

Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals

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Abstract This guidance is meant as a guidance to Part B of the EANM “Guidelines on Good Radiopharmacy Practice (GRPP)” issued by the Radiopharmacy Committee of the EANM (see www.eanm.org), covering the small-scale “in house” preparation of radiopharmaceuticals which are not

kit procedures. The aim is to provide more detailed and practice-oriented guidance to those who are involved in the small-scale preparation of, for example, PET, therapeutic or other radiopharmaceuticals which are not intended for commercial purposes or distribution.

This guideline summarizes the views of the Radiopharmacy Committee of the EANM and reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions. The guidelines have been reviewed by the EANM Dosimetry Committee and the Drug Development Committee. The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

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Abbreviations

API	Active pharmaceutical ingredient
BET	Bacterial endotoxin test
cGRPP	Current good radiopharmacy practice
EANM	European Association of Nuclear Medicine
HEPA filter	High-efficiency particulate air filter
HPLC	High-performance liquid chromatography
LAFW	Laminar air flow workbench
QA	Quality assurance
QC	Quality control
RPR	Responsible person for the small-scale preparation of radiopharmaceuticals
SOP	Standard operating procedure
SSRP	Small-scale “in-house” radiopharmaceutical

Definitions

Guidelines	Guidelines are not mandatory but recommendations for the effective implementation of EU Directives by the Member States.
Guidances	Guidances are not mandatory but recommendations in a more specific and detailed form for the effective implementation of Directives by the Member States.
European Regulations	European Regulations are mandatory in all countries, being directly applied without translation into the national legislation.
European Directives	European Directives are rules addressed by the EU Commission to the Member States to be translated into the respective national legislation and effectively implemented. Directives are mandatory.
Radiopharmaceutical	A radiopharmaceutical is any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.
Small-scale radiopharmaceutical	A small-scale radiopharmaceutical is any in-house radiopharmaceutical prepared on a small scale (for PET, SPECT or therapeutic applications), excluding preparations based on labelling licensed kits and generators, and excluding preparation of kits.
Finished product	A finished product is a medicinal product which has undergone all

Preparation	stages of production, including packaging in its final container. Preparation includes all operations involve in the purchase of materials and products, production, QC, release and storage of a medicinal product and the related controls.
Starting material	Starting material is any substance used in the preparation of a medicinal product, but excluding packaging materials.
Precursor	A precursor is an API used as a starting material for the preparation of a (radio)pharmaceutical.
Radionuclide precursor	A radionuclide precursor is any radionuclide produced for the radiolabelling of another substance prior to administration.
Substance for pharmaceutical use	A substances for pharmaceutical use are any organic or inorganic substance that is used as an active substance or excipient for the production of medicinal products for human or veterinary use. It may be used as such or as a starting material for subsequent formulation to prepare medicinal products.
Qualified Person	A Qualified Person typically is a licensed pharmacist, biologist or chemist (or a person with another permitted academic qualification) who has several years experience working in pharmaceutical manufacturing operations, and has passed examinations attesting to his or her knowledge (EU Directive 2001/83). The requirement for responsibility by a Qualified Person has been extended to material for use in clinical trials since the introduction of EU Directive 2001/20/EC. In countries that are part of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme, the same role may be termed Responsible Person or Authorized Person.
Responsible Person	A Responsible Person for the small-scale preparation of radiopharmaceuticals (RPR) is a person with an equivalent academic background to a QP with at least 2 years of practical experience in radiopharmaceutical preparation, having

shown sufficient scientific and technical education and experience in radiopharmacy practice and related fields. The EANM syllabus on radiopharmacy covers the main aspects of the knowledge required. RPRs are ultimately responsible for all aspects of the preparation of radiopharmaceuticals at small-scale radiopharmacies including the release of these items unless local or national regulations require different qualifications.

Small-scale radiopharmacy

A small-scale radiopharmacy is a facility where the small-scale preparation of radiopharmaceuticals is carried out under a license that is in accordance with national regulations. The term *small-scale* radiopharmacy is not related to the size of the facility, that may vary in a broad range, but only to the kind of radiopharmaceutical preparation performed.

Good radiopharmacy practice

Good radiopharmacy practice is described in the “Guidelines on Good Radiopharmacy Practice (GRPP)” issued by the Radiopharmacy Committee of the EANM (see www.eanm.org).

(see www.eanm.org) is a useful reference for QA into the small-scale preparation of radiopharmaceuticals and their nonradioactive precursors.

This guidance is intended to help small-scale radiopharmacies to implement cGRPP, and represents the views of the EANM Radiopharmacy Committee. The basis of this guidance is published in the cGRPP guidelines mentioned above and it covers topics comparable to those covered in the recently issued FDA cGMP guidance document on PET drugs [1]. It addresses resources, procedures, and documentation for small-scale preparations. The guidance provides practical examples of methods or procedures that small-scale radiopharmacies could use to comply with the proposed cGRPP requirements. It describes the thinking on a topic, has no binding value and should be viewed only as a recommendation. The use of the word *should* in this guidance indicates that something is suggested or recommended, but not mandatory. Readers should consult their competent authority to verify specific national requirements and regulations.

The present document also provides guidance on the EU requirements concerning quality of starting materials and finished radiopharmaceutical products. This guidance is of great importance because most of the existing rules are intended for medicinal products in general and are not specific for radiopharmaceuticals. Moreover, some of the current regulations do not take into account the special characteristics of radiopharmaceuticals, such as their short shelf life, which is due to the short physical half-life of the radionuclide, the small scale of the preparation and the low or absent toxicity of the final product, which is due to the peculiar no-carrier-added nature of radiopharmaceuticals.

Introduction

In Europe, radiopharmaceuticals are considered as a special group of medicines. Therefore, their preparation and use are regulated by a number of EU directives, regulations and rules that have been adopted by member states. The rate of adoption of directives varies between countries and each member state may introduce changes, provided the general scope and limits of each directive are maintained. Specific articles have been put in place concerning radiopharmaceuticals that are to receive marketing authorization or are prepared starting from licensed products (radionuclide generators, labelling kits and precursor radionuclides). However, radiopharmaceuticals may also be prepared outside the marketing authorization track or used outside the indications they have been registered for. Small-scale preparations at nonindustrial sites (hospital pharmacies, nuclear medicine departments, PET centres) indeed represent an increasingly important segment of application. The “Guidelines on Good Radiopharmacy Practice (GRPP)” issued by the Radiopharmacy Committee of the EANM

Personnel and resources

It is recommended that the number of personnel corresponds to the size and complexity of the operation of the small-scale radiopharmacy so as to enable the appropriate completion of all tasks before administration of a finished SSRP to humans. It is recommended that the responsibilities and assigned duties of all staff be clearly identified in written policies. An organizational chart that describes the cGRPP-relevant relationships between involved personnel would fulfil this purpose.

General

All operations should be carried out under the control of the RPR. Personnel involved in release of the prepared radiopharmaceuticals should be appropriately trained in quality systems, cGRPP and the regulatory requirements specific to this type of product. Release of the finished product may be delegated by the RPR to another person, albeit the responsi-

bility for the release of the radiopharmaceutical cannot be delegated.

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 product. In particular, they should be given detailed information and appropriate training on radiation protection. The radiation exposure of personnel is monitored with approved personnel dosimeters, which are regularly checked and their readings recorded. This monitoring may be supplemented with electronic dosimeters, finger dosimeters, etc. After completion of the radiopharmaceutical preparation, 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.

It is recommended that small-scale radiopharmacies have adequate ongoing programmes or plans in place for training staff in new procedures and operations and in the areas where deficiencies have occurred.

Small-scale radiopharmacies must maintain an up to date file (including, for example, curriculum vitae, copies of degree certificates, certificates of training) for each staff member. The personnel should include at least two persons, one of whom is the RPR with appropriate credentials. The second person must be at least very well trained in the upkeep of cGRPP procedures.

When only one person is involved in the preparation at some point in time in a small-scale radiopharmacy, all procedures (preparation, QC and release of the product) may have to be done by the same person (the RPR). Therefore rigorous SOPs have to be in place. If preparation by one person is necessary, an additional independent professional should be involved to double check the results and confirm their compliance (four eyes principle). This individual could be anyone trained to look at the appropriate results, understand their meaning and confirm their correctness.

All equipment should be remotely controlled or automated so as to produce reports which unequivocally show that the quality of the product meets specifications.

At a facility that produces multiple SSRPs, it is recommended that the number of personnel be sufficient to perform all tasks, i.e. the production, QC and QA functions, and to prevent mix-ups and cross contamination.

Responsibilities

The RPR should have the following responsibilities:

- To establish procedures for the examination and evaluation of incoming materials and ensure that each

lot of incoming material is examined and evaluated against specifications before use.

- To review the preparation batch records and laboratory control records for accuracy, completeness, and conformance to established specifications before authorizing the final release or rejection of a batch or lot of SSRP.
- To approve procedures, specifications, process, and methods including related SOPs.
- To ensure the personnel are appropriately trained and qualified.
- To investigate errors and ensure that appropriate corrective action is taken to prevent their recurrence.
- To ensure that the SSRP have adequately defined identity, strength, quality and purity.

The person responsible for QA should have the following responsibilities:

- To manage the general QA system.
- To verify that the documentation is correctly written and administrated.
- To conduct periodic audits to monitor compliance with established procedures and practices.
- To monitor, in cooperation with the other responsible persons, the general management of the activities performed in the small-scale radiopharmacy (e.g. out of specifications, personnel training, radioactive waste management, etc.)

At small facilities, for more efficient management, a QA entity located outside the in-house radiopharmacy may be chosen to help the RPR to oversee the areas mentioned above.

The person responsible for production should have the following responsibilities:

- To write the SOP related to radiopharmaceutical production operations, and to verify that the above instruction are adequately implemented.
- To approve the production operations.
- To evaluate, sign and store the production records.
- To ensure that the products are produced and stored according to the appropriate documentation in order to obtain the required quality.
- To verify that premises and production equipment are correctly maintained according to a established maintenance programme.
- To cooperate with the other responsible persons in the organization and training of the operating personnel.

The person responsible for QC should have the following responsibilities:

- To write the SOP related to QC operations, and verify that the above instruction are adequately implemented.
- To define specifications, test methods and other QC procedures.

- To approve or reject starting materials and packaging materials.
- To evaluate, sign and store the QC reports and records.
- To evaluate the batch records.
- To verify that premises and QC equipment are correctly maintained according to a established maintenance programme.
- To cooperate with the other responsible persons in the organization and training of the operating personnel.

Even though responsibility of production and QC should ideally be separated, in small facilities the responsibilities for QC and production may rest with the RPR.

Quality assurance

It is recommended that the small-scale radiopharmacy establishes a QA unit to comprehensively design and correctly implement a QA system, incorporating the principles of cGRPP and considering appropriate risk assessment. Indeed, risk assessment plays an essential role in all the steps involved in the preparation of SSRP, and may allow the appropriate level of controls and documentation to be estimated. For instance, operations which are routinely performed in the preparation or testing of “normal”, nonradioactive medicinal products may not be applicable to SSRPs, or at least they need to be adapted to comply with radiation protection principles. Risk assessment analysis may significantly help in the validation of alternative methods, SOPs, etc.

The QA system should be documented and its effectiveness monitored with the aim of supporting the RPR in overseeing preparation operations and of ensuring that SSRPs have adequately defined identity, activity, quality and purity.

In particular the QA unit should ensure that:

- Radiopharmaceuticals are designed and prepared according to the latest state of knowledge.
- Preparation and control operations are clearly specified and implemented according to the principles of cGRPP.
- Radiopharmaceuticals are only supplied for use in patients if they have been correctly processed, checked and stored in accordance with the defined procedures and released by a competent person (the RPR).
- Adequate measures are in place to ensure that radiopharmaceuticals are released, stored and handled in such a way that the required quality can be assured throughout their shelf-life and in accordance with the in-use expiry date.

cGRPP is that part of the QA system concerned with ensuring that SSRPs are consistently prepared to appro-

priate quality standards. QC is that part of cGRPP concerned with sampling, specification and testing, and with organization, documentation and release procedures, which ensure that the required and relevant tests are actually carried out and starting and packaging materials and finished products are only released if their quality complies with the requirements.

Facilities and equipment

General

Facilities should be adequate to ensure 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.

All equipment used in production (e.g. particle accelerator, synthesis units, or other specialized equipment) should be appropriately located and housed (e.g. with shielding) so that all the work areas during the normal course of production are easily accessible. It is recommended that related work areas are organized and proximally located so as to promote efficient operation and eliminate the potential for errors in the preparation and monitoring operations. Access to work areas should be restricted to authorized personnel.

Facilities

In small-scale radiopharmacies, the same area or room can be used for multiple purposes. But as the complexity increases (multiple preparations of multiple SSRPs), it is important to develop the appropriate level of control required to prevent mix-ups and contamination. Different operational areas should be clearly defined and separated, especially regarding the unidirectional flow of materials, precursors and finished products to avoid mix-up and unintended use. For example, the preparation (e.g. radiochemical synthesis), QC and laboratory operations (e.g. release testing), and storage of approved components, including containers and closures, can be located in the same room, although it is preferable to perform these tasks in different rooms. In particular, the inherent characteristics of the equipment typically used for the QC of radiopharmaceuticals, make an arrangement in nonclassified rooms preferable.

Components that are released for use as well as those that are under quarantine can be stored in the same area, but on separate shelves, provided each lot is properly labelled as to its status and contents. Rejected components, containers and closures, and other materials should be kept separate from quarantined or approved materials.

The aseptic work area should be suitable for the preparation of a sterile SSRP. Air quality in the aseptic processing area should be adequately controlled to limit the presence of microorganisms and particulate matter. There must be appropriate procedures for the sanitization of materials and equipment being transferred into the aseptic work area. Critical activities in the preparation and testing of a SSRP should be conducted in an aseptic workstation with a grade A rating (e.g. a LAFW or isolator). Critical activities are steps in the procedures that expose the SSRP or surfaces of the container/closures that will be in contact with the product to the environment. Examples of such activities include (1) the aseptic assembly of sterile components (syringe, needle, filter and vial) for sterile filtration of the SSRP, (2) open vial dispensing, (3) sampling of the sterility test samples, and (4) sterility testing of the finished SSRP.

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. Dispensing a SSRP that can be terminally sterilized can be performed in a grade C workstation, placed in at least a grade D environment. The preparation of SSRPs is usually performed using automated systems located in suitably shielded hot cells that ensure a grade C environment. The hot cells may in turn be located in a laboratory with a grade D environment.

Surfaces of the walls, floors, and ceilings in the aseptic work areas should be easily cleanable. Cleaning should be performed frequently to ensure consistent control of environmental quality. The aseptic processing area (e.g. LAFW) should be situated in the section of the room with the lowest traffic and lowest activity. Secondary packing, such as cartons and boxes, should not be stored or opened in the preparation area to minimize ingress of dust and particulates into the aseptic work area. The design of the room should minimize reduction of air quality upon maintenance of equipment; for example, a technical area could be constructed such that hot cells could be approached from a room other than the cleanroom. Only persons directly involved in the preparation should be present in the cleanroom during the preparation of a SSRP.

The aseptic workstation should provide an appropriate environment with air of grade A quality for aseptic procedures. Examples of aseptic workstations include a unidirectional LAFW or an isolator system. While working under aseptic conditions, the need for radiation protection of the operators should not be compromised. Whenever the aseptic operations include the handling and manipulation of radioactivity, suitable radiation protection should be in place, without disrupting the laminar flow. Particle monitoring and microbiological monitoring should be performed in grade A zones, and when relevant in other graded zones.

Active air sampling of workstations for radioactive products must be subject to safety risk considerations. A possible approach to testing particulate and microbiological quality of air inside these workstations is to gain information about air-borne particles during simulated operations (without radioactivity).

Additionally, settle plates should be used for microbiological monitoring during preparation or critical steps of the preparation. In this regard, a suitable sampling and testing plan should be defined on a risk-assessment basis, that would allow the extent and frequency of microbiological monitoring to be defined.

Preventive maintenance, calibration and qualification testing programmes should be operated in all facilities and for all equipment used in the preparation of SSRPs, including workstations with HEPA filters and prefilters. It is recommended that qualification testing (integrity testing of the HEPA filter) of an aseptic workstation is performed when the unit is initially installed and repeated at least every year thereafter to ensure the desired air quality. More frequent testing may be necessary if the air quality is found to be unacceptable, for example, as part of an investigation into a finding of sterility failure in a SSRP, or if leakage or a decrease in optimal air flow is found.

It is recommended that a qualified operator change the prefilters in the aseptic workstation periodically in accordance with written procedures and preventive maintenance schedules. Some laminar flow hoods are equipped with an easily readable static pressure gauge that indicates when the pressure has built up behind the filter because of clogging. It is recommended that operators be trained in the importance of minimizing the number of objects and equipment within the critical area so that unidirectional airflow is not disrupted.

When entering the preparation facilities, operators must wear clothes appropriate for the process and grade of the work area. Personnel should appropriately apply aseptic techniques throughout the handling of radiopharmaceuticals for injection. This implies the use of special clothing, sterile vials, sterile syringes, sterile needles and sterile diluents, and that the work is done in a well-planned and expedient way.

Outdoor clothing should not be brought into changing rooms leading to grade C/D areas.

Working regime recommendations are as follows:

- The aseptic workstation should be cleaned at appropriate intervals.
- Microbiological monitoring should be performed on workstations immediately after aseptic activities. During sterile component assembly no additional personnel should enter the room.
- Items within a unidirectional air flow aseptic workstation should be kept to a minimum and should not interrupt the air flow significantly.

- Materials entering a grade A zone should be previously sanitized.
- The surface of nonsterile items (e.g. test-tube rack, over-wrap for sterile syringes, and filters) should be sanitized immediately before being placed in the aseptic workstation.

Equipment

Equipment used in the preparation, QC and dispensing of SSRPs must be appropriate for its intended function and not contaminate the product. All equipment may potentially affect the quality and purity of a SSRP, or give erroneous or invalid test results when improperly used or maintained. For this reason, it is of paramount importance that the equipment is suitable for its intended purposes, properly installed, maintained and capable of repeatedly producing valid results. Equipment should be constructed so that surfaces that may come into contact with starting materials, reagents, solvents, the radiopharmaceutical itself or, in general, with any components involved in the preparation and dispensing of the SSRP, are not reactive, additive, or absorptive, so as to ensure that the quality of the finished product is not altered.

It is recommended that all the equipment be suitably located to facilitate its use, cleaning, and maintenance, and that the manipulation of all the materials needed for the production and the finished product be reduced to a minimum.

Each small-scale radiopharmacy also should establish and follow written procedures that address the following issues, where applicable:

- Assignment of preparation and QC functions
- Description of equipment cleaning procedures
- Description of use, calibration and maintenance procedures for each preparation, QC and dispensing instrument
- Calibration and maintenance plan, with clear indications of the frequency and characteristics of the maintenance and calibration to be performed
- The assignment of a log book for each preparation, QC and dispensing instrument
- Protection of equipment from contamination prior to use

It is recommended that newly installed equipment is qualification tested before use in the preparation, QC and dispensing processes to verify that it is installed correctly and is capable of operating as intended. Typically, installation qualification testing, which is intended to verify that the equipment is installed correctly, and operational qualification testing, is intended to verify that the equipment operates according to the specifications, may be performed by the equipment supplier. Before using the equipment for produc-

tion, personnel in the small-scale radiopharmacy should verify that the equipment, when operated using actual production parameters and under production conditions or using a selected method, produces consistent results within established specifications (performance qualification).

As stated above, the implementation of a preventive maintenance and calibration schedule is recommended, with a clear indication of the frequency of interventions, to ensure the correct performance of the equipment. Where needed, calibration should be performed prior to use of the equipment for the intended task. It is recommended that the facilities follow calibration procedures and frequency, as recommended by the equipment supplier, unless the RPR and the person responsible for QC have determined that a different frequency of calibration is more appropriate.

Requalification testing of equipment may be required following major repairs or upgrades. It is recommended not to use malfunctioning or incorrectly operating equipment until repairs or corrective actions have been made and the equipment has been found to be operating correctly. All qualification, calibration, and maintenance procedures should be properly documented and reported in a specific logbook. The date of such procedures, a description of the work performed and the name or signature of the person who performed the work must be documented in the logbook. In the case an instrument that has been developed “in-house”, or if no reference materials are available from the suppliers, the small-scale radiopharmacy should establish its own use, calibration and maintenance procedures, including the frequency of interventions, to ensure that the instrument provides reliable and consistent results.

Together with the general recommendations described above, specific equipment may require additional precautions. Representative SSRP preparation instrumentation is listed below, with a brief description of their characteristics and specific controls that have to be performed.

Production equipment

Automated radiochemical synthesis apparatus Automated apparatus enables the facility to carry out the preparation process safely, reliably and reproducibly. Such apparatus is usually located in suitably shielded hot cells. Prior to the preparation of a SSRP, the operator should conduct the following performance checks:

- To ensure that the synthesis apparatus and all components that are not disposable and are thus not replaced (e.g. in certain apparatus the Teflon tubing or valves) have been cleaned/flushed according to the established procedures.
- To ensure that, where applicable, all appropriate tubing, reaction vessels, purification columns or cartridges and other materials have been replaced and connected as required.

- To ensure that, if a semipreparative HPLC purification step is required in the preparation of a SSRP and a specific subunit for this purpose is built into the automated apparatus, the system is working properly by the analysis of a reference standard, and that there is no bleeding of unintended material (e.g. column material) into the mobile phase, and no leakage of mobile phase during the purification run. The actual purification chromatograms must be carefully compared with previous results.
- To ensure that monitoring and recording devices (e.g. temperature, pressure, flow rate) are functioning properly.
- When the process is under control of a microprocessor, to ensure that the system is functioning and recording correctly and that the correct program and operational parameters are being used.

Hot cells Hot cells are boxes shielded with lead bricks or layers of suitable thickness, where the radiosynthesis apparatus or other automated devices are usually located. Prior to beginning the preparation of a radiopharmaceutical, the following checks are recommended:

- The hot cell air tightness should be tested, verifying that the pressure meets the specifications. This test indirectly provides useful information about the ventilation system and filter integrity.
- Radiation monitoring devices typically installed in the hot cell working area should be tested. Opening of the hot cell doors should be interlocked with the radiation monitor and cyclotron targets, so that the doors cannot open if radiation levels are higher than the alarm set point, and cyclotron target unloading while the hot cell doors are open is avoided.

A suitable calibration and maintenance plan should include filter replacement and testing of the air cleanliness level.

Analytical weight balance It is recommended that written procedures are in place describing the proper use of the balance, assessment of accuracy and a schedule for calibration of the balance. Its performance should be checked by weighing two or more standard weights regularly (e.g. weekly). It is recommended that the calibrated weights used for assessing daily performance bracket the range of weights being measured. The balance should be fully calibrated periodically or upon failure to meet regular performance checks.

Temperature recording device It is recommended that temperature and humidity (where appropriate) of the dry heat oven, refrigerator, freezer and incubator are recorded when they are used. Automated recording devices are preferred for ease of documentation and for recording any deviations.

Radiopharmaceutical dispensing systems Dispensing systems are fully automated or remotely controlled systems used to prepare the individual radiopharmaceutical doses, starting with the “bulk” radiopharmaceutical solution, usually contained in a suitable glass vial. The dispensing systems are located in suitably shielded hot cells, capable of reliably providing a laminar flow over the entire work area.

If fully automated systems are used, the recommended tests are very similar to those previously described for radiosynthesis modules. In particular:

1. The dispensing synthesis apparatus should be cleaned/flushed according to the established procedures.
2. All appropriate, tubing, syringes, needles, valves, stopcocks, filters and other materials should be replaced and connected as required. When the process is under microprocessor control, the operator ensures that the system is functioning and recording correctly, with particular emphasis on the dose calibrator, and that the correct program and operational parameters are used.
3. It is mandatory to test the integrity of the hot cell HEPA filter, as radiopharmaceutical dispensing systems usually work in a class A environment. When specifically designed hot cells are used, the above test may be performed using built-in features, following the recommendations of the manufacturer.

Quality control equipment

It is recommended that the small-scale radiopharmacy has the appropriate equipment to adequately perform each QC function required. Representative QC equipment is described briefly below.

Gas chromatograph At the beginning of each day of use, the analyst should make sure that the GC system is functioning correctly by at least one injection of a standard preparation (reference standard or internal standard) before the injection of test samples, and the retention time must be within predefined limits.

HPLC system The actual purification chromatogram must be carefully compared with previous results. The HPLC system must have detectors suitable for the intended purpose and be of sufficient sensitivity. At the beginning of each day of use, the analyst should make sure that the HPLC system is functioning correctly by analysing a suitable reference standard. At least one injection of a standard preparation (reference standard or internal standard) should be done before the injection of test samples and the retention time must be within predefined limits.

Radionuclide activity calibrator The accuracy and linearity of a radionuclide activity calibrator used to measure the radioactivity of SSRPs should be assessed at installation and at appropriate intervals thereafter. The instrument should be calibrated in accordance with nationally recognized standards or the manufacturer's instructions. A system suitability test should include the measurement of a reference radionuclide standard source of suitable emission energy. For some radionuclides it is crucial to determine geometry correction factors on installation of a radionuclide activity calibrator.

Radiochromatogram scanner It is recommended that a radiochromatogram scanner (or equivalent equipment that provides a radiochromatogram) is used for measuring radioactivity distribution on thin-layer chromatography plates. The scanner should have sufficient sensitivity and spatial resolution for the intended discriminatory and quantitative objectives. Checks and maintenance recommended by the manufacturer should be performed.

Multichannel analyser A multichannel gamma spectrometer coupled to a calibrated sodium iodide scintillation detector, or preferably the higher resolution lithium-compensated germanium [Ge(Li)] detector, is typically used to determine radionuclidic purity and to identify any contaminant radionuclides. The overall system should have sufficient sensitivity and resolution for the intended purpose. Adequate calibration and preventive maintenance should be performed in accordance with the manufacturer's specifications. More frequent intervals should be used if problems in the operation of the multichannel analyser are encountered.

Documentation

QA is based on a suitable documentation system, organized in either written or electronic format, which includes any documents, SOP and records related to any relevant step in the process of radiopharmaceutical preparation, in order to assure the traceability of the entire process. All documents related to the preparation of SSRPs should be prepared, reviewed, approved and distributed according to written procedures. As stated before, written procedures should cover all the aspects involved in the process of radiopharmaceutical preparation, including but not limited to material specification and testing, production and QC procedures, general QA SOPs, cleaning and maintenance

Written procedures must specify how each material (components, containers, and closures) will be selected and controlled in small-scale radiopharmacies. Procedures should cover the life cycle of a material, from the time of receipt to ultimate consumption. Written procedures should

be established, maintained and followed describing, where applicable, 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.

Records of major equipment use, cleaning and maintenance should show the product name and batch number, where appropriate, in addition to the date and time and signature of the persons involved in these activities.

Records should be retained for at least 1 year. However, the archiving time must be in accordance with local and national regulations.

Preparation and process controls

Deviations and changes

Procedures in writing to deal with deviations should be in place. Deviations from the production protocol should be documented both to identify trends and to guarantee that corrective or preventive action will take place. Examples of frequent deviations are leakage from the reactor, deviations in the preparative HPLC chromatogram, clogging in the tubing and unexpectedly low radiochemical yield. A change control procedure should be in place to deal with all changes that may affect the quality of the radiopharmaceutical. This includes changes in the preparation method as well as in QC, equipment, software, manufacturing and suppliers.

Process controls

Process controls should include monitoring of all measurable parameters such as pressures, temperatures, radioactivity levels, and gas and liquid flow rates at relevant process locations and times, to ensure that the materials are controlled until required tests or other verification activities have been completed, or necessary approvals are received and documented.

Microbiological control of aseptic processing and sterile filtration

Even if care is taken to minimize microbiological contamination during synthesis, a SSRP is considered to be nonsterile until it has passed through a sterilizing grade filter. Generally, small-scale radiopharmacies can use commercially available, presterilized filters to sterilize these solutions, provided that the vendor has been shown to be reliable, the filter is certified as being compatible with the product, and it meets acceptable specifications.

Integrity testing of the membrane filter should be performed after filtration to ensure that the filter has

performed according to specifications and was not compromised during or before use. This can be accomplished by performing a pressure-retaining test or bubble-point test. The filter integrity test should ideally be performed immediately after the filtration process under conditions in compliance with radiation safety requirements. If radiation safety requirements forbid testing immediately after filtration, the use of two sterile filters in series instead of the filter integrity test could be considered, on a risk analysis basis.

Aseptic processing of SSRPs should involve microbiological control over various types of components, as discussed above. Additionally the bioburden of the processing system and/or critical steps in the process should be analysed. Regular intervals of testing may be defined based on risk analysis. Bioburden analysis can be achieved by running synthetic steps without radioactivity, collecting the effluent at intermediate steps and at the endpoint of the synthetic process without filter sterilization and subsequent sterility testing. In this context, special attention should be paid to the following items:

1. Transfer lines, valves and HPLC system

Transfer lines, which are used for synthesis and transfer of solvents or products, are usually made of durable plastic and are suitable for reuse. Appropriate cleaning with organic solvents after use, rinsing with water for injection, flushing with a volatile solvent, and drying with an inert gas (e.g. nitrogen, helium, argon) help control microbial contamination. Organic solvents such as ethanol and acetone are useful as a final rinse and can easily be dried from containers or lines.

For SSRPs with a very short half-life (^{15}O water and ^{13}N ammonia) a long transfer line may be used to deliver multiple batches to a remote area for further processing. It is recommended that procedures are established to ensure that these transfer lines are clean and free of bacterial and bacterial endotoxin contamination.

2. Resin and other columns

Resin columns are a potential source of microbes and bacterial endotoxins. If available, the purchase of resin material of low microbial grade may limit the bioburden. Material used for preparing resin columns should be suitably processed and rinsed with a large amount of water for injection to minimize contamination risk. The prepared column should be appropriately flushed. Refrigerated storage is helpful in controlling contamination. It is recommended that wet columns are not stored for a prolonged period of time. Other HPLC columns and outlet lines, although somewhat less susceptible to bacterial contamination, should also be monitored for bioburden regularly and flushed with 70% ethanol at predetermined intervals.

3. Aqueous solutions

Water should be used in sterilized form (water for injection). Once a sterilized water batch has been opened or

when a volume of water has been dispensed, the batch should be used only on the same day.

4. Glassware

Reaction vials from a synthesis module made of glass should be cleaned using validated methods to ensure that the vial is clean. Cleaning procedures should not affect the quality of the SSRP. It is recommended that glassware is dried and depyrogenized in a dry-heat oven.

Vials are removed from the oven prior to the radiosynthesis or alternatively stored in clean, dust-free sterile bags.

Master preparation and batch records

Master preparation and control records are the principal documents describing how a product is made. The master preparation record serves as a template for all batch records documenting how each batch is to be produced. The RPR should approve the master preparation and control records, or any changes to them, before they are implemented.

It is recommended that the master preparation and control records include logical, chronological step-by-step instructions to document how the SSRP is to be prepared. Preparation should be discussed under headings, where applicable, such as accelerator operation, radiochemical synthesis, purification steps, formulation of the finished product and QC. It is recommended that the entire preparation process is pre-established and fully described in the master preparation and control record. The SOP for performing a specific step can be referenced. The master preparation and control records would include specifications for each critical step. Critical steps include the process step, process conditions, or other relevant parameters that are controlled within predetermined criteria to ensure that the final product meets its specification.

Batch records should include documentation to show each significant step in the preparation was accomplished. An entry should be made in the batch record directly after performing an activity (the entries being in the order the activities were performed) and are to be dated, and the person making the entry identified (by signature or initials). Corrections to paper entries should be dated and signed or initialled, leaving the original entry still readable. It is recommended that each batch record is reviewed and approved for final release (signature/initials and date).

Laboratory controls

Laboratory requirements

The extent to which QC tests are performed should take into account stability information and the physical/chemical

properties of the SSRP, and should be defined on the basis of risk assessment. QC and release activities should be independent of preparation activities. Each QC laboratory should have and follow written procedures for the conduct of each test and for the documentation of results. Each laboratory should have scientifically sound sampling and testing procedures designed to assure that components, containers and closures, and SSRPs comply with the required quality criteria, which may or may not be defined by a specific monograph of the European Pharmacopoeia or other national pharmacopoeias. If such a monograph does not exist, quality criteria should conform to the principles established by general monographs and guidelines.

Laboratory analytical methods should be suitable for their intended use and should be sufficiently sensitive, specific, accurate, and reproducible. Alternative testing methods can be used, provided that the small-scale radiopharmacy has demonstrated that they are at least equivalent to the pharmacopoeia method. Analytical test methods should be validated if they are different from pharmacopoeia methods or if a specific monograph of a pharmacopoeia is not available for the radiopharmaceutical of concern.

The identity, purity and quality of reagents, solutions and supplies used in testing procedures should be adequate for their use. All the prepared solutions should be properly labelled to show their identity and composition. Each laboratory should keep complete records of all tests necessary to ensure compliance with established specifications. The records should include:

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. 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. Raw test data (such as chromatograms, spectra, and printouts) and any calculations performed can be documented and become part of the batch preparation and control record. Laboratory controls should be followed and documented at the time of performance.
4. A certificate of analysis, which should include the results of tests and whether the results comply with established acceptance criteria, signed by the person responsible for QC.

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 time and date the test was performed.

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

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

Control of starting material

The process for procurement and use of materials should include the following elements, where applicable.

Vendor selection It is recommended only qualified vendors be used. A vendor is qualified when there is evidence to support its ability to supply a material that consistently meets all quality specifications. Vendor qualification can be done on the basis of a visit (audit), on the basis of responses to a QA questionnaire, or simply on the basis of experience with this supplier. In any case, the vendor qualification should be documented. It is also recommended that small-scale radiopharmacies ask the vendor to report any major changes in the manufacture of an item. It is preferable to have more than one qualified vendor for a component. A vendor should be replaced if there is an indication that it is supplying unsatisfactory materials.

Receipt of materials It is recommended that each lot of material is checked upon receipt to determine that the order was fulfilled correctly and arrived in good condition. Each lot should be logged in and assigned a new identification code number. The code number would be used in the disposition of that lot. Sufficient information should be documented to enable the small-scale radiopharmacy to have full traceability of each lot. It is recommended that, before release for use, incoming materials are segregated and placed in an appropriately designated area under quarantine and labelled “*Quarantined*”. A lot can then be inspected, sampled, and tested, if applicable.

Release of materials All materials that meet a small-scale radiopharmacy’s specifications can be approved and released for use. Such release should be recorded and the examination and testing data maintained. It may be helpful to have a component log-book to record information such as receipt date, quantity of the shipment, supplier’s name, lot number, expiry date, results of any testing performed,

and person responsible for release. Approved materials can be labelled “*Released*” with an identifying code number, storage conditions, and expiry date. It is recommended that materials are stored under the proper storage conditions and in an area designated for approved materials. If a lot is rejected, it is recommended that it is labelled “*Rejected*”, segregated and properly disposed of, and that each of these actions is documented. Released materials have to be handled and stored in a manner that prevents degradation or contamination.

Process validation

For a small-scale radiopharmacy that has a well-established history of SSRP preparation, the process of validation can be accomplished using historical batch records, provided that there are adequate accumulated data to support a conclusion that the current process yields batches meeting predetermined acceptance criteria. The accumulated data should confirm that the preparation process was consistent and should document all of the changes to and failures of the process, if any.

It is recommended that new processes or significant changes to existing processes be shown to reliably produce SSRPs meeting the predetermined acceptance criteria before any batches are used for clinical purposes. This verification should be conducted in accordance with a written protocol and generally includes at least three consecutive successful preparation runs (“Master Batches”).

Due to the inherently short half-life of some of the positron-emitting radionuclides, process validation should take in to account the need to use the SSRP before all the QC tests have been completed. Validation should include a careful risk assessment, and the preparation and QC procedures should be sufficiently robust and reliable to guarantee that the radiopharmaceutical may be released before completion of all tests.

Such a decision should be justified in writing and approved by the RPR. In this situation, it is recommended that each batch be processed in strict adherence to the written procedures, fully tested (except for sterility testing) and found to comply with all procedural and quality test requirements prior to final release.

Finished product controls

Acceptance criteria

Each radiopharmaceutical should be tested to show that it meets the acceptance criteria before it is released.

Analytical methods should meet the criteria defined in specific monographs of the European Pharmacopoeia,

where applicable. If such a specific monograph is not available, analytical methods should be fully validated. Due to the inherent characteristics of radioactivity detectors, it may not be possible to validate the analytical methods for the determination of radiochemical and radionuclidic purity and therefore it might be difficult to meet all the criteria set by the reference guidelines [2]. In such cases, method validation could be limited to the determination of repeatability, linearity and specificity.

Analytical methods should be revalidated if significant changes are introduced into the analytical procedure. Examples of such changes include, but are not limited to, detector replacement and modification in the radiosynthetic procedure. The accuracy, sensitivity, specificity, and reproducibility of the test methods should be documented. SSRPs that have a very short half-life (e.g. ^{13}N ammonia) can be produced in multiple subbatches on the same day. End-product testing of the initial subbatch can be conducted, provided a sufficient number of subbatches have been demonstrated to produce a product meeting the predetermined acceptance criteria.

Actions if a batch of SSRP does not meet the acceptance criteria

A SSRP can be reprocessed if preestablished procedures (set out in production and process controls) are followed and the finished product conforms to specifications before final release. When the option for reprocessing is exercised, it is recommended that the event is documented and the conditions described in a deviation report. Examples of reprocessing could include a second passage through a purification column to remove an impurity, or a second passage through a filter if the original filter failed the integrity test.

It is worthwhile to implement a mechanism to inform the responsible clinician of a failure of a SSRP dose to comply with its release requirements such as quality and purity.

Stability testing

As with other drug products, SSRPs are expected to remain stable during storage. Although SSRPs may have extremely short shelf lives, because of the short half-lives of the labelling radionuclide, compared to other kinds of drug products, there are stability concerns due to radiation-related radiolysis. Certain SSRPs (e.g. [^{18}F] fluorodopa) can undergo very rapid chemical changes. Therefore, appropriate parameters should be evaluated to establish and document the stability of SSRPs under the proposed storage conditions. Examples of stability parameters include radiochemical identity and purity (including levels of radiochemical impurities), appearance, pH,

stabilizer or preservative effectiveness and chemical purity. It is recommended that appropriate stability-indicating methods that can distinguish degradation products and impurities are used. Stability testing of the SSRP should be performed at the highest radioactive concentration. At least three production runs of the final product should be studied for a time period equal to the labelled shelf life of the SSRP under worst-case conditions. Although stability studies in support of an expiry period would be needed for approval of a SSRP, subsequent changes to the expiry time could be made after adequate testing procedures, as described above.

Reference standards

Most analyses use reference standards. It is recommended that small-scale radiopharmacies establish the reference standards identified in the analytical procedure or SOP or described in the pharmacopoeia. If a small-scale radiopharmacy establishes its own reference standards, it is recommended that data to fully confirm the material's identity and purity be established and documented. Documentation such as reference spectra or other supporting data to prove the identity and purity of the reference standard may be available from the supplier.

Microbiological tests for sterile SSRPs

Sterility testing should start as soon as feasible after the completion of SSRP production. If the sample for sterility testing is held for a longer storage time, small-scale radiopharmacies should demonstrate that the longer period does not adversely affect the test results. Ideally sterility testing is performed outside a licensed laboratory. Aseptic techniques should be used for sterility testing and should comply with the standards of the European Pharmacopoeia.

Bacterial endotoxin tests

A BET should be performed for a sterile SSRP that is intended for injection. The BET may include gel-clot or rapid photometric methods for endotoxin measurement.

The product can be delivered after a pharmacopoeia recommended BET is initiated. However, the endotoxin results should ideally meet the acceptance criteria before administering the product to humans. Alternatively, BET is performed afterwards.

If the result of any BET exceeds the acceptance limit, or if a sterility test is positive for microbial growth, a complete investigation should be conducted immediately and documented. It is recommended that corrective actions based on the results of the investigations are implemented promptly.

Conditional final release

When one of the required finished product tests cannot be completed due to a breakdown of the analytical equipment, criteria should be set under which small-scale radiopharmacies may still release the SSRP. If equipment is properly maintained, breakdowns should be rare. It is recommended that small-scale radiopharmacies determine if the missing testing would adversely affect the safety and efficacy of the SSRP product. Conditional release should be extremely infrequent. Only products that meet all conditional release criteria would be able to be released. Conditional release of a SSRP would not be permitted if a small-scale radiopharmacy could not perform a radiochemical identity/purity test on the API of a SSRP. All activities of conditional release would have to be documented. Samples should be retained under appropriate conditions to ensure the opportunity for reanalysis for a period according to local requirements.

Labelling

Labels can be computer-generated or handwritten. Because of radiation exposure concerns, it is a common practice to prepare much of the labelling in advance. For example, an empty product vial can be prelabelled with partial information (e.g., product name, batch number, date) prior to filtration of the radioactive product, and upon completion of the QC test, the outer shielded container can be labelled with the required information (e.g. radioactivity). Alternatively, a label can be used to label the immediate container provided that there is a way to associate the label with the vial if the label were to come off. Different approaches can be used as long as the approach ensures that the required information is available on the label. A final check should be made to verify that the correct and complete label has been affixed to the container and the shield.

Complaint handling

It is recommended that a designated individual is responsible for collecting information about the drug and the nature of a complaint and for completing an investigation of the case immediately. Corrective action should be taken immediately if there is any reason to believe that an SSRP was implicated in the complaint.

Internal audits

The QA unit should monitor compliance with the QA system on established procedures and practices at least once

a year within an internal inspection. Additional internal inspections of personnel should be performed after new personnel have been trained and/or significant changes have been implemented in the whole process of SSRP preparation. Self inspections should be done in the form of an audit of a minimum two people, for which specific topics may be selected (e.g. personnel, equipment, batch records) allowing more specific recognition of shortcomings. Any failures in the QA system have to be documented including appropriate measures to overcome them. Any failures have to be the subject of the following audit.

Self inspections may also be outsourced to a quality department within the hospital, or to a consultant. Records of these inspections have to be kept.

Records

Records should be kept at an accessible location, and they should be easily available to any internal or external inspector within a reasonable time during the inspection.

Other records that would have to be kept include laboratory records, out-of-specification results, master and

batch records, distribution records, and complaint files. Records may be kept electronically, when appropriate protection and backup strategies are in place and established in writing. Records should be retained for at least 1 year. However, the archiving time must be in accordance with local and national regulations.

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