

Operational Guidance on Hospital Radiopharmacy

A Safe and Effective Approach



IAEA

International Atomic Energy Agency

OPERATIONAL GUIDANCE ON
HOSPITAL RADIOPHARMACY:
A SAFE AND EFFECTIVE
APPROACH

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APPROACH

INTERNATIONAL ATOMIC ENERGY AGENCY
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FOREWORD

Over the last decade, many IAEA programmes have significantly enhanced the capabilities of Member States in the field of nuclear medicine. However, due to the heterogeneous growth and development of nuclear medicine in IAEA Member States, the operating standards of practice differ considerably from country to country and region to region. This publication provides essential details for ensuring the use of a safe and effective approach to hospital radiopharmacy.

Specifically, this publication categorizes hospital activities according to three operational levels of hospital radiopharmacies ('hot laboratories'). It also outlines quality systems applicable at different clinical practice levels. The guidance in this report is not intended to override local guidance (national practice guidelines and rules) or to provide comprehensive advice on all aspects of radiopharmacy practice. Rather, it is a result of international professionals assisting the IAEA in the process of standardization and harmonization.

In many centres, nuclear medicine physicians take responsibility for the hot laboratory and routine service is provided with the aid of medical scientists or technologists. Therefore, the head physician clearly needs to know the safe level of operation. This report, while categorizing the level of operation, provides advice on staff qualifications, training, facilities, equipment, types of procedures, record keeping, quality assurance and quality control at that level. In addition, it provides nuclear medicine physicians with self-assessment tools for continuous quality improvement. This report also provides a framework for the design of new hot laboratories in nuclear medicine centres. The more developed centres will find the categorizations useful for improving operational performance. Normally, larger centres are served by qualified radiopharmacists, who take on much of the responsibility for ensuring that national and international requirements are met. This report is primarily aimed at nuclear medicine physicians and radiologists who are responsible for the hot laboratory. In-depth coverage of compounding, operating cyclotrons, synthesis of positron emission tomography radiopharmaceuticals and preparation of therapeutic radiopharmaceuticals is beyond the scope of this publication as the presence of a radiopharmacist or 'qualified person' is required by the competent authorities. These activities are normally undertaken in complex facilities, requiring highly trained staff for operational requirements, and taking responsibility for the safety and quality of the radiopharmaceuticals.

The IAEA is grateful to the key authors, contributors and reviewers of this report.

The IAEA technical officer responsible for the preparation of this report was K.K. Solanki from the Division of Human Health.

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1. INTRODUCTION

1.1. BACKGROUND

The practice of radiopharmacy combines the expertise of pharmaceutical preparation and the skills needed to handle radioactive substances. Diagnostic radiopharmaceuticals do not normally have any pharmacological effect and their administration is not associated with major clinical side effects. Their clinical use, however, is associated with a risk deriving from radiation exposure and possible contamination during radiopharmaceutical formulation by chemical, biological and microbiological impurities. This is particularly important since the majority of radiopharmaceuticals are administered intravenously. A thorough quality assurance (QA) programme should, therefore, be in place before administration to the patient.

Radiopharmaceuticals tend to differ from normal medicines in that they have a short half-life. Because of their rapid decay, they must be prepared shortly before their clinical use and comprehensive quality control (QC) of the final product is not possible: sterility testing, for instance, cannot be performed due to time limits. Safe and effective preparation and use of radiopharmaceuticals is, therefore, vital for the protection of the operator and the final user — the patient.

1.2. OBJECTIVE

The objective of the report is to provide practical assistance to nuclear medicine centres in setting up and running a hospital ‘hot laboratory’ or radiopharmacy service. It also provides clear boundaries for different levels of radiopharmacy operations with a view to providing more definitive advice on staff qualifications, training, facilities, equipment, types of procedures, record keeping, QA and QC essential at that level.

1.3. SCOPE

It is recognized that the practice of nuclear medicine varies greatly throughout the world depending on the size of the institution, and the level of expertise and equipment available. This report has been produced with a global perspective, taking into account diversity and the wide variation in available resources.

This report is not intended to override local guidance (national practice guidelines and rules) or to provide comprehensive advice on all aspects of radiopharmacy practice. Progressively, national and international standards are becoming harmonized. Central to this theme is patient protection, which includes radiation protection. IAEA Safety Standards publications and Safety Reports provide some background which should be taken into consideration when using this report [1–4]. The report complements IAEA activities such as expert missions and scientific visits, which aim to improve local knowledge and human resources, which is the only possible basis for the sustained development of nuclear medicine services throughout the world.

1.4. STRUCTURE

The advice provided in the report caters for simple dose dispensing using a laminar flow cabinet (LFC) (Fig. 1) to complex compounding of therapeutic radiopharmaceuticals. It is meant to help less developed centres to gain access to the expertise necessary to compound radiopharmaceuticals that would otherwise not be available.

This report is divided into modules of activities so that, according to the operational level of the intended service, the requirements needed can be accessed easily and consulted independently. Caution on radiation safety is advised at all levels.



FIG. 1. Setting up an LFC.

2. TERMINOLOGY USED IN THIS REPORT

approved or registered radiopharmaceuticals. Radiopharmaceuticals approved or registered by competent authorities, for example, the national food and drug administration (FDA), should not be compounded. When, however, approved reagent kits cannot be readily obtained, limited compounding should be undertaken to meet the urgent medical need of an identified individual patient. In this case, the prescriber should be informed that a reagent kit will be compounded to replace the commercial product.

compounding. Formulation of radiopharmaceutical reagent kits from raw ingredients for the preparation of radiopharmaceuticals by the addition of radioisotopes, adding reagents to commercial kits to modify or enhance the performance of radiopharmaceuticals (shelf life extension, fractionation) and/or synthesis from raw materials.

compounding authorization. Compounding is limited to clinical practice in accordance with the medical doctor's prescription or requisition for a specific patient. The process of compounding radiopharmaceuticals must be undertaken under the supervision and responsibility of an authorized nuclear physician or a suitably qualified professional, ideally a radiopharmacist. Compounded radiopharmaceuticals are not to be sold or advertised.

compounding protocols. Compounding to be undertaken within the professional guidance set out under medical or pharmacy practice. Where possible, it should follow recognized pharmacopoeia protocols and be approved if necessary by an institutional committee.

investigational drug. A medication approved by the health protection board or equivalent authority for limited use by approved investigators.

manufacturing. The manufacturing licence issued by competent authorities, for example, the FDA process, ensures that manufacturers have approval from government authorities for pharmaceutical production. The manufacturers have approval from the government to supply products which are registered or approved for safety, quality and efficacy. The manufacturer should follow national or international good manufacturing

practice (GMP) guidelines. Generally, the regulations for manufacturing are not applied for compounding (see table below).

COMPARISON BETWEEN MANUFACTURING AND COMPOUNDING

	Manufacturing	Compounding
Producer	Manufacturer/industry	Hospital radiopharmacy
Setting	Commercial	Clinical
Standard	GMP	Code of practice
Regulation	National medicinal regulatory authority (e.g. FDA)	Professional bodies/institution
Distribution	Public distribution	Practitioner–patient
Marketing	Yes	No
Permission	Investigational authority New drug application	Ethics committee

patented radiopharmaceuticals. Patent protected radiopharmaceuticals should not be compounded. However, when patented reagent kits cannot be readily obtained from a commercial source, limited compounding can be undertaken to meet the urgent medical need of an identified individual patient. In this case, the prescriber should be informed that a reagent kit will be compounded to replace the commercial product.

radiolabelling. The process of radiopharmaceutical formation.

radiopharmaceutical. Radioactive pharmaceutical/medicinal product for clinical use (diagnostic or therapeutic).

radiopharmaceutical reagent kit. Sterile and pyrogen-free reaction vial(s) containing non-radioactive start material that is required to compound or produce a specific radiopharmaceutical.

radiopharmacist (nuclear pharmacist). A professional with a state licence as a pharmacist or nuclear pharmacist (as applicable), who meets local/international training requirements.

radiopharmacy (nuclear pharmacy). A clinical service that procures, prepares or compounds, dispenses radiopharmaceuticals, and assures quality for diagnostic or therapeutic use in patients referred to the nuclear medicine service of a hospital.

3. OPERATIONAL LEVELS

The procedures performed in the field of hospital radiopharmacy can vary considerably in different parts of the world. However, for clarity, these differences can be classified into three broad categories: operational levels 1, 2 and 3. Each category can be further subdivided to provide essential advice on staff qualifications, training, facilities, equipment, types of procedures, record keeping, QA and QC essential at that level.

3.1. OPERATIONAL LEVEL 1a

Operational level 1a is the dispensing of radiopharmaceuticals purchased or supplied in their final form from recognized and/or authorized manufacturers or centralized radiopharmacies. This includes unit doses or multiple doses of prepared radiopharmaceuticals for which no compounding is required.

3.2. OPERATIONAL LEVEL 1b

Operational level 1b is the dispensing of radioiodine and other ready to use radiopharmaceuticals for radionuclide therapy or palliation. This includes ready to use injections of strontium and samarium for pain palliation.

3.3. OPERATIONAL LEVEL 2a

Operational level 2a is the preparation of radiopharmaceuticals from prepared and approved reagent kits, generators and radionuclides (closed procedure). This is the most common activity in nuclear medicine departments, with routine use of a technetium generator and reconstitution of pre-sterilized radiopharmaceutical cold kits.

3.4. OPERATIONAL LEVEL 2b

Operational level 2b is the radiolabelling of autologous blood cells. This includes radiolabelling of red blood cells, platelets and white cells commonly used for infection or inflammation imaging.

3.5. OPERATIONAL LEVEL 3a

Operational level 3a is the compounding of radiopharmaceuticals from ingredients and radionuclides for diagnostic application (including open procedure); modification to existing commercial kits; in-house production of reagent kits from ingredients, including freeze dried operation; related research and development.

3.6. OPERATIONAL LEVEL 3b

Operational level 3b is the compounding of radiopharmaceuticals from ingredients and radionuclides for therapeutic application (including open procedure) together with related research and development. Examples include radio-iodination of meta-iodobenzyl guanidine (MIBG-iobenguane) and rhenium labelled lipiodol.

3.7. OPERATIONAL LEVEL 3c

Operational level 3c is the synthesis of positron emission tomography (PET) radiopharmaceuticals. This includes the increasingly popular fludeoxyglucose (^{18}F) injections (FDG).

The compounding of radiopharmaceuticals produced from unauthorized or long lived generators such as gallium (^{68}Ga) or rhenium (^{188}Re) — mostly related research and development — also falls under operational level 3c.

4. STAFF AND TRAINING

4.1. SUPERVISION AND MANAGEMENT

The local regulations for hospital radiopharmacy services should be applied. If such regulations are not available, it is suggested that all operations should be carried out under the authority and supervision of the nuclear physician in charge and/or a qualified radiopharmacist, who is responsible for the setting up of the radiopharmacy and for an appropriate QA programme. If no radiopharmacist is available, then the local hospital pharmacist should assist with the setting up process and the QA programme. A medical physicist should assist with radiation protection issues. A training manual encompassing all grades of staff should be written and records of training should be documented.

4.2. OPERATING PERSONNEL AND TRAINING

The qualifications required for personnel should be in accordance with local regulations. When, however, these do not cover the qualifications needed for radiopharmacy staff, it is suggested that the preparation and dispensing of radiopharmaceuticals is carried out by one of the following professionals: a nuclear technologist, medical doctor, pharmacist, chemist, biologist or nurse after completion of a basic training programme in radiation physics and instrumentation; mathematics of radioactivity use and measurement; radiation protection and regulations; radiation biology; radiopharmaceutical chemistry; and the clinical use of radiopharmaceuticals.

All personnel should also receive practical training (hands on experience) in preparation, QC and analytical techniques, transport, laboratory cleaning and maintenance, equipment calibration and maintenance, preparation of individual doses and documentation as described in detail in the IAEA Nuclear Medicine Resources Manual [5]. Training should include a session on how to comply with aseptic procedures that must be in operation throughout the whole process. According to the level of operation, individual staff members should receive specific training. These are described under each specific operational level. Any compounding as described in operational level 3 requires a qualified professional with certified training.

5. FACILITIES

5.1. ADMINISTRATIVE AREA

An administrative area should be equipped with appropriate computer hardware (and software), which is networked with computers in other work areas of the radiopharmacy service. Appropriate manual and electronic record keeping facilities are required. Personnel should have access to a telephone, internet, hospital intranet, a fax machine, etc. The administrative area should have enough space to keep manual records, electronic data storage media and all the standard operating procedures (SOPs) documentation. There should be planned upgrades of all hardware and software facilities.

5.2. DISPENSING AREA

The radiopharmacy dispensing area should be a separate, dedicated and secure area. In general, the dispensing room should be close to the imaging and injection areas. The operational area should be in good condition, and hygiene must be ensured. The area should meet local and national safety codes, including fire safety codes.

The space should be specifically designed and maintained to handle unsealed radionuclides so as to meet the required radiation safety standards. All work surfaces should be smooth and impermeable, and should permit easy cleaning and decontamination. Pipe work and any cables should be encased and properly laid to facilitate cleaning and decontamination.

The space should be sufficient to accommodate all essential equipment and accessories, and should allow enough room for at least two staff members to operate simultaneously.

The work areas should maintain satisfactory lighting, temperature and humidity so as to ensure operator comfort, optimum equipment performance and expected radiopharmaceutical stability.

There should be enough space for a laminar flow hood, a pharmaceutical isolator or other environmental cabinet. Sufficient space is needed to locate L-shaped lead shields for handling radiopharmaceuticals, a radionuclide calibrator with adequate lead shielding around it, and shielded sharps waste storage containers (one for short lived radionuclides and the other for long lived radionuclides) as well as for storage of non-radioactive waste containers. A separate shielded area is required for used generators and for radioactive waste as applicable.

There should be a sufficient number of long handle forceps, tongs, syringe shields, vial shields, shielded syringe carriers for gamma or positron emitting radionuclides and suitable shielding devices for handling beta emitting radionuclides.

5.3. RECEPTION AREA

In the reception area, sufficient bench space is essential to perform routine procedures, for example, to receive radioactive packages, to perform surface contamination checks and to complete administrative records. A clearly distinguishable area for storage of radioactive and non-radioactive materials on location is required.

5.4. DECONTAMINATION KIT

To deal with accidental radioactive spillage, there should be a decontamination kit containing absorbent material, decontamination solutions or sprays, gloves, coveralls, plastic sheets, tape and bags to hold contaminated items.

5.5. DEDICATED SINK

There should be a dedicated sink (not located in the dispensing area) for cleaning contaminated items and for defined radioactive liquid waste disposal. Sinks should be excluded from dispensing areas. Any sink installed in other areas should be of suitable material and should be regularly sanitized. The sink draining heavily contaminated fluid should go directly to a shielded fluid storage tank for appropriate decay before final draining into the main outgoing drain, or in accordance with local or national regulations.

The radioactive liquid disposal drain should not be fitted with a trap unless specified by local or national requirements. The sink should be identified by a suitable sign (Fig. 2) containing disposal instructions. It is convenient to segregate technetium waste into weekly amounts, which allows ease of monitoring and waste management.



FIG. 2. Typical sign at a dedicated sink.

6. DOCUMENTATION

6.1. OPERATIONS

All operations should be performed in accordance with written SOPs. SOPs should contain detailed methodology and comply with local practice, which must be authorized and periodically reviewed by the responsible persons.

6.2. RECORD KEEPING

The central objective of any documentation is to provide an audit trail from the investigation request to equipment performance, the QC procedures and the administration of individual patient doses of radiopharmaceuticals. Records must be comprehensive and must cover details such as staff, patients, radiopharmaceuticals, reagent kits, radioisotopes, facilities, equipment, radiation safety and fire safety.

6.3. STAFF

Detailed staff records are important. These include records of staff radiation dose for the whole body, extremities, staff internal radiation dose and thyroid scans (as applicable). Training records for staff including inductions

and continuous professional education should be maintained. Staff vaccination records are essential before their involvement in the preparation of radio-labelling of autologous products, for example, radiolabelled white cells.

6.4. PATIENTS

Accurate patient details and complete records are important. The records must include the patient's name, hospital number or identification number, sex, date of birth, investigation requested, radiopharmaceutical used, dose activity measured, time of measurement, person administering, person checking, and date and time of administration.

For female patients of childbearing age, the documentation should include information on the stage of the fertility cycle and/or pregnancy status, and advice for breastfeeding mothers undergoing diagnostic or other procedures.

Abnormal biodistribution of radiopharmaceuticals (misadministration and maldistribution incident reports) should be recorded and reported to the relevant clinician, to the supplier of the radiopharmaceuticals and to the national regulatory/advisory body according to national arrangements.

Adverse reactions to radiopharmaceuticals should be recorded and reported to the relevant clinician, to the supplier of the radiopharmaceuticals and to the national regulatory/advisory body according to national arrangements.

6.5. RADIOPHARMACEUTICALS

6.5.1. Orders issued

Details such as date of order, supplier, type of preparation, quantity, expected delivery time, clinician involved and ordered by should be recorded.

6.5.2. Details of the delivery

Records should include time of delivery, received by, transport conditions person checking and accuracy of delivered items (preparation and radioactivity) checked by.

6.5.3. Preparation records

Records of prepared radiopharmaceuticals such as description of the product, including the radionuclide, product identification number, activity at the time of patient administration, volume, time of dispensing, patient's name, date, operator and checker identification should be kept. The same information should be displayed on a label to be applied to the patient dose.

6.6. PURCHASE ORDER AND RECEIPT OF RADIOPHARMACEUTICALS

6.6.1. Inspect and record

From the delivery note, the date, name of the radiopharmaceutical or radionuclide, radioactivity, lot number, person receiving, surface radiation, transport index, etc., should be recorded. Following administration, these should correspond to the patient's name and details.

6.6.2. Purchase order

The purchase order (request form) of the radiopharmaceuticals from a central radiopharmacy should be kept for future reference.

6.7. DISPENSING

The dispensing of a dose must ensure traceability to the original multidose vial. There should be a corresponding record of dispensing of unit doses such as date and time of dispensing, radioactivity of unit dose, syringe identification code, together with details of radioactivity dispensed. It is considered good practice to keep records of staff, name and a designation of to whom the dose was delivered

The identity of the dose must be checked against the dispensing document supplied by the radiopharmacy laboratory or the delivery note from the manufacturer.

The dispensing list (shipment list) together with the transport index should be checked and filed.

6.8. DOSE CALIBRATOR QA TESTS

There should be a routine dose calibrator QA test programme in place (Fig. 3). The dose calibrator QA should include constancy checks to be performed daily, linearity checks to be performed quarterly and accuracy checks to be performed annually. Geometry checks (i.e. each isotope in each configuration of volume and container type to be used) should be performed (in addition to accuracy and linearity tests) upon installation or after repair of the dose calibrator.

6.9. FACILITIES AND EQUIPMENT

QC checks on all radiation detection equipment such as radionuclide calibrators and contamination monitors should be performed at regular intervals. The performance and maintenance results for all equipment including any air handling units, isolators, LFCs and radionuclide calibrators should be recorded and reviewed on a regular basis.

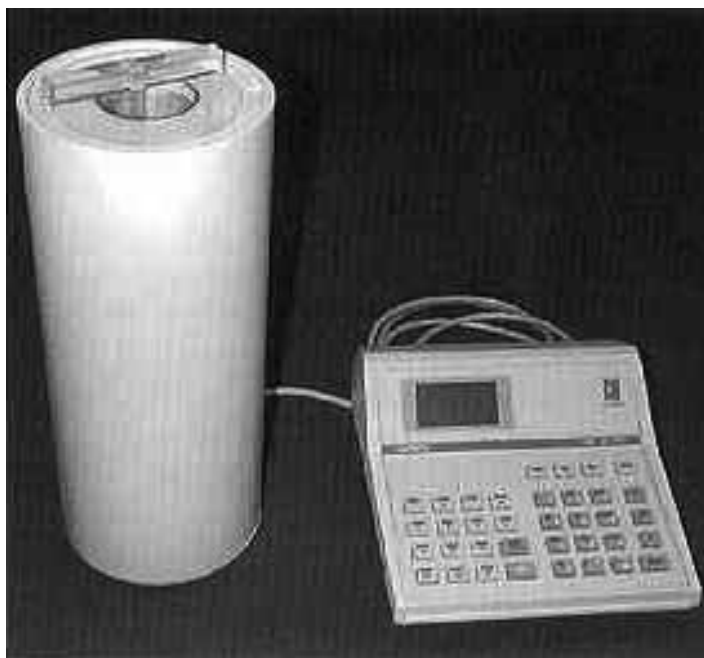


FIG. 3. Typical dose calibrator.

Each piece of equipment should have a service log and a sticker on the equipment stating the previous and next due date of service.

Refrigerator and freezer temperatures should be recorded daily using a maximum and minimum temperature gauge or a computerized central measurement.

6.10. STAFF MONITORING

It should be compulsory that staff wear personal monitoring devices (such as film badges, finger dosimeters and/or pocket dosimeters). All staff members should monitor and record themselves before leaving the supervised and controlled areas using a 'hand and feet contamination monitor' (Fig. 4). This is especially important before leaving the dispensing areas.

6.11. ROOM MONITORING

The radiation area should be monitored with an area survey meter at the end of each working session or at least once a day, at specific sites, according to the laboratory design and as noted in the SOPs for the facility. Wipe tests on work surfaces and any radioactive products received or shipped should be carried out daily.

6.12. CLEANING AND MAINTENANCE OF WORK AREAS

Cleaning sessions (such as changing the double absorbent paper, sanitation of laminar hoods and isolators, etc.) should be recorded.

Records of radioactive waste disposal and/or instances of radiation contamination/spillage should be maintained.

6.13. WASTE DISPOSAL

The date and time of disposal of radioactive waste, its identity and area of disposal should be recorded.

Used syringes are both biological and radioactive waste. Disposal has to take local regulations for both contamination sources into account. It is useful to segregate short half-life waste from long half-life radionuclides.



FIG. 4. Hand and feet contamination monitor.

7. QUALITY ASSURANCE AND QUALITY CONTROL

Only general aspects of QA are mentioned in this section. More specific details are provided under the sections on the different levels of operations.

7.1. ALARA

It is necessary to protect both patients and staff from unwarranted radiation exposure. In general, the risks associated with radiation exposure in nuclear medicine are negligible in most cases. The two leading principles in nuclear medicine, as in all medical practice, are justification and optimization; any nuclear medicine procedure must be justified by an appropriate request and the procedure must be optimized to obtain the best possible results. Staff should be familiar with the ALARA (as low as reasonably achievable) principle in order to reduce the exposure to radiation to the minimum level compatible with successful clinical use. In order for these principles to be implemented, a thorough programme of QA and QC must be practised in all aspects of nuclear medicine.

7.2. ESSENTIAL CHECKS

For patient safety, certain essential checks should be performed on radiopharmaceuticals, radiopharmaceutical reagent kits and radionuclide generators. However, it is accepted that full testing of products as called for by the pharmacopoeia is impractical. A suitably modified QA programme should be in place depending on the operational level.

7.3. PURITY OF INGREDIENTS

When compounding, pharmacopoeia grade ingredients should be used if available; otherwise, approved medicinal products or a high quality source of chemical reagents of analytical grade, supplied with a certificate analysis, should be used. The responsible person should verify the identity and purity of the ingredients by reasonable means, such as lot analysis, manufacturer reputation or reliability of source. All goods received should be visually inspected and identified. Records of batch numbers and quantities received should be kept for traceability.

7.4. QUALITY CONTROL PROCEDURES

QC procedures should follow pharmacopoeia descriptions if available; otherwise, scientifically verified procedures should be followed. All devices and instruments used for QA and QC should be checked and maintained on a

regular basis to guarantee optimum performance. Daily QA checks must be performed on radionuclide calibrators. Regular calibration of radionuclides, containers and sample volume used should be undertaken with radionuclides traceable to national standards. Quarterly linearity checks of the dose calibrator response over the complete range of activities measured should be performed. All procedures should be performed as described in the SOP.

7.5. AUTHORIZED RELEASE

A formal mechanism of acceptance by authorized persons must be undertaken before use of radiopharmaceuticals in patients. A defined process of checking should include checks related to both pharmaceutical and radionuclide quality parameters. An approved product should be clearly identifiable to the end user. All staff involved with patients should be aware of this process.

8. PATIENT RELATED ASPECTS

8.1. ADVERSE REACTIONS AND DEFECTIVE RADIOPHARMACEUTICALS

Adverse reactions to diagnostic radiopharmaceuticals are uncommon, usually transient and relatively minor in severity. However, when they occur, they cause alarm both to the patient and to staff. It is advisable for the nuclear medicine staff to familiarize themselves with the types of reactions and recognize such events when they do occur. Problems with defective radiopharmaceuticals are seldom encountered from vetted and licensed manufacturers. Such licensing is performed by the competent national authority and is enforced by ‘pharmaceutical or medicines’ inspectors from agencies such as the national FDA, etc. Difficulties commonly arise with unqualified manufacturers or suppliers. Following extensive quality, safety and efficacy assessments, approved or registered radiopharmaceuticals that are defective or substandard are seldom encountered. Poor transport and storage conditions can also result in a substandard product. Care is also advised when the formulation has changed or the product is approaching its expiry date. Products from a different manufacturer or supplier should be monitored more closely. Any changes to manufacturers’ stated directions should be validated before patient use.

8.2. MISADMINISTRATIONS: DIAGNOSTIC

Most national radiation committees (NRCs) have recently revised their definition of misadministration. Prior to the new rules, it was estimated that, in the USA, one in every 10 000 injections qualified as a misadministration. Further clear action is required for notification.

- (a) Old definition:
 - (i) Administering radiopharmaceutical to incorrect patient;
 - (ii) Diagnostic dose differing from prescribed dose by >50%;
 - (iii) Administration by an unprescribed route.
- (b) New definition: (i), (ii) or (iii) as in the old definition *and* a whole body dose of 48 mGy (5 R — where 1 R of X ray or gamma radiation from 0.1 to 3 MeV produces 0.96 rad in tissue).

8.3. MEDICAL EVENTS (PREVIOUSLY MISADMINISTRATIONS)

- (a) New definition:
 - (i) An administered dose that differs from the prescribed dose by 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent *and* the dosage delivered exceeds the prescribed dosage by >20% or the dosage delivered falls outside the prescribed dosage range;
 - (ii) An administered dose that exceeds 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent *and* is one of the following:
 - Wrong radiopharmaceutical;
 - Wrong route of administration;
 - Wrong patient.

In such cases, the action required is:

- Notification of the NRC by the next calendar day;
- Notification of the referring physician and patient within 24 h (if, in the opinion of the referring physician, notification of the patient would cause undue harm, the patient may not be notified);
- Provision of a written report with the details of the medical event to the NRC and the referring physician within 15 d.

8.4. MISADMINISTRATIONS: THERAPEUTIC

- (a) Old definition:
 - (i) A therapeutic dose differing from the prescribed dose by >10%.
- (b) New definition:
 - (i) A therapeutic dose differing from the prescribed dose by >20%.

In such cases, the action required is:

- Documentation details of misadministration;
- Notification of the NRC/State in writing about the misadministration, giving pertinent details.

8.5. PAEDIATRIC USE OF RADIOPHARMACEUTICALS

Although radiopharmaceuticals are routinely used in paediatric patients, few are generally licensed for this group of patients (where a system of licensing exists). Therefore, the responsible clinician must take a balanced view of the benefits against the risks to children who have rapidly growing and dividing tissues, which may be more sensitive to ionizing radiation. In addition, their organ size to body ratio may be different from that of an older child or adult. Doses given to children should be reduced either according to weight or surface area. Practitioners should refer to local guidance on paediatric doses. If none is available, Table 1 could be used.

9. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 1a

9.1. SCOPE

Operational level 1a refers to radiopharmaceuticals that are procured in their final form from a recognized or authorized manufacturer or a centralized radiopharmacy. This can include unit doses or multiple dose vial radiopharmaceuticals. In all these cases, no further preparation is required.

TABLE 1. FRACTION OF ADULT DOSE BASED ON THE SURFACE AREA SCALING FACTOR

Weight (kg)	Fraction of adult dose	Weight (kg)	Fraction of adult dose	Weight (kg)	Fraction of adult dose
3	0.1	26	0.56	50	0.88
4	0.14	28	0.58	52	0.9
6	0.19	30	0.62	54	0.91
8	0.23	32	0.65	56	0.92
10	0.27	34	0.68	58	0.93
12	0.32	36	0.71	60	0.95
14	0.36	38	0.73	62	0.96
16	0.4	40	0.76	64	0.97
18	0.44	42	0.78	66	0.98
20	0.46	44	0.8	68	0.99
22	0.5	46	0.82	70	1
24	0.53	48	0.85		

9.2. STAFF AND TRAINING

The activities required for operational level 1a can be performed by any staff member who has undergone training in the areas of dose dispensing, dose calibration, dose labelling, QC procedures, radiation safety, aseptic procedures and record keeping.

9.3. FACILITIES

There should be a radionuclide calibrator (re-entrant ionization chamber) with appropriate lead shielding. A shielded dispensing station should be available for use.

9.4. OPERATIONS

Access to the radiopharmacy laboratory should be limited to authorized staff only.

Safe laboratory practice should be observed. Smoking, drinking, eating, storage of food and beverage containers or utensils, and the application of excessive cosmetics should be prohibited within this facility.

9.4.1. Receipt of the prepared unit doses

A physical check of the unit doses should be performed upon receipt. The radioactivity of the individual dose should be measured again before administration. The identity of the dose should be counterchecked with the dispensing document supplied by the dispensing radiopharmacy laboratory or manufacturer.

When there are no other practical guidelines for ‘ward-based’ practices or for private clinics, it has been accepted that three or fewer registered or approved radiopharmaceutical products can be prepared (within the specification of the product approval) in less than European Union Grade 5 or International Organization for Standardization ISO 5 [6] air flow, air particulate count and microbiological quality of air (see also Table 2 in Section 11.3 for more specific advice), in a designated hygienic clean area. In addition, there should be no other source of direct contamination. Such a preparation should ideally be for single patient use and for immediate use after reconstitution or dispensing.

A visual examination behind appropriate shielding should be undertaken before patient administration. Any discrepancies should be reported.

9.4.2. Measuring radioactivity

Each unit dose should be checked using a dose calibrator.

9.4.3. Administration to a patient

The dose should be administered to a patient according to the instructions of the manufacturer and nuclear medicine physician. Ideally, the administration should commence shortly after reconstitution, and never later than the shelf life of the product (most frequently 8 h after preparation).

9.4.4. Disposal of used vials and syringes

Used vials and syringes should be disposed of in a radioactive waste disposal container. Radioactive materials must be handled with care and appropriate safety measures should be used to minimize radiation exposure to operators and members of the public.

9.5. RECORD KEEPING

9.5.1. Purchase order and receipt of radiopharmaceuticals

The order date, name of the radiopharmaceutical, amount of radioactivity, patient's name, lot number, received by, surface radiation, transport index, etc., should be inspected and recorded.

Purchase orders (request forms) of radiopharmaceuticals issued by the radiopharmacy should be kept for future reference.

9.5.2. Dispensing

When dispensing a dose, traceability of the dose should be ensured.

A record of the dispensing of a unit dose such as date and time of dispensing, radioactivity of unit dose, syringe identification code, name and designation of staff, and to whom the dose was delivered should be recorded.

The identity of the dose must be checked against the dispensing document supplied by the radiopharmacy laboratory or manufacturer.

9.6. QUALITY CONTROL

QC is limited to radioactivity measurement of the radiopharmaceutical. Adequate labelling should be undertaken to prevent misadministration.

The consistency of the radionuclide calibrator should be ascertained on a daily basis using a long lived radionuclide such as ^{137}Cs . This is done by a background check (no source in the calibrator) and a voltage check. The ^{137}Cs source is then used to do the daily consistency check by reading the activity on each individual radionuclide setting of the dose calibrator. It is good practice to undertake an annual linearity check using a range of radionuclides and clinically used amounts of activities.

Cross-calibration of the main radionuclides in use (e.g. $^{99\text{m}}\text{Tc}$, ^{67}Ga , ^{123}I , ^{111}In) should also be performed using sources from the national standards.

Dose calibrator geometry checks should be performed as suggested in Section 6.8.

9.7. SELF-ASSESSMENT OR AUDIT

In addition to traditional QC, a periodic review of operations is essential. Section I.1 of Appendix I provides a series of questions based on the requirements for operational level 1. This self-assessment questionnaire is intended to provide a working format for self-evaluation and to encourage a systematic approach. Each question has been graded A, B or C. These standards are set at three levels:

- ‘A’ standards are those required by legislation, IAEA technical publications or other external standard-setting bodies. Any failure to reach an ‘A’ standard is, therefore, regarded as serious and urgent corrective action should be instituted;
- ‘B’ standards are those that are not compulsory, but are expected to be reached by all departments. In case of failure, corrective action is recommended;
- ‘C’ standards are desirable, but not essential. Corrective actions may improve the overall functioning of the department.

Rather than a simple ‘yes’ or ‘no’ answer, the person using the questionnaire is asked to provide ‘verifiable’ details such as SOPs or text in the quality manual. The questionnaire encourages reviewers to add comments and to identify areas where further action is required. Once the desired action has been undertaken, this can be entered in the ‘date achieved’ column.

10. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 1b

10.1. SCOPE

Operational level 1b refers to the dispensing of radioiodine and other ready to use open source radionuclides for therapy and palliation, including ready to use injections of strontium and samarium for pain palliation.

Radioiodine preparations, either in liquid or capsule form, are purchased from recognized or authorized manufacturers. Typically, no further compounding is required. Any dilution of products should be undertaken within the product specifications.

10.2. STAFF AND TRAINING

The procedures for operational level 1b can be performed by one assigned staff member who has undergone training, in addition to what is specified for operational level 1a, in the following areas: use and maintenance of the fume hood, avoiding contamination, handling beta emitting radioisotopes with special emphasis on shielding materials for beta radiation, cross-contamination, and inhalation and importance of volatile radioisotopes such as ^{131}I . Specific radiation protection issues, such as environmental and personal monitoring, including measurement of thyroid uptake, should be covered.

10.3. FACILITIES

In addition to the facilities described in operational level 1a, a fume cupboard with suitable filters (Fig. 5) that can handle volatile radioactive materials is required for ^{131}I solutions. There is need for sufficient space for a non-radioactive waste container and sufficient bench space to receive radioactive packages, to perform QC procedures and space for record keeping and administration. There should be a secure system for delivery and storage of ^{131}I therapy doses.



FIG. 5. Typical fume hood.

There should be adequate shielding to provide protection from high energy gamma irradiation.

A secure waste storage area with shielded containers for ^{131}I use is necessary. There should be a sufficient number of lead lined sharps bins (at least two — one for short life radionuclides and the other for longer half-life radionuclides) with sufficiently thick walls to store radioactive waste.

A dedicated radioiodine sink can be used for radioactive liquid waste disposal. The sink drainage should go directly to the main outgoing drain and/or to a storage tank according to national regulations. The liquid disposal drain should not be fitted with a trap unless required by local or national requirements. Each disposal should be followed by ample water and chemicals such as sodium thiosulphate to prevent vaporization of radioiodine.

10.4. OPERATIONS

10.4.1. Receipt of the prepared unit doses

A physical check of the unit doses should be performed upon receipt. The radioactivity of the individual dose should be measured immediately prior to administration. The identity of the dose should be counterchecked against the dispensing documents supplied by the dispensing radiopharmacy laboratory or manufacturer.

10.4.2. Radiation safety precautions

The packaging in which the ^{131}I product arrives from the supplier should be checked for any signs of damage or spillage. The outer package should be disposed of after monitoring. Always leave the open ^{131}I iodine package in the fume hood to allow clearance of radioactive xenon. The long physical and biological half-lives of ^{131}I iodine dictate that the operator should take particular precautions to minimize exposure, skin contamination and inhalation.

The thyroid gland activity of the operator should also be monitored frequently or according to hospital guidelines.

SOPs should exist for the handling of spills and contamination.

10.4.3. Dispensing

If a multidose vial is used, then the liquid or capsules should be dispensed into a single dose unit for a particular patient.

Handling of ^{131}I , especially as a solution, should always be performed only inside the fume hood.

10.4.4. Administration to a patient

The therapy dose is administered to a patient according to the manufacturer's or medical physician's instructions. The patient's identity should be double checked, especially before giving a therapeutic dose of any radiopharmaceutical. Patient consent for the therapeutic procedure should be obtained.

The pregnancy status of female patients of childbearing age should be ascertained and, if not known, a pregnancy test should be performed. Breast-feeding mothers undergoing a therapeutic procedure should be cautioned about the excretion of ^{131}I into breast milk, and supplemental/alternative food should be considered. Advice should also be given on pregnancy/fathering a child immediately after a therapeutic procedure.

If the patient remains in hospital, there should be written protocols with:

- Instructions to the patient for before receiving the dose, during the hospital stay, and how to behave afterwards;
- Instructions to all sanitary staff (oral and written);
- An explanation of how radiation dose to the family and public can be minimized after returning home.

If the patient is an outpatient or is released from the hospital, there should be written protocols with:

- Instructions to the patient for before receiving the dose and after leaving the hospital;
- An explanation of how radiation dose to the family and public can be minimized after leaving the hospital.

10.4.5. Disposal of used vials and syringes

In general, the disposal procedures are the same as those stated under operational level 1a. The volatile nature of the ^{131}I solution should always be stressed.

Safe laboratory practice must be observed at all times when handling therapeutic radioactive isotopes.

10.5. RECORD KEEPING

In addition to the record keeping described for operational level 1a, radioiodine dispensing records should be kept and filed. Records of date, time, levels of activities and area of disposal of radioactive waste are needed.

10.5.1. Radiopharmaceuticals

The same level of detail as described for operational level 1a is required.

10.5.2. Staff, equipment, facilities and procedures

Staff should be trained in radiation protection of patients undergoing diagnostic and therapeutic procedures involving radiopharmaceuticals.

10.6. QUALITY CONTROL

At this operational level, the dose calibrator QC should carefully assess the accuracy of the measurement of the different therapeutic radionuclides used.

Before ordering products from a new supplier, the end user should obtain details of the certificate of analysis of the therapeutic radionuclide. It is important to check radionuclide and radiochemical purity periodically.

10.6.1. Equipment

Cross-calibration with the national standards laboratory for the main therapeutic radionuclides in use, for example, ^{131}I , ^{32}P , ^{186}Re , ^{89}Sr , ^{90}Y , is necessary.

10.6.2. Radiation monitoring

Radiation monitoring (at least twice a day (at the beginning and end of the day) and after every handling of ^{131}I) should be performed with an area survey meter. Monitoring the hands and feet of the operator, and wearing a film badge, finger ring dosimeter and pocket dosimeter (Fig. 6) should be stressed.

11. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 2a

11.1. SCOPE

Operational level 2a refers to the preparation of radiopharmaceuticals from prepared and approved reagent kits, generators and radionuclides for diagnostic or therapeutic purposes (closed procedure). This is the main activity in most nuclear medicine departments, with routine use of a technetium generator and reconstitution of pre-sterilized radiopharmaceutical cold kits.

11.2. STAFF AND TRAINING

To operate a radiopharmacy performing the procedures described for operational level 2a, at least two staff members are required. In particular, an assigned staff member is required who has received training, in addition to what is specified for operational levels 1a and 1b, in the following areas: maintenance and operating procedures of radioactive ^{99m}Tc generators, radiolabelling of commercially available kits using generator eluates, QC and generator performance, QC tests for radiopharmaceuticals, radiation monitoring, and safety regulations and related documentation. Training in aseptic procedure for generator elution, transfer of sterile solutions from one sealed vial to another, the use of biological containment devices (biological safety cabinet, isolators) and the use of shielded water baths is also required.



FIG. 6. Typical film badge, finger ring dosimeter and pocket dosimeter.

11.3. FACILITIES

11.3.1. General description

In addition to the details stated for operational level 1a, the procedures described in operational level 2a should be performed in a vertical laminar air flow (LAF) cabinet placed at least in a European Union Grade C [7] (ISO 7 [6] equivalent) environment; the environmental status conforms to the microbiological contamination limits specified in Table 2. It is recommended that a vertical LAF cabinet [8] is installed. Strict aseptic practices are essential during the dispensing process. Unless local rules state otherwise, these terms are considered an integral part of good radiopharmacy practices. When isolator technology is used, a European Union Grade D environment is sufficient. The actual dispensing zone, also known as the ‘critical zone’, should achieve operational European Union Grade A or ISO 5 environmental standards. No open procedures are performed at this operational level. A QC programme should be in place at all times to verify the status of the environment and the final quality of the radiopharmaceutical.

These conditions are best achieved if the dispenser uses isolator technology or Class II type safety cabinets.

It is recognized that approved solvent extraction generators are common in some parts of the world, which would need additional care and requirements, e.g. a fume hood. In addition, the final filtration of the ^{99m}Tc eluate must be performed within an LAF cabinet or isolator. The integrity of the LAF cabinet filter should be checked at regular intervals and according to the manufacturer’s guidelines.

TABLE 2. LIMITS FOR MICROBIAL CONTAMINATION IN EUROPEAN UNION AND ISO GRADED ENVIRONMENTS

European Union Grade	ISO	Settle plates 90 mm dia. cfu/4 h	Contact plate near the point of dispensing dia. 55 mm cfu/plate	Glove print, 5 fingers cfu/glove	Air sampling cfu/m ³
A	5	<1	<1	<1	<1
B	6	5	5	5	10
C	7	50	25	—	100
D		100	50	—	200

cfu: colony forming unit.

Where the above conditions are not achievable, three or fewer sterile products may be prepared in an environment lower than ISO Class 5 air provided that no direct contact contamination is present. Products prepared under these conditions should be administered within 1 h and be completed within 12 h of preparation; referred to as products for 'immediate use'.

11.3.2. Equipment

The radiopharmaceutical labelling/preparation should be performed in a Class II LAF cabinet or isolator. The $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator should be well shielded and stored in a similar environment as used for the labelling/preparation.

The performance criteria for microbiological safety cabinets (vertical LAF cabinet) are those stated in Ref. [8]. The LAF cabinets or isolators should be equipped with appropriate lead shielding to protect the operator. Ideally, Class II LAF cabinets or isolators should be located in a European Union Grade C (ISO 7) environment. If the cabinet cannot be placed in a European Union Grade C environment, advance process controls and stringent microbiological area monitoring are essential. Final product safety and quality require continuous monitoring. An appropriate lead shield radionuclide calibrator in the near vicinity is considered good practice.

In a situation where a European Union Grade C (ISO 7) environment exists, the microbiological area monitoring should be performed at least once a week to verify acceptable operational procedures.

A shielded water bath is required for the preparation of certain radiopharmaceutical kits such as $^{99\text{m}}\text{Tc}$ -mertiatide injection (MAG3), sulphur colloid and $^{99\text{m}}\text{Tc}$ -sestamibi complex injection (MIBI).

11.3.3. Other operational requirements

A sufficient number of lead lined sharps bins to store radioactive waste (at least two – one for short life radionuclides and another for longer half-life radionuclides (>8 h)) is required. There should be sufficient space for the storage of a non-radioactive waste container.

11.4. OPERATIONS

11.4.1. Receipt and use of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator

Upon receipt of the generator (Fig. 7), the presence of any physical damage should be checked for, and the generator should then be sited in a designated shielded area. The generator should be eluted after safe placement. The first eluate should not be used for radiolabelling of sensitive kits such as $^{99\text{m}}\text{Tc}$ exametazime complex injection (HMPAO), MAG3 and others. Elution should be performed in accordance with the manufacturer's instructions. Generator maintenance procedures such as recapping the outlet needle with a new disinfectant cap should be observed.

The radionuclide yield should be calculated and then compared with that stated by the manufacturer. In addition, molybdenum and aluminium breakthrough in the eluate has to be checked for.

The pH, clarity, radiochemical purity and sterility should be checked at least for the first and last eluate. If the generator is used for longer than two weeks, the eluate requires a check for sterility at least once a week.

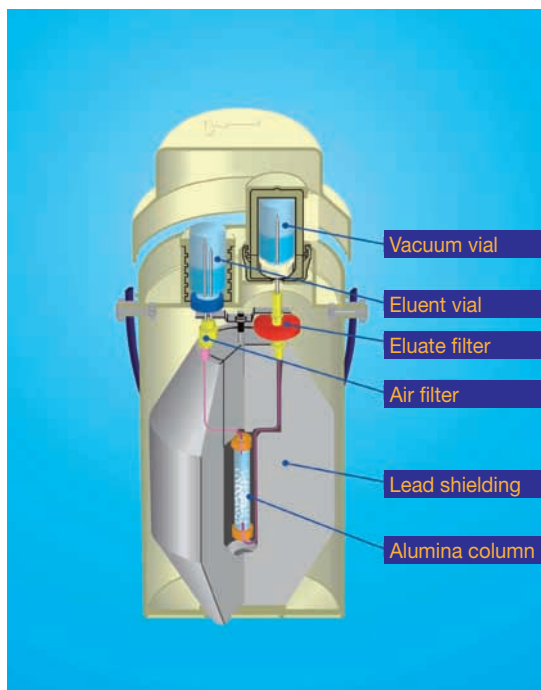


FIG. 7. Typical generator.

11.4.2. Receipt of cold radiopharmaceutical kits

A physical check of the radiopharmaceutical reagent kits should be performed upon receipt. The manufacturer's instruction manual should be checked for the required storage conditions. Additional checks are required for kits that require storage or transport in a refrigerator. The integrity of the cold chain, especially during transit, should be assessed. Any changes in the radiolabelling method to those stated by the manufacturer require special consideration and these fall into operational level 3a. It is good practice to assess batch by batch variation. Whenever manufacturers supply a new batch that is different from the previous batch in formulation, radiolabelling method and QC method, verification should be performed before actual patient administration.

11.4.3. Radiolabelling of radiopharmaceutical reagent kits

The radiolabelling of radiopharmaceutical reagent kits should be performed in accordance with the manufacturer's instructions. Only one kit should be prepared at a time. General aseptic practices and precautions, such as avoiding introducing air into the kits and avoiding puncturing the rubber septum from the same point to prevent a coring effect, are essential. Double checking critical steps, such as identification of the correct cold kit, correct radionuclides, recommended radioactivity, recommended volume of reconstitution, usage of new ampoule or vial of 0.9% sodium chloride (normal saline), are vital to reduce dispensing errors. After radiolabelling, the kit should be appropriately labelled and identified as such by including the date and time of reconstitution, expiry time, radioactivity added, lot number and storage condition/place.

While using the radiopharmaceutical reagent kits, the 'first in, first out' policy should be applied in order to make sure that the kits received last will be used last. No reagents (including kits) should be used after their expiry date or time.

11.4.4. Unit dose dispensing from a reconstituted multidose vial

Unit dose syringes should be properly labelled with date, identity of the radiopharmaceutical, radioactivity, calibration time, etc.

The drawing of the unit doses should be done only for one type of radiopharmaceutical at a time in order to avoid misadministration of radiopharmaceuticals.

While drawing unit doses, appropriate radioactive decay allowance should be made for the respective times of injection.

The unit dose should be pre-calculated to compensate for radioactivity decay. The actual dose at the time of injection should be stated on the label.

A simple spreadsheet should ensure the accuracy of the calculation and ease data storage. Many calibrators can be interfaced with a computer permitting 'real time' tracking. The unit dose should be labelled and identified appropriately.

If the prepared unit dose is not for immediate use, it is essential to undertake stability studies to verify the suitability of the syringe used for the respective radiopharmaceutical and its storage conditions.

11.4.5. Receipt of radiolabelled radiopharmaceutical kits

A physical check of the kits (e.g. ^{111}In -octreotide, $^{123/131}\text{I}$ -MIBG) should be performed upon receipt. The manufacturer's instruction manual should be checked for special instructions on storage conditions and dispensing methods. The quality of a product from a new supplier should be verified at the user end. Periodical checks thereafter are recommended to ensure consistent product quality.

11.5. RECORD KEEPING

A comprehensive documentation system is essential. Appendix II provides a useful list of the logbooks and records required for institutions. For radiopharmacy operations, in practice, a more detailed recording system such as that shown in Fig. 8 is essential.

The sections below list the additional records that should be maintained.

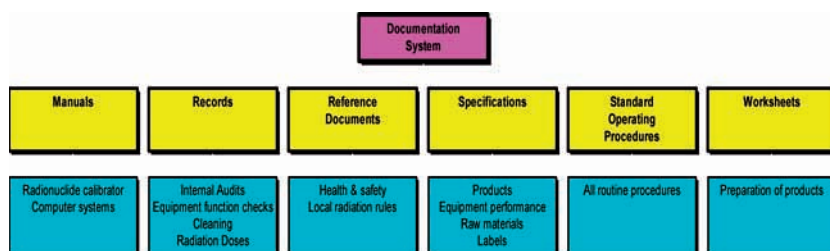


FIG. 8. Model recording system.

11.5.1. Generator

Generator specifications, such as manufacturer, lot number, manufacture date, expiry date, specific activity and transport index, should be recorded. The manufacturer's instruction manual for the generator should be kept and incorporated into relevant SOPs.

11.5.2. Radiopharmaceutical reagent kits

Kit specifications, such as description of material, lot number, manufacture date, expiry date, quantity and storage conditions, should be recorded. An inventory logbook is advisable. The manufacturer's instruction manual should be kept and incorporated into relevant SOPs.

11.5.3. Radiolabelled radiopharmaceutical kits

Kit specifications, such as description of material, lot number, manufacture date, expiry date, specific activity, transport index, storage conditions and radioactivity, should be recorded. A kit inventory logbook is advisable. The manufacturer's instruction manual should be thoroughly read and understood; any revisions should be made in the SOPs before filing. Records of the physician's order and patient identification should be kept and checked with individual unit doses.

11.5.4. Generator elution

The date and time of generator elutions should be recorded. ^{99m}Tc eluate lot numbers should be assigned for further reference. Any difficulties and non-conforming elutions should be recorded and followed up with the manufacturer. In addition, such variances should be reported to the national or regional reporting system for defective products.

11.5.5. Preparation

Every step of the radiopharmaceutical preparation, such as the date and time of preparation, amount of radioactivity added, kit lot number, description of the kit, saline batch number, incubation time and temperature, final volume, specific activity, physical appearance and expiry time, should be recorded. A lot number should be assigned for each radiolabelled kit. A simple spreadsheet programme can aid data management.

11.5.6. Radiopharmacy facilities

Details related to the maintenance of a radiopharmacy facility, such as maximum and minimum room temperature, maximum and minimum temperature of storage refrigerator, and flow rates for LFCs/isolators/fume cupboards, should be registered at each session. Daily and weekly microbiological monitoring of the LFC/isolator and surrounding areas should be maintained. Maintenance schedules, annual test results for main filter integrity of Class II type microbiological safety cabinets, results of service reports, and repairs of LFCs/isolators and fume cupboards should be recorded.

11.5.7. Results of batch QC

Radiochemical purity, molybdenum breakthrough, aluminium ion, pH and radionuclide purity test results should be recorded. Sterility and endotoxin test results, where applicable, should also be recorded.

11.5.8. Operator related tests

Microbiological broth transfer test results and finger dab results should be recorded, if applicable.

11.5.9. Generator disposal record

The records should include the fate of the generator: returned or stored until complete decay, description of generator returned to the supplier, batch number, date of return/dismantling, etc.

11.6. QUALITY CONTROL

Apart from QC procedures as described in operational level 1, additional QC procedures should be performed.

11.6.1. Generator and generator eluate

Radionuclide purity tests and a ^{99}Mo breakthrough test for the generator should be performed on the first elution. Sterility, pH, radiochemical purity and aluminium ion contamination of the generator eluate should also be tested on at least the first and last eluate. Longer lived generators require these tests more often.

11.6.2. Radiopharmaceuticals

Radiochemical purity tests of the radiopharmaceuticals should be performed on the first of each batch before patient administration. Chromatography tests are generally acceptable for routine radiochemical purity (RCP) tests. Table 3 lists some of the commonly used chromatography systems for radiopharmaceuticals.

TABLE 3. COMMON RADIOCHEMICAL PURITY SYSTEMS AND R_f VALUES

Radiopharmaceutical	Stationary phase	Mobile phase	R_f RHCs	R_f TcO_4	R_f Tc-bound
^{99m}Tc -pertechnetate	ITLC-SG	0.9% NaCl	0.0	1.0	—
^{99m}Tc -MDP	No. 1	Acetone	0.0	1.0	0.0
	ITLC-SG	1M sodium acetate or 0.9% NaCl	0.0	1.0	1.0
^{99m}Tc -DTPA	No. 1	Acetone	0.0	1.0	0.0
	ITLC-SG	0.9% NaCl	0.0	1.0	1.0
^{99m}Tc -DMSA	No. 1	Acetone	0.0	1.0	0.0
^{99m}Tc -HIDA/DISIDA	ITLC-SG	0.9% NaCl	0.0	1.0	1.0
	ITLC-SA	20% NaCl	0.0	1.0	0.0
^{99m}Tc -MAA	ITLC-SG	0.9% NaCl	0.0	1.0	0.0
^{99m}Tc -MAG	No. 1	Acetonitrile	0.0	1.0	1.0
	ITLC-SG	0.1M HCl	0.0	1.0	0.0
^{99m}Tc -tetrafosmin	No. 1	Ethyl acetate	0.0	0.0	1.0
^{99m}Tc -sestamibi	No. 1	Ethyl acetate	0.0	0.0	1.0

Note:

Stationary phases:

ITLC-SG: Instant Thin-layer Chromatography, silica gel, Pal Gelman Laboratory.

ITLC-SA: Instant Thin-layer Chromatography, silica acid (poysilicic acid).

No. 1: Whatman No. 1 chromatography paper.

Mobile phases:

0.1 M HCl: 0.1 M hydrochloric acid.

0.9% NaCl: 0.9% sodium chloride solution (normal saline).

1 M sodium acetate can be prepared with 82 mg/mL anhydrous sodium acetate or 136 mg/mL sodium acetate trihydrate.

Terminology:

R_f : relative front.

1.0: front.

0.0: origin.

RHC: reduced hydrolysed colloids.

Upon each preparation, the radiopharmaceutical should also be visually inspected. pH should also be tested on the first of each batch received. Particle size determination is also important for preparation and dispensing of colloids and aggregates: the first vial in each batch should be examined. Sensitive kits should be tested each time they are made, e.g. MAG3, HMPAO.

Periodic testing is recommended to ensure the consistency of a product. These tests provide an assessment of the stability of kits under local conditions. A sterility test programme for prepared kits should be implemented.

11.6.3. Radiation monitoring

Radiation monitoring (at least twice a day or after every high activity procedure) should be performed with an area survey meter. Monitoring the hands and feet of the operator, and wearing a film badge, finger dosimeter and pocket dosimeter should be stressed.

11.7. COMMENTS

Under specific protocols, compounding can also be performed from certified sterile ingredients obtained from approved suppliers, for example, the hospital pharmacy department or any external pharmaceutical or teaching establishment which has suitable facilities and expertise for preparing sterile solutions or lyophilized vial ingredients as required by the relevant protocols. There should be an underpinning QA programme for each protocol.

12. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 2b

12.1. SCOPE

Operational level 2b refers to the laboratory practices and environmental conditions necessary for safe manipulation and radiolabelling of autologous blood cells and components for re-injection into the original donor/patient.

Guidance on radiolabelled autologous products, including biological safety practices, QA systems, methods for radiolabelling red and white cells,

and their clinical utility, is within the scope of a separate comprehensive report. The essential elements are presented in this section.

12.2. STAFF AND TRAINING

Operating a radiopharmacy performing the procedures described for operational level 2b requires at least two staff members. In particular, an assigned staff member is required who has received, in addition to what is specified for operational level 2a, comprehensive operator training for safe operations, such as aseptic cell manipulation, radiolabelling of autologous blood cells, transfer of sterile solutions from one open container to another, handling of biological materials, operator protection methods from biohazardous material, operation and maintenance of centrifuges, microscope and haemocytometer use, and comprehensive cleaning procedures of equipment and facilities between successive patients to prevent any cross-infections.

12.3. FACILITIES

Manipulation of cells for clinical diagnosis requires the use of a Class II LAF cabinet/isolator located in a dedicated room (meeting the European Union Grade C (ISO 7) level of cleanliness) with appropriate internal finish to allow effective sanitation to reduce particulate and microbiological contamination of the environment. The use of an open or closed vial system on a laboratory workbench is not an alternative to a controlled sterile environment.

A shielded centrifuge is required for operator safety. A centrifuge with closed buckets is required for blood cell component separations to ensure containment in case of spills. Centrifuge buckets should be disinfected with 2% glutaraldehyde or 1% sodium hypochlorite on a regular basis. Local chemical guidelines should be followed. The hypochlorite wash should be followed by a wash with sterile water to reduce the particulate contamination due to hypochlorite crystals.

Specific products and fumigation facilities for the sanitation of internal cabinet surfaces and all associated cell labelling equipment with a wide spectrum of antiviral and antimicrobial disinfectants between successive patients are also required.

12.4. OPERATIONS

During cell manipulation and radiolabelling for clinical diagnosis, it is necessary to maintain both cell viability and sterility, and to avoid operator exposure to biological and radiation hazards. Operator protection is of paramount importance. Universal blood and body substance precautions must be followed at all times. Strict adherence to safe laboratory practice is essential.

12.4.1. Staff health programme

All personnel involved in blood cell radiolabelling procedures should be vaccinated against hepatitis B. Radiolabelling of cells for patient re-injection should only be performed by validated staff. Operators who suffer from bacterial or viral infections or have open exudate lesions or weeping dermatitis should not be engaged in any open procedure.

12.4.2. Whole blood collection and transport

Whole blood from patients should be collected by trained personnel skilled in venopuncture techniques. Gloves should be worn at all times.

Thorough coating of the inner wall of the disposable syringe with an appropriate anticoagulant is important before withdrawing the patient's blood.

To prevent cell haemolysis and cell damage during blood collection, a 21 or larger gauge needle should be used wherever applicable.

All blood specimens must be clearly labelled with the patient's name, unique identification number, and date and time of collection.

Syringes containing patient blood should be transported to the blood cell radiolabelling laboratory according to hospital policy and by gloved personnel. The transport of radioactive blood or biological substances requires additional protective shielding, as specified by local regulations.

12.4.3. Safe laboratory practice and procedures for autologous blood cell radiolabelling

Only one blood radiolabelling procedure should be performed at a time.

Surfaces should be decontaminated with an appropriate sanitizing agent (e.g. 70% isopropyl alcohol/ethanol or 0.25% chlorhexidine gluconate in 70% ethanol) prior to use, after all procedures are completed and whenever surfaces are overtly contaminated. The floor should be similarly decontaminated at suitable intervals.

Prompt decontamination of spills should be standard practice.

Appropriate protective attire should be worn while in the laboratory, and discarded before leaving the laboratory.

After radiolabelling or handling blood, hands should be washed thoroughly with a suitable sanitizing agent (e.g. 5% chlorhexidine gluconate) when the operator removes their gloves.

Access to the laboratory should be limited to authorized personnel.

To avoid needle-stick injuries, needles should never be broken or bent by hand or unnecessarily removed from disposable syringes. If needles are to be re-sheathed, a re-sheathing apparatus must be used at all times.

In the event of a needle-stick or other injury due to sharp objects potentially contaminated with blood or the splashing of mucosal surfaces, the operator should follow the recommended hospital policy for decontamination and notify the incident promptly.

12.4.4. Dispensing radiolabelled blood

Radiolabelled blood should be checked for aggregation or clumping of cells before release.

The final disposable dispensing syringe must be clearly labelled with patient identification and code numbers. Ideally, it should be delivered personally to the staff member in charge of the injection room.

After verifying that the patient is to receive his or her own radiolabelled cells (by asking the patient to say or spell his/her full name and date of birth), the syringe should be inverted several times to re-suspend the cells. Radiolabelled cells should be injected slowly.

12.4.5. Waste disposal

Used syringes, needles, cannulas and other sharp items should be placed in hospital approved puncture resistant containers, which should be located as close as practicable to the point of use. They must be disposed of in accordance with hospital policy. Biological waste should not be left unsealed or left lying around in the laboratory. If waste is radioactive, the puncture resistant containers should be dealt with as radioactive waste.

Cleaning personnel should be made aware of contaminated bins and must be alerted to the potential hazards and carefully instructed about the proper precautions to be taken.

12.5. RECORD KEEPING

Details of the cell labelling method should be recorded together with the patient's particulars.

12.6. QUALITY CONTROL

In the radiolabelling of white cells, operators should adhere to the shelf life of ^{99m}Tc -labelled-HMPAO (i.e. 30 min), ^{111}In -oxine and ^{99m}Tc -colloids. The percentage of radiolabelling of white cells should be calculated routinely. The integrity of the cells can be ascertained with trypan blue. Any changes to standard procedure for cell labelling should additionally be checked for chemotaxis.

12.7. SELF-ASSESSMENT OR AUDIT

In addition to traditional QC methods, a periodic operational review is essential. Section I.2 of Appendix I provides a series of questions based on the requirements for operational level 2. At this operational level, both questionnaires in Appendix I should be completed.

13. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 3a

13.1. SCOPE

Operational level 3a refers to compounding radiopharmaceuticals from radionuclides for diagnostic application, modification to existing commercial kits and the in-house production of reagent kits from ingredients (including freeze dried operation). Research and development frequently falls within operational level 3a.

Guidance on hospital compounding of radiopharmacy products, including safety practices, QA systems, methods for common formulations and their clinical utility, is within the scope of a separate comprehensive report. The essential elements are presented in this section.

13.2. STAFF AND TRAINING

All staff members at this level, particularly if involved in research and development, should have training in good clinical practice, experimental design and interpretation of experimental results, preparation of scientific reports for internal use or external assessment and publication as well as in budgeting of research projects.

To carry out the compounding procedures at this level, ideally three designated staff members are necessary. An additional independent qualified internal or external QA staff member is required, for example, hospital QA pharmacy staff or the use of staff from an external agency.

The responsibilities of the staff members could be distributed as follows:

- Staff member A is responsible for all the activities carried out such as the overall planning of compounding, writing SOPs, verifying, keeping and monitoring all the records related to production, QC, staff training, etc.;
- Staff member B executes compounding procedures;
- Staff member C is responsible for QC and performs other general laboratory duties as required.

All responsible staff should have a science degree (in pure science, applied sciences or health sciences) or equivalent and specific job related training of at least one year. Additionally, staff member A should have undergone comprehensive training in compounding radiopharmaceutical reagent kits from raw materials. He/she should also have relevant supervisory and management experience, and should be able to train staff in relevant techniques. Staff members B and C could interchange duties. Appropriate backup arrangements should exist for all staff members.

Staff must also receive training, in addition to what is specified for operational levels 2a and 2b, in the following areas:

- Knowledge of and experience in the application of good laboratory practice principles in hospital environments, and in aseptic handling of synthetic reagents and biological products are essential;
- Special attention should be paid to ensure that the product is suitable for human administration and that associated risks related to the following procedures are eliminated:
 - Freeze drying;
 - Analytical balance, QC and operation;
 - pH meter calibration and operation;

- Individual radiolabelling methods;
- Sterility and pyrogenicity testing;
- Biodistribution in animal models (in-house or outsourced);
- In vitro biological reactivity (if applicable);
- Submission procedures to the ethics committee.

13.3. FACILITIES

All the equipment for compounding and performing QC of radiopharmaceutical reagent kits should be designed, placed and maintained to suit its purpose. When designing the facilities, at least the following areas must be taken into account:

- General laboratory area;
- Waste storage area;
- Changing area;
- Compounding area;
- Air handling unit.

13.3.1. General laboratory area

The general laboratory area should have adequate bench space to properly perform QC and to accommodate the following equipment/accessories depending on the scale of operations:

- Data recording personal computer;
- Chromatography instrumentation (note: access to high pressure liquid chromatography (HPLC) and other chromatography systems should be available either in-house or externally);
- General laboratory instrument area (balances, pH, centrifuges);
- Calibrated dose calibrators with suitable shielding;
- Scintillation counter with an NaI(Tl) crystal;
- Radiation shielding for operations that do not require clean environments;
- Pharmacy grade refrigerator with temperature recorder;
- Hot plate (with thermostat);
- Hot water bath;
- Cleanable storage trolleys for consumable materials;
- Glassware washing and drying facilities;
- Oven for apyrogenic treatment of glassware;

- Double distilled deionized water production unit;
- Autoclave facility;
- Separate refrigerator/freezer for storage of radioactive materials
- If applicable, -20°C freezer;
- Storage for inflammable products if applicable;
- Storage for general chemicals (chemicals cabinet);
- Access to an animal house (experimental surgery);
- Biological reactivity binding assessment facility;
- Refrigerated centrifuge.

If in-house microbiological and pyrogen testing is performed, the following equipment/accessories are also required:

- Separate refrigerator for microbiology test media;
- Microbiological incubator;
- Limulus amoebocyte lysate (LAL) testing facilities (including a thermostatic heat block).

13.3.2. Waste storage area

Sufficient space and facilities to store radioactive, non-radioactive, biological and radioactive biological waste separately are required. Adequate waste disposal records should be kept.

13.3.3. Compounding area

Dedicated facilities, equipment and laboratory glassware should be used for compounding any radiopharmaceutical reagent kits and radiopharmaceuticals.

In addition to the details stated in operational level 2a, the procedures described for operational level 3a should be performed in a Class II LAF cabinet/isolator placed in a clean environment (meeting European Union Grade C (ISO 7) or better air quality). The compounding of radiopharmaceuticals or radiopharmaceutical reagent kits should be carried out under negative pressure surrounded by a positive pressure environment.

The compounding area should be fitted with visual and/or audible warning devices to indicate any failure of air supply.

There should be a changing room between the compounding area and the general laboratory area, through which staff may enter or leave, taking into account a 'clean-grey-black' design (with segregation of clean, grey and black areas).

Sterilized articles for use in the clean room should enter via a pass-through hatch.

Suitable shielding for all unsealed sources handled in the compounding area should be available. Shielding materials should ease sanitization and decontamination.

The following equipment/accessories should be placed in the compounding area depending on operation needs:

- Freeze drying equipment;
- pH meters, balance, vortex mixer and any other equipment which is necessary for reagent kit compounding;
- Calibrated and suitably shielded dose calibrator;
- Nitrogen gas supply. Nitrogen should be filtered through a 0.22 µm pore size filter before use in order to remove possible microbial contamination and particulate residues from the cylinder;
- Generator storage in a shielded area, which should be kept under additional clean air flow using a desk top air filter unit.

13.3.4. Air filtration unit

The air should be terminally HEPA filtered. The air conditioning should maintain operating temperatures between 18 and 22°C with regulated humidity. A completely aseptic environment is needed.

13.3.5. Facility cleaning procedures

The following cleaning procedures should be followed:

- Access to clean rooms should be restricted to the minimum number of authorized staff possible;
- Suitable garments (sterilized, non-lint, whole body protection) should be used in the clean rooms;
- A written protocol of the cleaning procedure should exist describing which disinfectant is used, concentration, time of cleaning and operator;
- Cleaning procedures should be monitored at planned intervals and records should be kept;
- High standards of personal hygiene should be maintained;
- Cleaning procedures should be validated once a year;
- De-pyrogenation of glassware should be performed.

13.4. OPERATIONS

13.4.1. Raw materials

The following points are important for handling raw materials:

- Purchase and receipt documents related to raw materials should be kept;
- Raw materials should be stored in appropriate room conditions. If storage space is not available in the laboratory area, raw materials should be placed in a room near the hospital radiopharmacy service. All water used for kit compounding should be of at least ‘water for injection’ quality as described in international pharmacopoeias. Saline solutions should also have 0.9% wt/vol. sodium chloride for injection;
- Acceptance of raw materials must be based on the certificate of analysis provided by the supplier. These records should be kept during the shelf life of the compounding kits.

13.4.2. Radiopharmaceutical reagent kits

The following records should be kept:

- A unique identifying number for all raw materials and batch compounding;
- Date of batch compounding;
- Date of batch release;
- Expiry date of batch;
- Sample retention for QC during shelf life;
- Operator or authorized signatory who released the batch;
- Retrospective sterility and pyrogen testing.

The following suggested measures should prevent cross-contamination between different ingredients in the compounding area:

- Avoiding the compounding of different radiopharmaceuticals or radiopharmaceutical reagent kits at the same time;
- Controlling transfer of materials by means of airlocks, changing clothes and through washing and decontamination of equipment; for example, in the case of freeze drying used for kit preparation, the freeze drier itself has to be cleaned and sanitized before each compounding is performed;
- Taking care to prevent aerosol formation;

- Venting radioactivity from operation areas through appropriate filters, which should be monitored for performance and radioactivity on a regular basis and replaced when necessary.

13.4.3. Air handling unit service

The air handling unit should receive regular maintenance and an annual service. Reports and detailed data from these activities should be kept and reviewed periodically.

13.4.4. All other equipment

All the equipment used in the general laboratory area and in the compounding area should be calibrated. The most recent calibration date and the initials of the operator that performed the calibration should be kept and attached to a visible part of the equipment.

Service reports, whenever done, should be kept safe yet available for inspection and review.

13.4.5. Computer data backup

All the information related to the hospital radiopharmacy service activities, and the records already described, should be stored on suitable, safeguarded electronic media, with the corresponding data backed up elsewhere.

13.4.6. Animal biodistribution studies

Biological batch evaluation, transport and animal use in research studies should be undertaken in agreement with international guidelines for biomedical research with animals [9, 10]. The radiopharmacy department should have access to animal laboratory facilities. Animal disposal should be handled in agreement with biological and radioactive waste disposal procedures.

13.5. RECORD KEEPING

Detailed control and record keeping of each batch is paramount. Careful monitoring of yields and full accountability of each operation should be undertaken after each batch run including in-process checking. An integral

part of the official batch release should include a report of any change, exceptions and/or deviations.

All temperature and pressure controls records should be retained.

13.6. QUALITY CONTROL

QC includes operational level 1 and 2 procedures. In addition to biological testing, more extensive chemical purity tests and specific activity measurements are required:

- Sterility test;
- Bacterial endotoxin test;
- Specific activity;
- Chemical purity;
- HPLC;
- Gas chromatography;
- Thin layer chromatography (TLC);
- Radiochemical purity;
- Stability studies (where applicable);
- Toxicity studies (where applicable).

14. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 3b

14.1. SCOPE

Operational level 3b refers to compounding of radiopharmaceuticals from basic ingredients or unlicensed intermediates and radionuclides for therapeutic application (open procedure), and/or related research and development.

Guidance on the complex area of compounding of therapeutic radiopharmaceutical products, including biological safety practices, QA systems, methods for therapy formulation and their clinical utility, is within the scope of a separate comprehensive report. The essential elements are presented in this section.

14.2. STAFF AND TRAINING

Staff should have training in all aspects, with particular emphasis on radiation protection related to compounding, dispensing, internal dose and use of therapeutic radionuclides in clinical settings.

14.3. FACILITIES

A separate fume hood externally ducted for radio-iodination and/or a Class II LAF cabinet/isolator with appropriate safety systems sited in a separate European Union Grade C (ISO 7) environment with appropriate shielding (for gamma as well as beta radiation) is required. If large quantities of radioactivity are manipulated, properly shielded hot cell facilities are essential. An adequate facility is required to perform terminal microfiltration, sterility testing and endotoxin testing of therapeutic radiopharmaceuticals. Appropriate storage facilities for biological and radioactive waste disposal systems are essential.

14.4. OPERATIONS

A full QA programme should be in place when preparing therapeutic radiopharmaceuticals for human administration. Due care is essential to prevent any cross-contamination with manipulation of beta or even alpha emitters. In addition:

- Consideration should be given to both radiochemical and radionuclide purity, taking into account the radiation safety of the patient. Records should be kept, including QC method and name of checker;
- Release specifications should be written, including radiopharmaceutical stability, time of release and time of expiry;
- When manipulating open sources of beta emitters, there is a risk of the operator receiving high dose rates; such solutions should be handled properly;
- Operators should be periodically monitored for ingestion and internal exposure to beta radiation. Detailed staff records should be kept.

14.5. RECORD KEEPING

Detailed control and record keeping of the therapeutic radioisotopes is paramount. Careful monitoring of yields and full accountability of radionuclide should be undertaken after each batch run. Loss must be accounted for as an integral part of the official batch release.

14.6. QUALITY CONTROL

The radionuclide purity of the prepared radiopharmaceutical is critical. The dose calibrator should be monitored and validated routinely to ensure accuracy both in vials and syringe measurement. Annual checks against national or international standards are mandatory. Both physical and biological (in vivo) stability should be carefully assessed for each batch.

15. DETAILED GUIDANCE FOR OPERATIONAL LEVEL 3c

15.1. SCOPE

Operational level 3c refers to the synthesis of PET radiopharmaceuticals and compounding of radiopharmaceuticals produced from unauthorized long lived generators such as ^{68}Ga or ^{188}Re as well as related research and development.

Guidance on preparation of PET radiopharmaceuticals, including parametric release, safety practices, QA systems, actual formulations and their clinical utility, is within the scope of a separate comprehensive report. The essential elements are presented in this section.

15.2. STAFF AND TRAINING

Staff should have training in all aspects related to compounding, dispensing and use of positron emitting radionuclides, internal dose and their generators in clinical settings. Competency in PET radiochemistry is essential.

15.3. FACILITIES

Hot cells (Fig. 9) and complete chemistry systems are essential for PET. Ideally, the synthesis boxes and hot cells should be placed in a European Union Grade C (ISO 7) environment next to a European Union Grade A (ISO 5) LAF work bench used for dispensing. The whole system should be located in a room that meets a European Union Grade D level of cleanliness.

Long lived generators should be housed in a separate Type II LAF/isolator with an operational European Union Grade A (ISO 5) environment or isolator technology, and within at least European Union Grade D (ISO 8) background in the room.

Suitable shielding, according to the energy and kind of emission of the radionuclide, should be taken into account and validation of cabinet performance should be performed.

15.4. OPERATIONS

A full QA programme should be in place when preparing PET or therapeutic radiopharmaceuticals for human administration. Due care is essential to prevent any cross-contamination.



FIG. 9. Typical PET hot cell.

15.5. RECORD KEEPING

Detailed control and record keeping for each batch is paramount. Careful monitoring of yields and full accountability of each operation should be undertaken after each batch run including in-process checking. Any deviation and changes must be taken into account and should form an integral part of the official batch release.

15.6. QUALITY CONTROL

The very short half-lives of many PET radionuclides have additional implications for quality systems. Radiochemical purities can be rapidly quality controlled using an HPLC system while in transit but before release of products for clinical use. Better communication links and follow-up are required. Pre-validation of the system and the whole operation is essential to ensure consistency. Any changes or deviations with respect to starting material, equipment or process must be validated before the initial production run for clinical use.

Sterility, apyrogenicity and physicochemical purity tests should be routinely performed and closely monitored for all PET radiopharmaceuticals together with long lived generators. If tests cannot be prepared before release, they should be undertaken retrospectively.

Ongoing microbiological assessment is essential.

Appendix I

SELF-ASSESSMENTS FOR OPERATIONAL LEVELS 1 AND 2

This review, as described in Tables 4 and 5, is part of the quality system. The process of quality management requires self-assessments at least once a year. The ‘class’ indicates the standard of conformance which is set at three levels:

- ‘A’ standards are those required by legislation, IAEA technical publications or other external standard setting bodies. Any failure to reach an ‘A’ standard is, therefore, regarded as serious and urgent corrective action should be instituted;
- ‘B’ standards are those that are not compulsory, but are expected to be reached by all departments. In the case of failure, corrective action is recommended;
- ‘C’ standards are desirable, but not essential. Corrective actions may improve the overall functioning of the department.

TABLE 4. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONAL AT RADIOPHARMACY OPERATIONAL LEVEL 1

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
Staffing						
1.1	Is there a responsible professional for the radiopharmacy? Provide details.	A				
1.2	Is the radiopharmacy unit operated under the direction of a person with appropriate training as defined by local or national regulations?	A				
1.3	Are there written staff training manuals for all grades of staff?	B				
Facilities						
1.4	Does the unit have appropriately finished rooms (including adequate lighting, appropriate finishes to walls, floors, ceilings and ventilation) and a shielded dispensing station?	A				

TABLE 4. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONAL AT RADIOPHARMACY OPERATIONAL LEVEL 1 (cont.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
1.5	Is there a shielded dispensing station available?	A				
1.6	For operational level 1b: Is there a shielded dispensing station and/or a fume hood available? [Is there a fume cupboard with suitable filters for volatile radioactive materials such as ¹³¹ I solutions?] [If only radioiodine capsules are handled, is the package opened in a well ventilated area?]	A				
1.7	Is there a validated (annual check on air flow, safety and challenge testing) fume hood with suitable filters for handling radioiodine solutions?	A				
1.8	Are there records and logs kept for all equipment irrespective of whether maintenance and calibration is performed in-house or by external contractors?	B				

TABLE 4. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONAL AT RADIOPHARMACY OPERATIONAL LEVEL 1 (cont.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
Purchase of materials						
1.9	Are there suitable protocols and trained staff for the purchase of approved or marketing authorized radiopharmaceuticals?	A				
1.10	Are all goods received checked and recorded against the order for correctness of delivery?	B				
1.11	Are records of batch numbers and quantities received kept?	B				
1.12	Are visual inspections and label checks carried out prior to acceptance?	B				
Dispensing protocols						
1.13	Are there specific written radiopharmacy procedures for dispensing operations undertaken in the radiopharmacy?	B				

TABLE 4. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONAL AT RADIOPHARMACY OPERATIONAL LEVEL 1 (cont.)

No.	Component	Class	Y/N	Verifiable – manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
1.14	Under operational level 1a: Are there written procedures for the aseptic dispensing and labelling of unit doses of ready to use radiopharmaceuticals?	B				
1.15	Is there a system for labels which assesses quality, number produced and number applied to dispensed doses?	A				
1.16	For operational level 1b: Do the written procedures contain clear safety and monitoring instructions for dispensing radiiodine solutions or capsules?	A				
1.17	Under operational level 1b: Are there written procedures for calibration assays, and preparation and dispensing of individual patient radionuclide therapy?	A				

TABLE 4. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONAL AT RADIOPHARMACY OPERATIONAL LEVEL 1 (cont.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
1.18	Can the audit and documentation for each radiopharmaceutical batch be traced from the prescription to the actual administration of individual patient doses?	A				
QA/QC						
1.19	Are daily QC checks performed on radionuclide calibrators?	A				
1.20	What quality checks are undertaken on a supplier before purchase?	B				
1.21	Are periodic quality checks on radiopharmaceuticals performed?	B				
1.22	Is there a written procedure for dealing with products failing to meet the required standard?	B				

TABLE 4. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONAL AT RADIOPHARMACY OPERATIONAL LEVEL 1 (cont.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
1.23	Is there a record of complaints and any associated follow-up and investigation?	B				
1.24	Are there written procedures and records for regular contamination surveys of the radiopharmacy unit?	A				
Waste						
1.25	Are there written procedures for the disposal of radioactive and non-radioactive waste specific to the radiopharmacy?	A				
1.26	Is there a periodic review/audit of arrival, use and disposal of all radioactive materials?	A				
1.27	Are there written logs for each solid source that indicate usage, transfer and disposal of the source?	A				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
Staffing						
2.1	Have all staff working at operational level 2 received specific staff training on the following: Calibration of equipment; Working practices in the radiopharmacy; Preparation of individual doses; QC and analytical techniques; Dose release; Record keeping; Cleaning. Provide details and training records.	A				
2.2	Is there a system for formal approval of all documentation including radiopharmaceutical preparation, QC and formal release to patient?	B				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.3	What training is provided to staff performing the final checks on all products prepared before release for patient use?	A				
2.4	Are there training records for all staff performing cell labelling, e.g. RBC, WBC?	B				
2.5	Is there an annual performance review to check the competencies of radiopharmacy staff?	B				
Facilities						
2.6	For operational level 2: Are there regular checks on validated Class II type B microbiological safety cabinets located in a dedicated room?	A				
2.7	Are manometer readings of pressure differentials across HEPA filters recorded daily?	B				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.8	Are there periodic records of air velocity determination for LAF cabinets or isolators?	B				
2.9	Is challenge testing of the HEPA filters in LAFs and isolators carried out annually?	B				
2.10	For negative pressure isolators: Before preparation takes place, are gloves or gauntlets visually inspected and integrity tests carried out and recorded?	B				
2.11	Is there a system and record of planned preventative maintenance for all equipment in the radiopharmacy including the refrigerator?	B				
2.12	When clean rooms are used, are the over-pressure gauges monitored and recorded daily?	B				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
Purchase of materials						
2.13	Do all products, kits and generators have product approval, marketing authorization or bear a product licence number?	A				
2.14	How many unlicensed or unapproved products are used each year and is there a record of them?	A				
2.15	For all unlicensed kits, radiopharmaceuticals or radiochemicals, are the prescribers or responsible medical doctors made aware of their responsibilities?	A				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)
(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.16	Do the suppliers of reagents and unapproved products provide a “certificate of analysis”?	B				
Preparation protocols						
2.17	Are there written and approved procedures for the use of generators and reconstitution of each radiopharmaceutical kit used?	A				
2.18	Are SOPs independently reviewed and approved at specified intervals?	B				
2.19	Is the preparation of ^{99m} Tc radiopharmaceuticals from kits and generators carried out in an LAF cabinet?	A				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.20	Are there set criteria before release for preparation for patient use? Are these undertaken by the same operator or a different individual?	B				
2.21	Can each individual patient's dose be traced to a specific generator and kit batch number?	A				
2.22	Under operational level 2b: Do the written procedures for any autologous preparation, e.g. red and white blood cells, include clear instructions on safety, cleaning and decontamination?	A				
2.23	Are there written procedures for the preparation and dispensing of approved kit formulations of radiolabelled biological, e.g. monoclonal antibodies, peptides?	A				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.24	<p>QA/QC</p> <p>For operational level 2: Are there records for the following: Purchase of radioactive products and ingredients; Generator elution, yield, ⁹⁹Mo breakthrough and aluminium ion breakthrough; Product preparation, QC and release; Environmental and microbiological monitoring; Aseptic process, aseptic operator validation and trend analysis; Laboratory cleaning and maintenance; Equipment and plant calibration and maintenance; Radioactive contamination monitoring and radioactive waste disposal; Product defects and SOPs non-conformance, i.e. when a procedure is performed in a manner other than that described in the relevant SOP; Independent inspection and audit.</p>	B				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.25	In line with the IAEA Operational Guidance on Hospital Radiopharmacy publication, are there records of routine microbiological monitoring of the preparation area in the radiopharmacy?	A				
2.26	Are there calibration and linearity checks of the dose calibrator response over the complete range of activities measured at least annually?	A				
2.27	Is there a set programme for checking the quality of radiopharmaceuticals?	B				
2.28	Considering patient safety, are certain simple checks performed on prepared radiopharmaceuticals, e.g. mini-chromatography?	A				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.29	For operational level 2: Is a ^{99}Mo breakthrough measurement performed on the first eluate from each $^{99\text{m}}\text{Tc}$ generator and repeated when the generator is moved?	A				
2.30	Is aluminium ion breakthrough checked on the first eluate from a $^{99\text{m}}\text{Tc}$ generator?	A				
2.31	Are changes in the source of any kits, diluents or vehicle used, needles, syringes, swabs and sterile containers used within radiopharmacy recorded?	B				
2.32	On first use of a new batch or first new delivery of radiopharmaceutical kits, is radiochemical purity performed?	B				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.33	Are rapid alternative methods employed for swift prospective QC for critical radiopharmaceuticals, e.g. the determination of RCP for ^{99m} Tc HMPAO?	A				
2.34	Is there regular pH testing of radiopharmaceuticals carried out?	B				
2.35	Prior to release for patients, is each individual radioactivity dose checked?	A				
2.36	Is there a record of the formal approval/release by an authorized person before a product is administered to a patient?	A				
2.37	Are there written procedures for the recall of defective products?	A				

TABLE 5. SELF-ASSESSMENT FOR DEPARTMENTS FUNCTIONING AT RADIOPHARMACY OPERATIONAL LEVEL 2 (cont.)

(It is essential that the requirements for operational level 1 are met while working at operational level 2.)

No.	Component	Class	Y/N	Verifiable — manual, reference documents, SOP, QC data, file record, etc.	Comments/planned action	Date achieved
2.38	Is there a record of complaints and any associated follow-up and investigation?	B				
2.39	Is there a system of recorded self-inspection and reports evaluation?	B				
2.40	Is there a system for an external audit or peer review process?	B				

Appendix II

ESSENTIAL LOGBOOKS AND RECORDS

Licensure of Institution required by a State department of nuclear safety/ nuclear regulatory commission, or a “timely filed notice”.

Radiation safety rules (e.g. no smoking, eating) must be posted in each laboratory in which radioactive materials are used.

IDNS/NRC regulations and telephone numbers must be posted in each laboratory in which radioactive materials are used. The chart is supplied by the regulatory agency.

Ring/whole body badge monthly reports must be posted on the bulletin board on a monthly basis. The employer is responsible for informing each employee on an annual basis of his cumulative radiation dose.

Thyroid monitoring logbook. All nuclear medicine personnel involved in the use of ^{131}I sodium iodide in quantities >1 mCi must have a routine thyroid count performed every six months; in addition, 24 h after an iodination procedure or administration of ^{131}I sodium iodide in liquid from the thyroid must be counted.

Leak testing of sealed sources logbook. All sealed sources (gamma counter calibration sources, dose calibrator standards, etc.) must be leak-tested every six months and the results of this testing recorded in the appropriate logbook.

Area room monitoring logbook

- (1) On a daily basis, every room in which radioisotopes are used must be surveyed with a properly calibrated Geiger–Müller (GM) counter. It is important to specify in the logbook exactly which meter was used, whether the readings are in units of counts/min or mrad/h, what the normal background reading for each room is and what the ‘action level’ is (how many times background required before immediate action must be taken).
- (2) On a weekly basis, a wipe test must be performed in every room in which radioisotopes are used. An accurate area map must be drawn and 5–7 wipes are taken in each room. Results of the counting procedure are

correlated with the area map to identify areas with count rates higher than normal room background. These areas must be decontaminated to background and new readings recorded in the logbook.

Personnel monitoring logbook. At the end of the day, each radiopharmacist and support staff member is obliged to monitor his/her hands with a Geiger counter to detect inadvertent contamination. Results of this survey are recorded in the appropriate logbook on a daily basis. If hands are 'hot', they must be decontaminated to background and new readings recorded in the logbook.

Incoming package logbook. Every package containing radioisotopes must be logged in appropriately. This includes recording the product name, lot number, calibrated activity and date, received activity and date, shipper's package number and the initials of the person receiving the package. In addition, if your licence requires you to monitor every package received by your department, results of this monitoring must be recorded in this logbook.

Hot sink logbook. One sink in each laboratory may be designated as a 'hot sink'. This is the only permissible location for disposing of radioactive liquid waste in your department. The logbook should be set up so each liquid waste disposal is documented by radioisotope, amount, date and initials of the person involved.

Radiopharmaceutical manufacturing or compounding logbook.

- (1) Generator elution data:
 - (a) ^{99}Mo breakthrough;
 - (b) Al^{3+} ion breakthrough;
 - (c) Hydrolysed reduced $^{99\text{m}}\text{Tc}$.
- (2) Radiopharmaceutical disposition;
- (3) Patient dose sheet;
- (4) Radiopharmaceutical QC.

Dose calibrator QC test logbook.

- (1) Accuracy test;
- (2) Constancy test;
- (3) Linearity test;
- (4) Geometry test.

Equipment (general) logbook.

- (1) Equipment repair logbook;
- (2) Hood certification logbook;
- (3) Temperature monitoring logbook;
- (4) Centrifuge calibration logbook;
- (5) Survey meter/GM counter calibration logbook.

Miscellaneous

- (1) Annual summary reports;
- (2) Individual folder or computer record for each patient;
- (3) Continuing pharmaceutical education requirements;
- (4) Annual summary report for radioactive drug research committee;
- (5) Personnel training and evaluation records.

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This report provides practical assistance to nuclear medicine centres in setting up and running a hospital 'hot laboratory' or radiopharmacy service. It also provides clear boundaries for different levels of radiopharmacy operations with a view to providing more definitive advice on staff qualifications, training, facilities, equipment, types of procedures, record keeping, quality assurance and quality control essential at that level. The report is divided into modules of activities so that, according to the operational level of the intended service, the requirements needed can be accessed easily and consulted independently. Caution on radiation safety is advised at all levels.