total radioactivity and volume of the PET radiopharmaceutical
- (2) The name and weight or measure of each active ingredient and a statement of the total weight or measure of any dosage unit
- (3) A complete list of components designated by sufficiently specific names or codes
- (4) A statement of the weight or measure of each component, using the same weight system for each component. Reasonable variations may be permitted in the amount of component necessary if they are justified in the master production and control record
- (5) A statement of practical yield, including the maximum and minimum percentages of practical yield beyond which investigation is required
- (6) Complete preparation and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed; and
- (7) A description of the radiopharmaceutical containers, closures, and packaging materials, including a specimen or copy of each label.

(d) Each time a batch of a PET radiopharmaceutical is prepared a unique batch production and control record should be prepared. The batch production record should identify by number or other unique identifier the specific batch that was prepared, and include the equipment used, each preparation step (obtained from the approved appropriate master production or control record), actual amounts of components used, dates, testing results, labelling, and names (initials or signatures) of persons performing or checking each significant step in the operation and any investigations conducted.

(e) The preparation and dispensing area and all equipment should be inspected to ensure cleanliness and suitability immediately before use. Activities should be documented.

(f) Process controls should include control of in-process materials to ensure that the materials are controlled until required tests or other verification activities have been completed, or necessary approvals are received and documented.

(g) **Microbiological Control on Aseptic Processing and Sterilising Filtration:**

Most PET radiopharmaceuticals are designed for parenteral administration and are prepared by aseptic processing. The goal of aseptic processing is to make a product that is free of microorganisms and toxic microbial by-products, most notably bacterial endotoxins. The use of aseptic technique and control of microbiological impurities in components can eliminate microbial and endotoxin contamination from PET drugs. Aseptic processing of PET drugs should involve microbiological control over relevant components.

The selection of a reliable vendor and high-quality materials are effective ways to limit the risk of microbiological contamination. Components that support microbial growth during storage should be kept under controlled conditions and periodically assessed for microbial growth/ contamination.

Only personnel trained in aseptic techniques should conduct aseptic processing. Personnel performing aseptic processing should be qualified by media fill, which is a simulation of the preparation process.

Aseptic processing in PET radiopharmaceutical preparation normally consists of, but is not limited to, (1) the aseptic assembly of the container/closure system (syringe, needle, filter and vial) and (2) sterile filtration of the PET radiopharmaceutical. Prospective operators can qualify for aseptic processing by performing media fill runs using bacterial growth media instead of the actual radiopharmaceutical. An operator should complete three successful media fills to qualify as a new operator. Each operator should be re-qualified periodically.

Even if care is taken to minimise microbiological contamination during synthesis, a drug is considered to be non-sterile until it is passed through a sterilising grade filter. Generally, PET centres can use commercially available, pre-sterilised filters to sterilise these solutions, provided that the vendor has been shown to be reliable, the filter is certified as compatible for the product, and it meets acceptable specifications.

Integrity testing of the membrane filter should be performed post filtration to ensure that the filter has performed according to specifications. This can be accomplished by performing a pressure-retaining test or the bubble-point test to show that the integrity of the filter was not compromised during or before use.

Environmental monitoring is crucial to maintaining aseptic conditions. Microbiological testing of the aseptic workstation should be performed periodically. Methods can include using swabs or contact plates for surfaces, and settling plates or dynamic air samplers for air quality.

(h) The process for producing each PET radiopharmaceutical should be validated according to established procedures, and the quality assurance unit should approve both the validation process and the results of each validation activity. Validation activities and results should be documented. Documentation should include the date and signature of the individual(s) approving the validation, the monitoring and control methods and data, and the major equipment validated.

(i) For one year after the date on which a batch of a PET radiopharmaceutical is prepared, a reserve sample from the batch should be retained, to permit a repeat quality control

6--Laboratory Controls

I--Laboratory requirements

(a) Each laboratory used to conduct testing of components, in-process materials, and finished PET radiopharmaceuticals should have and follow written procedures for the conduct of each test and for the documentation of the results.

(b) Each laboratory should have scientifically sound sampling and testing procedures designed to assure that components, radiopharmaceutical containers and closures, in-process materials, and PET radiopharmaceuticals conform to appropriate standards, including standards of identity, concentration, quality and purity, when such standards exist.

(c) Laboratory analytical methods should be suitable for their intended use and should be sufficiently sensitive, specific, accurate, and reproducible. Alternate testing methods can be used, provided the PET centre has demonstrated at least equivalency to the regulatory method. Analytical test methods should be validated, if they are different from pharmacopoeia methods.

(d) The identity, purity and quality of reagents, solutions and supplies used in testing procedures should be adequately controlled. All prepared solutions should be properly labelled to show their identity and composition.

(e) All equipment used to perform the testing should be suitable for its intended purposes and capable of producing valid results.

(f) Each laboratory should have and follow written procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, and that these activities are documented.

(g) Each laboratory performing tests related to the preparation of a PET radiopharmaceutical should keep complete records of all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing including its source, batch or lot number,

date and time the sample was taken, date and time the sample was received for testing, and its quantity.

(2) A description of each method used in the testing of the sample, a record of all calculations performed in connection with each test and a statement of the weight or measure of the sample used for each test.

(3) A record of relevant data obtained in the course of each test, including graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or radiopharmaceutical for each lot tested.

(4) A statement of the results of tests and how the results compare with established acceptance criteria.

(5) Deviation from written procedures should be documented and justified. Any out-of-specification results obtained should be investigated and documented.

(6) The initials or signature of the person performing the test and the date the test was performed.

II--PET radiopharmaceutical stability through expiry

(a) The stability characteristics of PET radiopharmaceuticals should be assessed according to a written testing program. This stability program should include suitable storage conditions as well as the use of reliable, meaningful and specific test methods.

(b) The results of such stability testing should be documented and used in determining appropriate storage conditions as well as expiration dates and times. At least three preparation runs of the final product should be studied for a time period equal to the labelled shelf life of the PET radiopharmaceutical.

Chapter 7. Finished Radiopharmaceutical Controls and Acceptance Criteria

I-- Controls and acceptance criteria for finished PET radiopharmaceuticals

(a) Acceptance criteria should be established for the radiopharmaceutical including criteria for identity, concentration, quality, purity, and, if appropriate, sterility. Each batch of a PET radiopharmaceutical should meet its established acceptance criteria, except for sterility, before it is released.

(b) Sterility testing need not be completed before release but should be started as soon as possible after preparation. If the product fails the sterility test, the results should be immediately communicated to all receiving facilities, with appropriate recommendations and follow-ups. In addition, the doctor who wrote the prescription for the PET radiopharmaceutical should be notified. Such notifications should be documented.

(c) Each PET radiopharmaceutical should be tested to show, that it meets the acceptance criteria before release of the radiopharmaceutical. The accuracy, sensitivity, specificity, and reproducibility of the test methods should be documented.

(d) The PET radiopharmaceutical may not be released until:

(1) Appropriate laboratory testing is completed;

(2) Associated laboratory data and documentation are reviewed; and

(3) Release is authorised by the dated signature of a designated, qualified individual.

(4) In many cases, modifications to this standard procedure for product release may be appropriate. For example, transportation deadlines may justify a pre-release for distribution before all elements of testing and review are finalised. Other than sterility and apyrogenicity testing, all end product tests should be completed or in progress at the time of shipment or distribution. These tests should be completed prior to final release for human administration. When it is determined that all acceptance criteria have been met, the PET centre should then provide a notice of final release to the receiving facility so that the dose can be given to the patient. There should be effective procedures for immediate notification of the receiving facility if there is evidence of an out-of-specification result and for documenting the fate of such a radiopharmaceutical.

(e) Products that fail to meet acceptance criteria should be rejected. Appropriate reprocessing may be performed. If the material is reprocessed, pre-established procedures should be followed (see production and process controls) and the finished product should meet acceptance criteria before release.

II-- Actions if a batch of PET radiopharmaceutical does not meet the acceptance criteria

(a) If a batch of PET radiopharmaceutical does not meet the acceptance criteria the product should be clearly labelled and segregated to avoid mix-ups and the quality assurance unit notified. Procedures to investigate the cause(s) of the non-conforming product should be in place and followed. Such an investigation should include, but is not limited to, examination of processes, operations, records, complaints, and any other relevant sources of information concerning the non-conforming product.

(b) Any investigation for a PET radiopharmaceutical that does not meet acceptance criteria should be documented and it should include what happened to the rejected PET radiopharmaceutical.

(c) Action should be taken to correct any identified problems to prevent recurrence of the non-conforming product or other quality problem.

Chapter 8. Labelling and Packaging

(a) Packaging and shipping containers are designed and constructed to protect against alteration or damage during the established conditions of storage, handling, distribution, and use.

(b) Each PET radiopharmaceutical should be labelled with the name of the product, its concentration, the batch number or other unique batch identifier, the date and time it was prepared, and an expiration date and time determined by appropriate stability testing.

(c) Labels should be legible and applied so as to remain legible and affixed during the established conditions of processing, storage, handling, distribution, and use.

(d) Labelling and packaging operations should be controlled to prevent labelling and product mix-ups.

(e) Relevant information from each label should be contained in each batch production record.

Chapter 9. Distribution

(a) Procedures should be followed for the distribution of PET radiopharmaceuticals to ensure that only those products approved for release are used, that prescriptions (if applicable) are reviewed to assure that they have been properly filled, and that the process of shipping will not adversely affect the quality, purity, and identity of the PET radiopharmaceutical.

(b) Distribution records for PET radiopharmaceuticals should be maintained that include or refer to the following:

- (1) The name and address of the receiving facility that received a batch of a PET radiopharmaceutical;
- (2) The name and quantity of the PET radiopharmaceutical shipped;
- (3) The patient's prescription, if applicable, or any control number(s) used; and
- (4) The date and time the product was shipped.

Chapter 10. Complaint Handling

(a) Written procedures should be followed for the receipt and handling of all complaints regarding a PET radiopharmaceutical.

(b) Such procedures should include provisions for review by the quality assurance unit of any complaint involving the possible failure of a radiopharmaceutical to meet any of its specifications and any investigation conducted to determine the cause of the failure.

(c) A written record of each complaint should be maintained in a file designated for radiopharmaceutical complaints. The record should include the name and concentration of the radiopharmaceutical, its batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It should also include the findings of any investigation and follow-up, or a reason why no investigation was conducted and the name of the person who determined this.

(d) A PET radiopharmaceutical that is returned because of a complaint may not be reprocessed and should be destroyed.

Chapter 11. Self inspection

The Quality Assurance System established at the Radiopharmacy Department should be verified by internal inspections. Internal inspections of the premises should be done at least twice a year.

Internal personnel inspections should be done after new personnel is schooled and has worked at his own responsibility for a while. Further personnel inspections must be random.

Chapter 12. Records

(a) All records should be maintained at the PET centre or another location that is accessible to responsible officials of the PET centre and to government employees designated to perform

inspections (inspectors). Such records, including those not stored at the inspected establishment, should be legible, stored to prevent deterioration or loss, and readily available for review and copying by inspectors.

(b) All records and documentation referred to in this guideline should be kept for the legally required period of time from the date of release of a PET radiopharmaceutical.