EANM
European Association of Nuclear Medicine

The Radiopharmacy

A Technologist's Guide

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Contributors

James R Ballinger, PhD

Chief Radiopharmaceutical Scientist
Guy's and St Thomas' NHS Foundation Trust
London, United Kingdom

Clemens Decristoforo, PhD (*)

Chair of the EANM Radiopharmacy Committee
Clinical Department of Nuclear Medicine
Medical University Innsbruck
Innsbruck, Austria

Brit Farstad

Member of the EANM Radiopharamcy Committee
M.Pharm/Radiopharmacist
Department Head, Isotope Laboratories
Institute for Energy Technology
Kjeller, Norway

Brendan McCoubrey

Radiation Safety Officer
Dept. of Diagnostic Imaging
St. James's Hospital
Dublin, Ireland

Geraldine O'Reilly, PhD

Radiation Protection Advisor
Dept. of Medical Physics and BioEngineering
St. James's Hospital
Dublin, Ireland

Helen Ryder

Clinical Specialist Radiographer
Dept. of Diagnostic Imaging
St. James's Hospital
Dublin, Ireland

Tanja Gmeiner Stopar, PhD

Member of the Education Board,
EANM Radiopharmacy Committee
Radiopharmacy, Head
University Medical Centre Ljubljana
Department for Nuclear Medicine
Ljubljana, Slovenia

Wim van den Broek

Chair of the EANM Technologist Committee
Chief Technologist
Dept of Nuclear Medicine
University Medicine Centre
Nijmegen, The Netherlands

Editors

Suzanne Dennan

Vice-Chair of the EANM Technologist Committee
Acting Radiographic Services Manager
Dept. of Diagnostic Imaging
St. James's Hospital
Dublin, Ireland

Clemens Decristoforo, PhD *

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Foreword

Wim van den Broek

Since it was formed, the EANM Technologist Committee has been devoted to the improvement of nuclear medicine technologists' (NMTs') professional skills. Publications that will assist in the setting of high standards for NMT's work have been developed and since 2004 a series of brochures, "Technologists Guides", have been published yearly. This booklet about radiopharmacy is already the fifth volume. The new and stricter regulations in the field of preparation of radiopharmaceuticals changed the daily practice in the radiopharmacy in the last 5 years.

Nuclear medicine is a multidisciplinary specialty in which medicine, physics and pharmacy are involved. The Radiopharmacy is an integral part of a nuclear medicine department and its prime responsibility is the preparation of high quality radiopharmaceuticals, the base for a high quality nuclear medicine examination. The majority of these radiopharmaceuticals is mainly used for diagnostic imaging, which is the main activity of nuclear medicine. Radiopharmaceuticals are medical products defined in the European directive 2004/27/EC amending the directive 2001/83/EC. As in other disciplines the complex changes driven by European legislation had their impact on everyday practice in the preparation of radiopharmaceuticals.

Only trained people should be responsible for and participate in the preparation and quality control of radiopharmaceuticals. Training should be provided for all staff working in radiopharmacy departments in the aspects of quality assurance in which they are involved. This includes: preparation, release, quality control and analytical techniques, cleaning, transportation, calibration of equipment (especially for the measurement of radioactivity), working practices in the radiopharmacy, preparation of the individual doses, documentation, hygiene, pharmaceutical microbiology, and microbiological monitoring. Often a Nuclear Medicine Technologist is the person who is involved in the preparation and quality control of the radiopharmaceuticals.

I am grateful for the effort and hard work of all the contributors, who are the key to the contents and educational value of this booklet. The most essential and relevant aspects of radiopharmacy in daily practice are emphasised here. This booklet is prepared in cooperation with the Radiopharmacy Committee of the EANM. This Committee is very active and critical in the field of regulations and guidelines for the production of radiopharmaceuticals and constantly proposes practical solutions. Many thanks to Suzanne Dennan who coordinated this project.

With this new booklet, the EANM Technologist Committee offers to the NMT community again a useful and comprehensive tool that may contribute to the advancement of their daily work.

Introduction

Clemens Decristoforo, PhD

I want to congratulate the Technologists Committee of the EANM for this excellent Technologists Guide on the Radiopharmacy. Issues of quality assurance especially in the field of pharmaceutical preparations are becoming increasingly important. The Radiopharmacy Committee of the EANM therefore recently has issued general guidelines for "Current Good Radiopharmacy Practice" describing the quality standards in the preparation of conventional and PET radiopharmaceuticals (http://www.eanm.org/scientific_info/guidelines/gl_radioph_cgrpp.php). These serve as a general reference standard for radiopharmaceutical preparation as radiopharmacy practice still shows a great variability all over Europe.

Technologists in many countries are the backbone for radiopharmacy services within nuclear medicine departments. This is especially true for the preparation and handling of conventional radiopharmaceuticals including eluting radionuclide generators, preparation of ^{99m}Tc-radiopharmaceuticals from kits, dispensing and cell labelling. Therefore the current issue of the Technologists Guides is dedicated to radiopharmacy practice.

The Technologists Committee of the EANM has been very active in promoting professional skills of technologists and to support high quality standards in daily practice. The series of "Technologists Guide" booklets by the Eductional Sub-Committee has been a valuable part of these initiatives. The current issue of this series intends to provide guidance for a "good radiopharmacy practice," to describe quality standards and to bring radiopharmacy practice to equal standards throughout Europe.

This booklet contains chapters of all relevant topics of daily radiopharmacy practice of technologists such as radiopharmacy design, preparation and dispensing as well as documentation written by European experts in the field, both radiopharmacists and technologists.

I am very confident that this booklet will not only provide valuable information and quick reference for problems arising in daily practice, but also will help to continuously improve quality standards of radiopharmacy practices in nuclear medicine.

Chapter 1 – Radiopharmacy Technology

Brit Farstad

Radiopharmacy

Radiopharmacy encompasses studies related to the pharmaceutical, chemical, physical, biochemical, and biological aspects of radiopharmaceuticals. Radiopharmacy comprises a rational understanding of the design, preparation and quality control of radiopharmaceuticals, the relationship between the physiochemical and biological properties of radiopharmaceuticals and their clinical application, as well as radiopharmaceuticals chemistry and issues related to the management, selection, storage, dispensing, and proper use of radiopharmaceuticals.

Characteristics of radiopharmaceuticals

A radiopharmaceutical is a pharmaceutical that, when ready for use, incorporates one or more radionuclides (radioactive isotopes). Radiopharmaceuticals are used for diagnosis or therapeutic treatment of human diseases; hence nearly 95% of radiopharmaceuticals are used for diagnostic purposes, while the rest is used for therapy.

Radiopharmaceuticals usually have no pharmacologic effects, as they are used in tracer quantities. There is no dose-response relationship in this case, which thus differs significantly from conventional drugs.

Radiation is an inherent characteristic of all radiopharmaceuticals, and patients always receive an unavoidable radiation dose. In the case of therapeutic radiopharmaceuticals, radiation is what produces the therapeutic effect.

A radiopharmaceutical can be as simple as a radioactive element such as ^{133}Xe, a simple salt such as ^{131}I-NaI, or a labelled compound such as ^{131}I-iodinated proteins and ^{99m}Tc-labeled compounds.

Usually, radiopharmaceuticals contain at least two major components:

- A radionuclide that provides the desired radiation characteristics.
- A chemical compound with structural or chemical properties that determine the in vivo distribution and physiological behaviour of the radiopharmaceutical.

Radiopharmaceuticals should have several specific characteristics that are a combination of the properties of the radionuclide used as the label and of the final radiopharmaceutical molecule itself.

Decay of radionuclides

Radionuclides are unstable nuclei that are stabilised upon radioactive decay. Approximately 3000 nuclides have been discovered so far; most of these are unstable, but only about 30 of these are routinely used in nuclear medicine. Most of these are artificial radionuclides, which may be produced by irradiation in nuclear reactors, cyclotrons, or large linear accelerators.

A radionuclide may decay by emitting different types of ionising radiation: alpha (α), beta (β^-), positron (β^+) and gamma (γ) radiation.

Depending on the radiation characteristics of the radionuclide, the radiopharmaceutical is used either for diagnosis or for therapy. Diagnostic radiopharmaceuticals should decay by gamma emission or positron emission, and never emit alpha particles or even beta particles. On the other hand, therapeutic radiopharmaceuticals should decay by particulate decay (alpha or beta) since the intended effect is in fact radiation damage to specific cells.

Gamma radiation is characterised as electromagnetic radiation. When used in diagnostic radiopharmaceuticals, the finally produced gamma rays should be powerful enough to be detected outside the body of the patient. The ideal energy for conventional (SPECT) nuclear medicine equipment is around 150 keV. Normally, these radiopharmaceuticals are in such small quantities that the radiation dose received by the patient can be compared to that of a simple radiology investigation.

Alpha decay is characterised by the emission of an alpha particle from the nucleus. This particle is a helium ion containing two protons and two neutrons. In beta decay a negatively charged particle with the same charge and mass as an electron is emitted. Alpha emitters, which are monoenergetic and have a very short range in matter due to their mass, thus leaving much of its energy on a very small area (only a few cell diameters), are used only for therapeutic purposes. Their clinical use is very limited, and they are mainly used for research purposes, or still are in early phase clinical trials.

Neutron rich radionuclides disintegrate by beta (β^-) decay. Beta emitters represent different energy levels, and have different range in matter (40 – 100µm) depending on their energy. Beta emitting radionuclides are also used in radiopharmaceuticals mainly for therapeutic purposes.

Positron (β^+) decay occurs in proton rich nuclei. The range of a positron is very short in matter. At the end of the path of β^+-particles, positrons combine with electrons and are thus annihilated, giving rise to two photons of 511 keV that are emitted in opposite directions. Positron emitters are used to label radiopharmaceuticals for diagnostic purposes by imaging.

Radioactivity units

Radioactivity is expressed in Becquerels (Bq) as the SI-unit. One Becquerel is defined as one disintegration per second (dps). Normally, activities used in radiopharmacy are in the range of megabecquerels (MBq) or gigabecquerels (GBq). There is a non-SI-unit for radioactivity called Curie (Ci), which is used in some occasions. One Ci represents the disintegration of one g of radium. The equivalence between the Bq and the Ci is as follows:

$1\ Bq = 2{,}7 \times 10^{-11}\ Ci$
$1\ Ci = 37\ GBq$

Every radionuclide is characterised by a half-life, which is defined as the time required to reduce its initial activity to one half. It is usually denoted by $t_{½}$, and is unique for a given radionuclide.

Principles of radiation protection

Production, transportation and use of radiopharmaceuticals, as radioactive products, are governed by regulatory agencies dealing with radiation protection and nuclear safety. Only licensed personnel in an authorised facility are authorised to handle and use radiopharmaceuticals.

The general principles of **radiation protection** are:

- **Justification:** All procedures involving radioactive material must be justified.
- **Optimisation:** The radiation exposure to any individual should be as low as reasonably achievable. This principle is the widely known ALARA concept (as low as reasonable achievable).
- **Limitation:** The radiation dose received by the personnel handling radioactive material will never exceed the legally established dose limits.

When planning facilities and procedures for handling of radioactive materials according to the ALARA principle, it is important to keep in mind the basic principles for **reduction of radiation doses:**

- **Time:** The shorter the time of exposure to radiation, the lower the dose to the operator.
- **Distance:** The radiation dose decreases with a factor equal to the square root of the distance from the radiation source. The operator's distance from the source can be increased by using forceps, tongs, or manipulators in handling the radioactive material.
- **Shielding:** The radiation dose can be reduced by placing shielding material between the source and the operator. For protection against gamma radiation, walls made of heavy concrete or lead bricks are used. For transport containers, material such as tungsten may be used for higher energy gamma irradiation radionuclides, giving a higher shielding per weight unit when compared to lead.

Formulation and production of radiopharmaceuticals

When designing a radiopharmaceutical, one should have in mind the potential hazard the product may have to the patient. The goal must be to have a maximum amount of photons with a minimum radiation exposure of the patient.

The function of the carrier molecule in a radiopharmaceutical is to carry the radioactivity to the target organ, and to make sure the radioactivity stays there. The uptake of radioactivity should be as specific as possible, in order to minimise irradiation of other organs and parts of the body. This is particularly important when using radiopharmaceuticals for therapy. But also for use in diagnostics, it is desirable that the radiopharmaceutical is localised preferentially in the organ under study since the activity from non-target areas can obscure the structural details of the pictures of the target organ. It is therefore important to know the specific uptake in an organ for a potential chemical carrier, and also the rate of leaking out of the organ/organ system. Thus, the target-to-background activity ratio should be large.

In a radiolabelled compound, atoms or groups of atoms of a molecule are substituted by similar or different radioactive atoms or groups of atoms. When a labelled compound is to be prepared, the first criterion to consider is whether the label can be incorporated into the molecule to be labelled. This may be assessed from knowledge of the chemical properties of the two partners. Furthermore, one needs to know the amount of each component to be added. This is particularly important in tracer level chemistry and in ^{99m}Tc-chemistry.

As the radiolabelled substances emerge from the laboratory to the clinics, there will be a need for scaling up the batch size of the product. This can be done either by increasing the total volume of the produced batches or by increasing the specific activity of the product, or both. When doing this, one has to consider two important aspects:

- The influence on the stability of the product itself due to possible radiolysis.
- The need for additional operator protection due to handling of increased amounts of radioactivity.

Manufacturing of radiopharmaceuticals is potentially hazardous. Both small- and large-scale production must take place on premises designed, constructed, and maintained to suit the operations to be carried out. Radiation protection regulations stipulate that radionuclides must only be used in specially designed and approved "radioisotope laboratories". National regulations with regard to the design and classification of radioisotope laboratories must be fulfilled. Such laboratories are normally classified according to the amount of the various radionuclides to be handled at any time, and the radiotoxicity grading given to each radionuclide.

Premises must be designed with two important aspects in mind:

- The product should not be contaminated by the operator.
- The operator and the environment should be protected from contamination by the radioactive product.

This is the basic principle of GRP – Good Radiopharmaceutical Practice.

Quality considerations

The key elements of GRP comprise a previously defined manufacturing process known to lead to a radiopharmaceutical of the defined quality administered to the patient in the prescribed dosage and form. GRP is carried out and recorded by trained and qualified staff provided with the necessary facilities, including adequate premises, suitable equipment, correct materials and established procedures in written form. Quality must also be maintained during transportation and storage.

Training and qualifications should cover general principles of GMP (Good Manufacturing Practice) and radiation protection. All training must be recorded. Premises and equipment must have a layout and design that minimise the risks of errors by avoiding cross-contamination and build up of dust and dirt, as well as permit effective cleaning and maintenance. They must also be designed to give proper radiation protection to personnel and the environment. Documentation is an essential part of a quality system. Its purpose is to define the control system, to reduce the risk of error that is inherent in oral communication and to ensure that detailed instructions are available to personnel. The documentation system should allow tracking of use and disposal of any batch.

Radiopharmaceuticals are a special form of drugs that require much more handling immediately before administration to the patient, when compared to other drugs. Due to the short half life of the radionuclide, it is necessary for the final preparation of many radiopharmaceuticals to take place shortly before use. Only a minor proportion of all radiopharmaceuticals is delivered to hospitals in a ready-for-use-form. Handling of radiopharmaceuticals in hospitals is thus an integral part of the system by which the quality of these pharmaceuticals is established.

Quality control of radiopharmaceuticals

All quality control procedures that are applied to non-radioactive pharmaceuticals are in principle applicable to radiopharmaceuticals. In addition, tests for radionuclidic and radiochemical purity must be carried out. Furthermore, since radiopharmaceuticals are short-lived products, methods used for quality control should be fast and effective. Still, some radiopharmaceuticals with very short half-lives may have to be distributed and

used after assessment of batch documentation even though all quality control tests have not been completed.

Hospital departments dealing with radiopharmaceuticals should have a programme for quality control of products before administration to the patient. The complexity of the quality control depends on whether the product is a ready-for-use-form, or the product is labelled in the department prior to administration (labelling kits).The specifications and quality control testing procedures for most of the currently used radiopharmaceuticals are given in the European Pharmacopeia, or other Pharmacopeia (BP, USP etc.). For labelling kits, a simple quality control procedure should be stated in the package insert for the particular product. The quality control system should include a procedure which describes measures to be taken if unsatisfactory test results are obtained.

Chapter 2 – Radiopharmacy Design

James R. Ballinger, PhD

Facilities

Although many of the principles of radiopharmacy design are universal, there may be differences between countries in how rigorously these principles are regulated. The radiation aspects are covered in the EC Euratom Directive [1] while pharmaceutical manufacturing is controlled under EudraLex [2]. The EANM Radiopharmacy Committee has issued guidance on Good Radiopharmacy Practices [3] which addresses both aspects. With respect to both facilities and operations, there can be conflicting requirements between radiation safety and aseptic processing. Another important consideration is complete segregation between radiopharmaceutical preparation (aseptic processing) and blood cell labelling, to minimise the risk of cross contamination.

In general, the radiopharmacy should be at one end of a nuclear medicine/radiology department rather than in the middle. Indeed, it is best if it is on an outside wall as there is less concern about shinethrough of radiation. Although high levels of radioactivity are handled, in most cases local shielding is used (e.g. around generators and individual vials) rather than extensive shielding in walls.

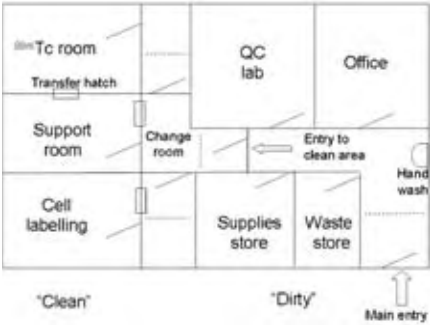
The radiopharmacy should be conveniently located for deliveries and shipments (if supplying external units). There should be arrangements for receipt of out of hours deliveries, such as a locked cupboard adjacent to the unit but not requiring direct access to the radiopharmacy by unauthorised personnel such as couriers.

Layout

Restricted access is important, from both a radiation security and pharmaceutical manufacturing point of view. Only persons with business in the radiopharmacy should be allowed access. Within the radiopharmacy, there will be further restriction of access to the clean areas. The principle is moving from dirty to clean areas with appropriate change of apparel and sanitation of materials at each interface. The dirty areas include delivery and dispatch, an office for preparation of paperwork, a supplies store, a waste store, and a QC laboratory. It is particularly important to unpack supplies in the dirty area where there is bulk storage; only minimal supplies are kept in the clean area. Some radiopharmacies may have a separate area for handling of ^{131}I. The clean areas include a ^{99m}Tc dispensing room, a support room, and a separate blood cell labelling facility. The layout should enable an orderly flow of work, both within and between rooms.

Figure 1 presents a sample layout of a large radiopharmacy with ideal separation of different working areas required for handling and radiolabelling of ^{99m}Tc and other SPECT radiopharmaceuticals.

Figure 1: Sample layout of a radiopharmacy



Equipment and fittings

Standard equipment includes one or more dose calibrators (ionisation chambers), laboratory equipment (e.g. balance, centrifuge), and appropriate radioanalytical equipment (radiochromatogram scanner, gamma counter; more advanced laboratories may have a multichannel analyser and radio-HPLC system). This equipment should be dedicated to use in the radiopharmacy and not shared with outside users.

Radiation survey meter(s) must be available to check for contamination within the unit and at the boundary of the radiation controlled area. If radioactive material is shipped, there must be a dose rate monitor (i.e. calibrated in μSv/h) to allow determination of the Transport Index.

Refrigerators and other areas where sensitive supplies are stored should have temperature monitoring. This can be as simple as manual recording on a daily basis of minimum and maximum temperatures on a calibrated thermometer or an electronic output to a chart recorder or monitoring software.

Volatile materials such as ^{131}I products and organic solvents should be handled in a fume cupboard with a minimum inflow of 0.5 m/s. The exhausted air is vented to the atmosphere and care must be taken in the location of the stack. Filters are not generally used as they could become radiation hazards themselves.

The clean areas should be lined (floor, walls, and ceiling) with a smooth, continuous, impervious, non absorbent, cleanable material such as welded sheet vinyl. Corners should be coved (curved) to minimise dirt collection. Light fixtures should be recessed and flush with the surface. Benches must be made of impervious material (solid is preferred over laminate) and may require additional support for lead shielding.

There should be transfer hatches with interlocking doors so supplies can be sanitised and passed into the next room without allowing direct contact. Entry/change rooms should have interlocking doors and a physical barrier, or at least a line on the floor, to demarcate the two sides. Changing on entry will involve, at a minimum: clean low-lint lab coat, shoe covers, hair cover, and gloves.

Aseptic manipulations should be performed either in a pharmaceutical isolator or a laminar airflow hood.

The bulk of the work for the foreseeable future will continue to be reconstitution of kits with ^{99m}Tc pertechnetate. Thus, a single workstation is adequate even if there is occasional handling of other radionuclides (e.g. preparation of ^{111}In pentetreotide or ^{90}Y ibritumomab tiuxetan). However, if the usage of other radionuclides is more extensive, a separate workstation should be provided. In addition to minimising the potential of cross contamination of ^{99m}Tc products with longer lived and/or particle emitting radionuclides, it also reduces the risk that a major spill of one of these radionuclides could impede ^{99m}Tc dispensing for a number of days. In the future, some products such as ^{90}Y or ^{177}Lu labelled peptides might be prepared by automated synthesis units located in a separate workstation.

In general, radiation safety is maintained by local shielding (e.g. vial shields, syringe shields, bench top shields) rather than shielding in the walls. The waste store may require shielding, as may an area where high levels of radioactivity are handled if there is a significant radiation field in the adjacent room. The ^{99}Mo/^{99m}Tc generator usually requires additional external shielding.

It is simplest to dispose of all sharps into rigid biohazard containers behind a lead shield. Once the radioactivity has decayed to background levels, the containers are disposed as biohazard waste. Radionuclides should be segregated by half life to minimise the build up of waste.

The blood labelling suite will require a variable speed centrifuge capable of accepting a range of tube sizes. Ideally the centrifuge will be located within the workstation, to minimise the number of transfers out of the Grade A environment.

Area designation

A radiation controlled area is one in which a full time worker might receive an exposure of 6 mSv/yr whole body or 150 mSv/yr extremity. For a radiation supervised or monitored area, the exposure limits are 1 mSv/yr whole body or 50 mSv/yr extremity. Because of the presence of generators and the amount of radioactivity handled, the hot lab will be designated a controlled area. Other areas may be classified as supervised.

Radiation designated areas must be physically demarcated and have signs indicating the type of hazard. There should be washing and changing facilities available at the perimeter; and radiation monitoring for contamination must be performed. Eating and drinking is prohibited in designated areas.

Conflicts between radiation and aseptic regulations

As noted above, there can be conflicts between the requirements of different regulatory systems. However, there are also areas of agreement. For example, segregation of activities, with change of apparel and dedicated equipment, minimises cross contamination with both radioactivity and microbes, as does a separate air handling system and the use of containment hoods/glove boxes. Specialist trained staff are required and meticulous record keeping is important.

However, even within these areas, there are conflicts. For radioprotection, the production area should be at negative pressure relative to the outside world (containment of gaseous or aerosol discharge), while pharmaceutical aseptic units are at positive pressure to minimise ingress of microbes. The compromise is a negative pressure isolator within a positive pressure room. From a pharmaceutical point of view, there should be a minimum number of trained staff, whereas for radioprotection there should be a rotation of staff to share the radiation dose. Radioprotection requires handwashing facilities at the perimeter of the controlled area, while the medicines inspectors don't want a sink anywhere near a cleanroom. Radiopharmacy managers must find a delicate balance to satisfy both sets of inspectors.

Chapter 3 – Radiopharmacy

Preparing & Dispensing Radiopharmaceuticals

Geraldine O'Reilly, PhD

Introduction

The radiopharmacy would normally be designated as a controlled area; and access will be restricted. Only properly trained staff should be permitted to work in the radiopharmacy; and strict adherence to work procedures is essential. There are three fundamental parameters that affect staff doses in the radiopharmacy:

1. the distance between the staff member and the source,
2. the time spent manipulating the source and
3. the amount of shielding used to reduce the dose rate from the source.

Sometimes there is a trade off between these parameters as using more shielding might increase handling time. With this in mind, careful design of procedures should optimise the workflow. Skill and expertise of the staff carrying out the procedures are also important factors. Thus, it is crucial that staff are adequately trained.

Work practices in the radiopharmacy should be standardised and incorporated in standard operating procedures (SOPs). These procedures should be documented and made readily available to those working in the radiopharmacy. This will ensure harmonisation of practice and maintenance of standards. Accurate and comprehensive record keeping is an essential part of good work practice in a radiopharmacy.

Most radiopharmaceuticals are administered by IV injection; so good pharmaceutical practice is an important consideration in their preparation. All manipulation of radioactive materials should be carried out, using aseptic techniques, within the shielded contained workstation or laminar flow cabinet (LAFC) (Figure 1). No food or drink, cosmetic or smoking materials, crockery or cutlery should be brought into an area where unsealed radioactive substances are used.

Figure 1: Laminar flow unit for preparation of 99mTc radiopharmaceuticals

Personnel monitoring

All staff classified as radiation workers must wear a personal dosimeter (TLD, film badge, electronic dosimeter). In addition to their regular whole body dosimeter, staff preparing and handling radioactive materials should wear a finger TLD to monitor extremity dose. Prior to each use, the TLD should be wiped, using an alcohol wipe, and worn inside the glove. Upon leaving the preparation area, the finger TLD should be removed and appropriately stored.

Protective clothing

Prior to commencing work in the radiopharmacy, staff should ensure that they wash their hands thoroughly. Before a person enters an area where radioactive substances are handled, any cut or break in the skin should be covered. Dressings should incorporate a waterproof adhesive strapping. Protective coats or gowns should be worn for preparation and dispensing of radiopharmaceuticals. Disposable gowns offer benefits in terms of maintaining sterility. Gloves worn in the LAFC or contained workstation must be powder free in order to prevent clogging of the air filters within the cabinet. Alcohol rub should be rubbed onto gloves and allowed to evaporate before entering the LAFC. After handling radioactive materials, gloves must always be removed and disposed of as radioactive waste before handling/touching any other materials/surfaces within the radiopharmacy. Hands should be washed again after removal of gloves. Upon leaving the radiopharmacy, disposable gowns should be removed. Prior to disposal, they should be stored as radioactive waste until monitoring confirms that they are at background radiation levels.

Protective equipment

The use of protective equipment, when handling radioactive materials, can have a significant impact on reducing staff dose. Laboratories and other work areas for manipulation of unsealed radioactive substances should be provided with equipment kept specifically for this purpose, and should include the following:

1. tools for maximising the distance from the source, for example tongs and forceps,
2. syringe shields,
3. vial shields,
4. drip trays for minimising the spread of contamination in the case of spillage,
5. shielded syringe carriers and
6. decontamination kit

Unshielded syringes or vials should never be used during manipulation of radiopharmaceuticals. Equipment should be stored outside the laminar flow cabinet when not in use and should be cleaned regularly in accordance with local recommendations.

Work procedures

General

Before starting the preparation and dispensing of radiopharmaceuticals, all of the materials required should be assembled and placed in or close to the contained workstation/LAFC (Figure 2). All vials containing radioactive materials must be shielded while handling; and vials should only be removed from their shields for assay, inspection or disposal. All syringes containing radioactive liquids must be shielded while handling, except during an assay. Unshielded vials or syringes should not be handled directly. Long handled tongs should be used to place and remove unshielded materials in the dose calibrator.

Work procedures should be designed so as to minimise exposure from external radiation and contamination. Care must be taken to prevent spillage from occurring. All manipulation for dispensing radioactive materials should be carried out over a drip tray, in order to minimise the spread of contamination due to breakages or spills. Should a spill occur then it should be cleaned up before proceeding any further. All items that might be contaminated should be removed from the affected area and stored safely. Care should be taken doing this, in order to minimise the spread of contamination. As with all spills, it is more convenient to allow natural decay to take care of the contamination, if the items are not required immediately. For those items that are needed, they should be cleaned with alcohol swabs taking care not to spread the contamination. Using multiple swabs which are then disposed is the most effective way to remove contamination.

Figure 2: Preparation of work area (courtesy of VirRAD)

Reconstitution of pharmaceuticals

The manufacturer's recommendations should be followed closely as many pharmaceutical kits have specific reconstitution instructions in terms of the activity and volume to be added to the kit. Recommended incubation times also vary and must be adhered to. Some radiopharmaceuticals must be refrigerated after preparation. Therefore consideration should be given to the provision of suitably shielded refrigeration facilities. Most radiopharmaceuticals are reconstituted with ^{99m}Tc; and this assumption applies to the following paragraphs.

Protective caps should be removed from the pharmaceutical vials; and the vials should be placed in the appropriate labelled vial shields. The rubber septum of each pharmaceutical vial should be swabbed with alcohol; and the alcohol should be allowed to evaporate (Figure 3).

- Shielded 10ml or 5ml syringes capped with 21G needles are generally used to reconstitute the pharmaceuticals.
- The appropriate activity of ^{99m}Tc solution should be added to each shielded pharmaceutical vial; and the pharmaceutical should be allowed to incubate for the specified length of time.
- Having introduced ^{99m}Tc solution to a pharmaceutical vial, the needle should not be placed back into the shielded elution vial. In the event that additional ^{99m}Tc solution is required, a new syringe and needle must be used.

- When introducing ^{99m}Tc solution or saline to a vial, it may be necessary to equalise pressure by withdrawing an equivalent volume of air at the same time. This can be done gradually as the solution is added. In general, breather needles are not recommended and should not be used unless specifically recommended by the manufacturer of the pharmaceutical.

- The activity and volume of ^{99m}Tc solution added to each pharmaceutical should be recorded in the laboratory log book.

Figure 3: Disinfection of a kit before use (courtesy of VirRAD)

Preparation of patient injections

- After the recommended incubation time has elapsed, patient activities are withdrawn using shielded 2ml syringes capped with 21G.

- Each patient activity must be measured and recorded in the radiopharmacy log. The activity withdrawn for each patient must be within 10% of the required activity at the specified injection time.

- Patient injections are usually prepared in a volume of 1ml. There are exceptions to this: the manufacturer's instructions on the volume should be followed. Saline may be used to increase the volume if the volume in which the required activity is obtained is below 1ml.

- Once the patient injection is prepared, the green needle must be replaced with a needle of the appropriate gauge, and the air in the syringe must be expelled. When expelling the air, ensure that the needle is capped.

- When changing needles, withdraw the plunger sufficiently so as to pull liquid from the syringe tip.

- If, at any time, there is a droplet of liquid visible in the needle cap, replace the needle and cap.

- Each patient injection must be labelled with an appropriate label detailing the patient name, scan type, activity to be administered, date and time of injection.

Waste management procedures

Non-radioactive waste should be separated from radioactive waste to minimise storage requirements; and it should be disposed of as normal hospital waste. Shielded waste bins should be lined with plastic liners that can be easily removed when full.

Technetium 99m is the main isotope in use in the radiopharmacy: the duration of storage will be determined by its half life of 6.02 hours. Longer lived waste should be stored separately. Radioactive waste generated daily within the radiopharmacy includes syringes, elution vials, pharmaceutical vials, needles and swabs. Waste arising from the preparation and dispensing of radiopharmaceuticals should be primarily disposed in the waste bin built into the contained workstation/LAFC. Some bulky items such as paper waste and gloves may be disposed in a shielded waste bin in the pharmacy, as long as there is no risk of contaminating the room by removing them from the cabinet. Radioactive waste contaminated by blood (e.g. syringes following cell labelling procedures) should not be left in the workstation but removed to a shielded bin.

The waste container in the workstation should not be allowed to overflow and should be emptied regularly. The bin is best emptied before starting work in the cabinet, when the waste in the bin has decayed over night.

Segregation of waste according to half-life is good practice and can reduce the length of time that waste arising from shorter lived isotopes has to be stored.

Paper waste

Any gloves used in the cabinet or used to handle blood or isotopes will be considered to be contaminated. Paper tray liners in the cabinet or paper used to clean surfaces in the cabinet are also considered to be contaminated. Contaminated gloves and paper should be disposed in a shielded bin in the pharmacy, as long as there is no biological contamination (blood or plasma). Otherwise this waste should be placed in a sharps bin, using tongs. For long term storage of waste, the waste should be removed from the shielded bin, labelled with details of the contents and stored as radioactive waste in a designated store.

Sharps bins

Syringes, needles, butterflies etc. should be disposed of after use to shielded sharps bins. Bins should not be allowed to overfill. Full sharps bins should be closed, marked 'radioactive', dated and removed to the radioactive waste store.

Disposal of waste

All radioactive waste - sharps bins, paper waste, ventilation kits - should be securely stored and monitored regularly. Waste should be checked by using a suitable meter in a low background environment and should be disposed of, once it has decayed to background level. Any items above background should be retained for a further period of decay in storage. All radioactive warning labels should be removed from waste, prior to disposal in hospital waste. The hospital waste disposal policy should be adhered to.

Dose calibrator quality assurance

The accuracy and constancy of the dose calibrator should be checked regularly with a reference source. Isotopes such as Co-57, Ra-226 or Cs-137 with a relatively long half life are suitable. The use of more than one source will allow checking of the calibrator over a range of energies. A daily check of system operation, accuracy and constancy should be carried out. Linearity tests may be carried out less frequently.

Before starting the QA, remove all radioactive sources from the vicinity of the calibrator and record the background reading. The isotope selected on the dose calibrator should be that of the reference source. The accuracy test ensures that the activity is within 10 percent of a given calibrated reference source of known activity (within 5%). At least two sealed sources with different principal photon energies, one of which has a principal energy between 100 keV and 500 keV, should be used to determine accuracy upon installation, and at least annually thereafter. For the routine accuracy check, place the reference source in the dose calibrator and record the activity measured. The value recorded should be within the allowable tolerance (typically 10%).

The constancy test looks at reproducibility in measuring the activity of a known source over a long period of time. The dose calibrator should be checked daily for constancy at the setting of the most frequently used isotope. To carry out this test, the reference source is left in place; but the setting is changed to Tc-99m and the value indicated is recorded. This can also be done for other isotopes that are selectable on the dose calibrator. The ratio of the values indicated to that of the activity of the reference source should be constant over time.

The linearity test ensures that the dose calibrator can indicate the correct activity over the range of use of administered or measured activities. The dose calibrator should be tested for linearity upon installation and at least quarterly thereafter. Technetium-99m is most frequently used for the linearity test because of its availability and short half-life. The variation between indicated and known activity should not exceed 10%.

The results of the routine QA should be documented and stored as part of the radiopharmacy records.

Chapter 4 – Radiopharmacy

Kits & Techniques

Helen Ryder

Radiopharmaceuticals have been defined as 'radioactive drugs that, when used for the purpose of diagnosis or therapy, typically elicit no physiological response from the patient.'

In the main this is true, and though some radiopharmaceuticals have been known to cause minor side effects (such as urticaria, or changes in blood pressure), these are not commonly seen in practice.

Ideal radionuclide

Properties of the ideal diagnostic radionuclide include:

1. **Pure gamma emitter, with a gamma energy within the range of 100 - 250 keV, to match the optimum scanning range of a gamma camera.**
   The radiation emitted by a radionuclide should be sufficient to be detected outside the patient for imaging purposes, thus limiting the choices to X-rays or gamma rays. However, too high an energy will result in the gamma ray penetrating the detector of the imaging device without being stopped and hence recorded.
2. **A half-life which is suitable for diagnostic use i.e. 1.5 X test duration**
   The half-life of a radionuclide determines the rate of radioactive decay. If the half-life is very short, then the activity may have decayed to a very low level before imaging can be started. This can result in either a long scanning time, where there may be patient movement; or too short a time per image resulting in poor count statistics. If the half-life is too long, then there may be excessive radiation exposure to the patient over its period of decay.
3. **High target - background ratio**
   The radionuclide is only of use if it accumulates within the target organ, and this is often enhanced by binding the radionuclide onto a tracer that will take it to the organ under study. The binding should be sufficient that little radionuclide is left free in the body tissues, thus enhancing the target-to-background ratio.
4. **Low dose rate to both patient and personnel**
   To avoid excessive received radiation dose, it is necessary to avoid those radionuclides which have significant particulate emissions i.e. alpha and beta particles. The short range of emission means that these are absorbed within the patient, adding to the radiation dose with no increase in image quality. Because of the reality of radiation decay, that is the attempt to balance the particles in the nucleus, beta rays are often found as a product of decay. The rate of emission of these rays can be significantly lower in two particular decay processes: isomeric transition and electron capture.
5. **Non-toxicity of radiopharmaceuticals**
   Most radiopharmaceuticals must be injected, with a small amount being ingested or inhaled. Thus they must be non-toxic in nature, sterile and pyrogen-free.

6. **Chemical stability during use**
   Not all radioisotopes are suitable for binding to tracers. Technetium 99m has 'the ability to readily bind to a wide variety of compounds under physiological conditions [1] without causing physiological changes in the patient.
7. **Inexpensive and readily available**
   Many suitable radionuclides are obtainable from a generator, which may be delivered to a nuclear medicine facility and eluted as required. This results in economical use of the radionuclide.
   Other radionuclides are produced in cyclotrons as specialised units and are shipped ready for use. These are decaying from the moment they are manufactured and thus must be ordered for use on a particular day, either as the resultant product or for preparation with other tracers. This can be expensive and uneconomical for everyday requirements.
8. **Ease of preparation and appropriate quality control**
   Preparation requirements of more than three steps do not usually meet the definition of 'ease of preparation'. Nor should a complex variety of equipment be required. Quality control procedures should be available to check each batch of the radiopharmaceutical reconstituted in the working laboratory. This ensures that the preparation received by the patient will result in high-quality images without detrimental effect on the patient.

Radionuclide generator

A radionuclide generator is a source of radionuclides for the preparation of radiopharmaceuticals. It is based on the separation of a short lived radionuclide (daughter) from a long lived radionuclide (parent). Examples of radionuclide generators are provided in Table 1. The most commonly used generator in Nuclear Medicine is the ^{99}Mo/^{99m}Tc generator.

Table 1: Radionuclide generators

parent	$t_{1/2}$	daughter	$t_{1/2}$	application
Mo-99	66.7h	Tc-99m	6.02h	SPECT
Rb-81	4,6h	Kr-81m	13,3sec	SPECT
W-188	69d	Re-188	17h	Therapy
Sr-90	28,5a	Y-90	2,7d	Therapy
Ge-68	287d	Ga-68	68,3min	PET
Zn-62	9,1h	Cu-62	9,7min	PET

Molybdenum/Technetium (^{99}Mo/^{99m}Tc) generator

The molybdenum/technetium generator consists of an alumina-filled column onto which is absorbed ^{99}Mo. The ^{99}Mo is present as $^{99}MoO_4^{2-}$, which decays to its daughter radionuclide ^{99m}Tc as pertechnetate $^{99m}TcO_4^-$ (Figure 1). ^{99m}Tc is removed from the columns as $^{99m}TcO_4^-$ by drawing over a solution of sodium chloride (NaCl) 0.9% w/v across the column (Figure 2). This process is known as 'eluting the generator' and the resultant eluate is used to compound the radiopharmaceuticals (Figure 3).

Figure 1: Decay scheme for ^{99}Mo and ^{99m}Tc (courtesy of VirRAD)

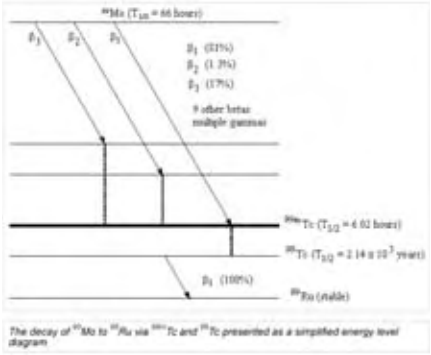


Figure 2: Molybdenum/Technetium generator

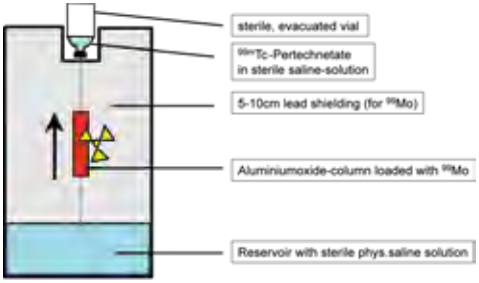


Figure 3: Eluting the generator (courtesy of VirRAD)

Attach Saline Vial

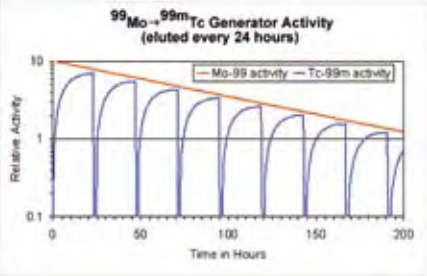
Insert Elution vial in lead shielding

Attach Elution vial and wait until elution is completed

Remove elution vial and attach protecting vial/Cap

The time of maximum yield of ^{99m}Technetium is 23 hours, after which the ^{99m}Tc appears to decay with the half-life of ^{99}Mo (66hrs). This time of almost one day is therefore eminently suitable for the requirements of the Nuclear Medicine department (Figure 4).

Figure 4: Plot of logarithm of ^{99}Mo and ^{99m}Tc activities against time showing transient equilibrium. The generator is eluted daily and the ^{99m}Tc activity grows again until transient equilibrium is reached (courtesy of VirRAD).



Preparation of ^{99m}Tc-radiopharmaceuticals from kits

Categories of radiopharmaceuticals:

- Ready-to-use radiopharmaceuticals
- Instant kits for preparation of ^{99m}Tc products
- Kits requiring heating
- Products requiring significant manipulation

Reconstitution of proprietary kits:

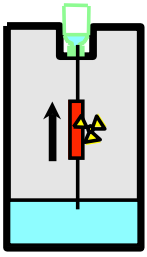
The basic steps involved in the reconstitution of ^{99m}Tc radiopharmaceuticals from generators and kits are outlined in Figure 5. Appendix 1 further details the procedure for reconstitution of proprietary kits. An example of how to calculate the required activity is provided in Appendix 2.

Figure 5: Reconstitution of ^{99m}Tc radiopharmaceuticals from generators and kits

Appendix 1: Reconstitution of proprietary kits with ^{99m}Tc

- Record the following information in the injection log:
  - The batch number and expiry date of the elution vial, pharmaceutical vials and saline bottles.
  - The activity and volume of the eluate.
  - The activity and volume of ^{99m}Tc solution introduced to each pharmaceutical vial during labelling.

- The generator is eluted every morning and used for reconstitution of the kits. Some departments may have a 'high' generator and a 'low' generator. The low generator is useful for lung perfusion scanning, Meckel's diverticulum and thyroid scintigraphy.



- Remove the flip/foil cap from the pharmaceutical vial and place the vial in a labelled shielded container. Swab the rubber septum with alcohol, and allow the alcohol to evaporate.

- When reconstituting the pharmaceutical use a shielded 5ml syringe capped with a green needle. 10ml and 2ml syringes may also be used, depending on the quired volume.

- The required activity of ^{99m}Tc solution may need to be topped up to the required volume with saline.

- Patient injections are typically made up to a volume of 1ml. The required activity of radio-labelled pharmaceutical may need to be topped up to 1ml with saline.

- All patient injections are to be labelled with an appropriate label, detailing the patient name, date and time of procedure, procedure type and activity to be administered.

99mTc-Cardiolite
Act.....MBq Date .....
Pt. Name

Appendix 2: Calculation of activity

Example calculation of activity to add to vial

Example: What is the minimum activity of ^{99m}Tc eluate needed to be added to a vial of ^{99m}Tc-Cardiolite at 8a.m., to obtain five injections of 740Mbq each – 2 injections at 8a.m., 3 injections at 11a.m.?

The equation to calculate radioactive decay is:

$$A_t = A_o e^{-\lambda t}$$

1. Calculating λ
   λ is the decay constant which for any radionuclide is defined as

$$\lambda = \frac{\ln 2}{T_{1/2}}$$ where ln2 is the natural log of 2 = 0.693

$$\lambda = \frac{0.693}{6} = 0.115$$ and $T_{½}$ for ^{99m}Tc is 6 hours

2. Where Ao = 740MBq, t= -3

(When calculating an activity *prior* to the time of known activity, the value of t is negative. To calculate the decay of a radionuclide *from* a known activity to a later time then t has a positive value.)

$A_t = A_o e^{-(0.115)(t)}$
$A_t = A_o e^{-(0.115)(-3)}$
$A_t = 740 \times e^{0.346}$
$A_t = 740 \times 1.413 = 1045.6$MBq

Therefore the required activity to be drawn up per injection at 8a.m. is 1045.6MBq.

The total activity of ^{99m}Tc to be added to the vial of Cardiolite is:

a. 2 x 740MBq for two injections at 8a.m. =1480MBq
b. 3 x 81045.6MBq for three injections at 11a.m. = 3136.9MBq
c. Add (a) to (b) to get total of 4616.9MBq to add to vial of HDP

Quality control in the radiopharmacy

Rationale for performing quality control

If a radiopharmaceutical is improperly prepared it can result in a non-diagnostic study. The procedure must then be repeated resulting in increased radiation dose and patient discomfort. Many different classifications of impurities affecting the imaging process can be distinguished, as outlined in Table 2. Methodologies for detecting these impurities are briefly outlined in Table 3.

Table 2: Classification of impurities

Type of Impurity	Example	Effect
Radionuclidic	^{99}Mo	Increased radiation dose; poor image quality
Radiochemical	Free ^{99m}Tc-pertechnetate	Poor image quality; increased radiation
Chemical	Al^{3+}	Poor image quality due to labelling problems

Table 3: Detection of impurities

Method	Type of Impurity
Dose calibrator/multichannel analyzer	Radionuclidic
Thin layer chromatography	Radiochemical
Colorimetric	Chemical

QC test procedures for Mo/Tc generator

1. Mo-99 breakthrough:
Mo-99 is assayed directly in the special lead pig supplied by the manufacturer of the dose calibrator. ^{99m}Tc is then assayed directly in the plastic sleeve in the dose calibrator. The activity of ^{99}Mo must not exceed 0.1% of the total ^{99m}Tc-activity. Dose calibrators have different methods how to determine whether this amount is exceeded dependent on manufacturer and age.

The timetable of required testing is shown in Table 4, and for optional testing in Table 5.

Table 4: Required QC testing of a $^{99}Mo/^{99m}Tc$ generator

Test	Frequency	Specifications
Mo breakthrough	Every elution	<0.1% of ^{99m}Tc activity at time of injection
Al^{3+} ion breakthrough	Every elution	<10 ppm of Al^{3+}; may be expressed as µg/ml

Table 5: Optional QC testing of a $^{99}Mo/^{99m}Tc$ generator

Test	Frequency	Specifications
Hydrolyzed Reduced Tc	Every elution	< 5% (Reasonable limit)

2. Aluminum ion breakthrough:

Al^{3+} ion is measured colorimetrically. A drop of the eluate is placed on one end of a special test paper; a drop of a standard solution of Al^{3+}, concentration 10 ppm, is placed on the other end of the test strip (Figure 6). If the colour at the centre of the drop of eluate is less red than that of the standard solution, the eluate has passed the Aluminum Ion Breakthrough Test. Units may be expressed as ug/ml.

Figure 6: Aluminium breakthrough test (courtesy of VirRAD)

Radiochemical purity, paper and thin layer chromatography

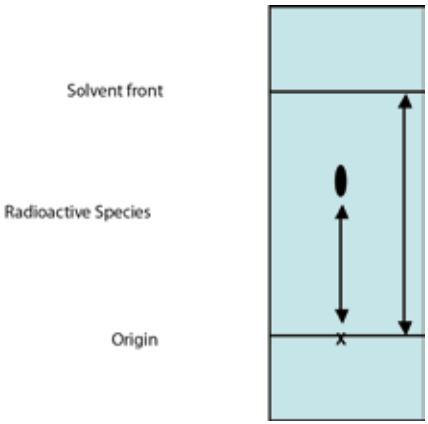
The radiochemical purity (RCP) of a radiopharmaceutical is the ratio of the radionuclide present in a bound form (i.e. as a bound radiopharmaceutical) to the radionuclide present in its unbound form (i.e. 'free'radionuclide).

It can happen that, during the binding of radionuclide to pharmaceutical, the complete reduction of pertechnetate does not occur and some free or unbound technetium is present in the resulting solution. This can also happen if the reduced radionuclide becomes oxidised again. A result can be poor imaging of the radiopharmaceutical and increased radiation dose for the patient. To ensure radiochemical purity, it is important to perform regular quality control on the radiopharmaceuticals.

General principles of planar chromatography for radiochemical purity testing

The test strip or chromoplate may be obtained as a commercial product, and different types are produced for different pharmaceuticals. Generally a few microlitres of the product to be tested is applied near the bottom (origin) of the chromoplate. The chromoplate is then placed in a solvent, ensuring that the bottom (origin) point is not immersed. The solvent is then allowed to rise or migrate up along the plate. The different chemical species separate; the most soluble product moving the furthest distance along the chromoplate. (Figure 7)

Figure 7: A chromatography strip with the position of the origin and solvent front shown. The sample is placed at the point marked on the origin.



When the solvent has moved the required distance along the chromoplate (the solvent front), then it is removed from the solvent and allowed to dry. As a next step, this is read by scanning the radiochromatogram, either by passing it under a scintillation detector or on the surface of a gamma camera. The distance travelled along the chromoplate by each of the radiochemical species is expressed as a fraction of the distance travelled by the solvent front (R_f value). From these R_f values can be determined the quantity of activity in each portion and thus the respective binding quality of the radiopharmaceutical.

Radiochemical impurities in ^{99m}Tc radiopharmaceuticals

Common impurities in ^{99m}Tc-kits are ^{99m}Tc-pertechnetate and ^{99m}Tc-colloid. However a number of ^{99m}Tc-preparations may contain different impurities that have to be covered by respective validated tests (e.g. ^{99m}Tc-Tartrate in ^{99m}Tc-MAG3). A number of recommended chromatography methods are shown below in Table 6 and Table 7.

Separation of radiopharmaceutical and impurity

Radiochemical purity testing can be based on thin layer or paper chromatography (TLC), solid phase extraction methods based on cartridges (SPE), filtration methods, HPLC or electrophoresis. Methods may derive from the European Pharmacopeia, the SPC of the labelling kit or validated literature methods. In many cases a variety of methods are available for one particular radiopharmaceutical. TLC methods and SPE are most commonly used and recommendations in this guidance are based on these methods.

Equipment and location:

The determination of the radiochemical purity in the hospital with TLC can be performed with little expenditure of material and equipment. It should be performed in a dedicated area with radiation protection and proper ventilation (organic solvents).

Quantification:

A variety of methods may be used to quantify impurities including cut and count in the dose calibrator, using dedicated scanner, gamma cameras and others. The differences are in sensitivity, resolution, linear range, speed, availability and practicability and should be chosen dependent on available space, throughput and general organisation of the radiopharmacy. Equipment used for quality control should be regularly calibrated. Generally, the quantification of the radiochemical purity is based on the equation below.

In case the radiochemical purity limit is not reached, the preparation has to be discarded and clearly labelled that it may not be used for patient application.

$$\text{radiochemical purity [\%]} = \frac{\text{radioactivity of component}}{\text{total radioactivity}} \times 100$$

Table 6: Recommended methods for quality control based on TLC

	Solid Phase / Mobile Phase	Rf Radio-pharmaceutical	Rf Impurity
Pertechnetat	ITLC-SG/0.9% NaCl	Front	Start
^{99m}Tc-DMSA	ITLC-SG/ 2- Butanone	Start	Front
^{99m}Tc-Diphosphonates MDP, DPD, HEDP	A) ITLC-SG/ 1M NaAcetate B) ITLC-SG/ 2-Butanone	Front Start	Start Front
^{99m}Tc-DTPA	A) ITLC-SG / NaCl B) ITLC-SG / 2-Butanone	Front Start	Start Front
^{99m}Tc-ECD	Ethylacetate / Baker Silica gel	Front	Start
^{99m}Tc-HMPAO	A) ITLC-SG/ 2-Butanone B) ITLC-SG/ 0.9% NaCl	Front Start	Start Front
^{99m}Tc-IDA-Derivates	A) saturated saline solution / ITLC-SG B) 50% Acetonitril / ITLC-SG	Start Front	Front Start
^{99m}Tc-Colloids	ITLC-SG / 2-Butanone	Start	Front
^{99m}Tc-MAA	ITLC-SG / 2-Butanone	Start	Front
^{99m}Tc-EC	A) ITLC-SG/2-Butanone B) ITLC-SG/ 0.3M Acetic acid	Start Front	Front Start
^{99m}Tc-MIBI	Ethanol /Baker Aluminiumoxide	Front	Start
^{99m}Tc-Depreotide	A) ITLC-SG / saturated NaCl B) / ITLC-SG Methanol/1Ammonacetate (50/50)	Start Front	Front Start
^{99m}Tc-Tetrofosmin	ITLC-SG / Aceton : Dichloromethane =35:65 /	Middle	Start/Front
^{99m}Tc-monoclonal Anti-bodies; HIG, Zevalin	ITLC-SG/ 0.9% NaCl	Start	Front
^{111}In Octreotide	0.1M Na-Citrat pH5 / ITLC-SG	Start	Front

Table 7: Recommended methods for quality control based on SPE

	Cartridge / Solvent	Radiopharma-ceutocal	Impurity
^{99m}Tc-MAG3	SEPPAK C18 light 1.) 0.001N HCl, 2.) Ethanol/0,9% NaCl (50% – 50%)	Eluate 2	column/ eluate 1

Chapter 5 – Radiopharmacy

Blood Labelling

Tanja Gmeiner Stopar, PhD

Several blood cellular elements can be radiolabelled with different radionuclides and radiolabelling approaches for varies clinical applications (Table 1). Regardless of the nature of the blood cells, of the radionuclide used or of the clinical application, it is necessary to maintain both cell viability and sterility and to avoid the operator's exposure to biological and radiation hazard during cell manipulation and radiolabelling. Manipulations and radiolabelling procedures of cells require strict aseptic conditions and should follow the EANM guidelines on current Good Radiopharmacy Practice (cGRPP) in the Preparation of Radiopharmaceuticals [1]. The use of an open or closed vial system on a laboratory workbench is not an alternative to a controlled sterile environment. Cross contamination or mix-up of blood should be prevented at all times. Preparation of radiolabelled cells must be performed successively or by different people in different locations. All surfaces should be properly cleaned, decontaminated and disinfected prior to use, after all procedures are completed, and whenever surfaces are overtly contaminated.

During radiolabelling, approved written procedures should be followed at all times. All materials used should be identified and certified for human use. Whenever possible radiochemical purity should be checked and radiolabelling efficiency (percentage of radiolabelling of cells) calculated. Before release, radiolabelled blood should be checked for aggregation of clumping of cells and for presence of particulate contamination. At regular intervals, the integrity of the cells should be ascertained by use of suitable procedures i.e. using trypan blue. Prior to administration, control of patient identity should be performed [1-3].

Red blood cells

Red blood cells (RBCs) are the most common type of blood cell. Their main function is delivering oxygen from lungs to body tissues. Erythrocytes are continuously being produced in the red bone marrow of large bones. They develop from committed stem cells through reticulocytes to mature erythrocytes and live a total of about 120 days. The aging of erythrocyte undergoes changes in its plasma membrane making it susceptible to recognition by phagocytes and subsequently they are destroyed in the spleen, liver and bone marrow [4].

Table 1: Clinical applications of radiolabelled cells and radiolabelling approach

Clinical application	Blood cellular element	Radionuclide /radiolabel	Radiolabelling approach
Cardiac and vascular imaging	Red cells	^{99m}Tc-pertechnetate	In vivo In vivo/in vitro
Gastrointestinal bleeding	Red cells	^{99m}Tc-pertechnetate	In vivo In vivo/in vitro
Spleen imaging	Denaturated red cells	^{99m}Tc-pertechnetate	In vitro In vivo/in vitro
Blood volume and red cell volume	Red cells	^{99m}Tc-pertechnetate ^{51}Cr-chromate	In vitro
Red cell survival	Red cells	^{51}Cr-chromate	In vitro
Site of red blood cell destruction	Red cells	^{51}Cr-chromate	In vitro
Infection and inflammation	White blood cells	^{111}In-oxine ^{111}In-tropolone ^{99m}Tc-HMPAO	In vitro
Abnormal platelet deposition	Platelets	^{111}In-oxine ^{111}In-tropolone ^{99m}Tc-HMPAO	In vitro

Radiolabelling with ^{99m}Tc

Radiolabelling approaches may by in vivo, in vitro and combined in vivo/in vitro. The basic mechanism of the radiolabelling of RBCs with ^{99m}Tc is in all approaches the same. The RBCs are "pre-tinned" by stannous ions for 10-30 min before ^{99m}Tc-pertechnetate is added to the cells. The stannous ions diffuse into the cell and are firmly bound to cellular components. The pertechnetate diffuses freely across the cell membrane and becomes reduced in the presence of stannous ions in the cell and subsequently binds to the beta chain of haemoglobin. At physiological pH, stannous ions are likely to hydrolyse and precipitate and are rapidly removed from the blood by the reticuloendothelial system. To prevent hydrolysis and precipitation, stannous ions are thus usually in a complex of a weak chelator, such as pyrophosphate or medronate. The amount of stannous ions required for optimal radiolabelling is in the range of 10-20µg per kilogram of body weight.

In vitro radiolabelling

In vitro radiolabelling of RBCs gives by far the highest labelling efficiency and the most stable labelling over time. It may be used for the determination of red cell and blood volume. It may also be employed in patients who are taking drugs which may interfere or inhibit stannous ion transport through the cell membrane such as heparin or hydralazine, resulting in lower labelling efficiency.

A small volume of anticoagulated blood (heparin or ACD) is incubated with an aliquot of a reconstituted stannous agent. Any excess of Sn^{2+} is oxidised by addition of 0.1% sodium hypochlorite and may be removed by centrifugation. The cells are separated and incubated with ^{99m}Tc-pertechnetate for 5-20 minutes with occasional mixing. After incubation, unbound activity is washed away by addition of a few mls of saline and centrifugation. The cells are separated and re-suspended in saline before re-injection.

In vivo radiolabelling

This is the simplest and least time consuming radiolabelling technique. An injection of a reconstituted solution of stannous agent is followed by injection of ^{99m}Tc-pertechnetate 20-30 min later. The major disadvantage of this radiolabelling approach is a generally lower and more variable labelling efficiency. This may be due to insufficient Sn^{2+} incorporation into the cells which results in reduction of ^{99m}Tc-pertechnetate outside the RBC. Reduced ^{99m}Tc is then not able to diffuse across the red cell membrane, resulting in a high background activity. Low labelling yields may also be a consequence of low haemoglobin concentration and/or low haematocrit.

In vivo/in vitro radiolabelling

More variations of the in vivo/in vitro radiolabelling approach are in use. In all approaches, the intravenous administration of a stannous agent is followed by withdrawal of an aliquot

of pre-tinned blood 15-30 min after application. The excess of Sn^{2+} not incorporated into cells may be removed by centrifugation before ^{99m}Tc-pertechnetate is added to the cells. Alternatively blood may be taken into a shielded syringe containing an anticoagulant and the required amount of ^{99m}Tc-pertechnetate.The blood is then mixed with the ^{99m}Tc-pertechnetate and allowed to incubate for 5-20 min at room temperature with occasional mixing. The unbound activity is washed away by centrifugation before reinjection. Radiolabelled blood may alternatively also be re-injected without removal of unbound activity. With the later approach in which no washing step is involved one can expect lower radiolabelling efficiency and higher background activity, depending on the complexity (number of washing steps avoided) of the procedure.

Heat-damaged RBCs

When radiolabelled RBCs are damaged by heat, they will be recognised by phagocytes and subsequently destroyed in the spleen, liver and bone marrow. This mechanism enables the use of heat-damaged ^{99m}Tc-RBCs for spleen imaging studies. Radiolabelled RBCs are damaged by incubation in water bath at 49.5 °C for 15 min before reinjection. To sufficiently denature RBCs but prevent bursting them, the temperature and incubation time are critical. Localisation in liver indicates presence of cell destruction formatting bursting fragments.

Radiolabelling of RBCs can be affected by patient medication. Drugs may interfere directly by reaction with Sn^{2+} by preventing accumulation of Sn^{2+} in the cells or indirectly by affecting the RBC membrane or reducing the haematocrit and/or haemoglobin concentration. For more detailed information see [2,5-7].

The usual administered activity of ^{99m}Tc-RBCs for adult patients is within the range of 500 – 1050 MBq. For children the activity may be adjusted according to body weight, with a minimum activity of 80 MBq in order to obtain images of sufficient quality [8]. Only when in vivo radiolabelling approach is employed, breast feeding should be interrupted and the expressed feeds discarded due to the presence of free ^{99m}Tc-pertechnetate which concentrates in the mammary gland. The total fractional activity ingested by the baby from in vivo radiolabelled RBCs is estimated to be 3 – 5 times higher than the activity in milk from in vitro radiolabelling. After in vitro radiolabelling breast feeding can be continued [9].

General recommendations for application of radioactive drugs are applicable for administration of radiolabelled RBCs. Use of a teflon catheter or cannula should be avoided for administration of Sn^{2+} compounds because Sn^{2+} can react with the catheter [10]. To prevent reaction of ^{99m}Tc-pertechnetate with traces of Sn^{2+} the stannous agent in the cannula and ^{99m}Tc-pertechnetate should not be given through the same system.

Radiolabelling with ^{51}Cr

Radiolabelling of RBCs with ^{51}Cr is carried out in vitro: ^{51}Cr in the form of sodium chromate is incubated with whole blood containing ACD for approximately 10 -15 min. Chromate ion freely diffuses into the RBCs, where it is reduced to chromic ion (Cr^{3+}). Cr^{3+} bound to beta globin chain of the haemoglobin molecule is retained in the cell. The labelling process is stopped by adding ascorbic acid which reduces the chromate outside the cells to chromic ion. Alternatively, free chromate is washed away by centrifugation.

Non imaging studies

The basic principle in all non-imaging studies using radiolabelled RBCs is the same: a known quantity of radiolabelled RBCs is added to an unknown volume of blood in the body. Radiolabelled blood is allowed to mix, and a known quantity of the mixture is then removed and quantitated (counted in a gamma counter). The ratio of the quantity measured after mixing (number of counts per mass) to the quantity added is the base for calculation of the unknown volume [2,11,12].

RBC mass and volume determination

For RBC mass and volume determination, one part of the radiolabelled blood is injected to the patient and the other part is used as a standard for further calculations. When complete mixing of re-injected radiolabelled blood has taken place (after 30 min or longer if the patient has splenomegaly), blood samples are taken for counting in a gamma counter. The red cell mass and plasma volume are calculated by using the dilution equations. The true blood volume is then obtained by summing up the red cell mass and the plasma volume. The total body haematocrit can be calculated by dividing the red cell mass by the true blood volume.

RBC survival

For RBC survival and sequestration studies, ^{51}Cr-RBCs are reinjected to the patient and blood samples are obtained 3 times a week for 2 to 4 weeks after injection. To eliminate the need for decay correction, the samples are counted at the end of the study. For the ^{51}Cr survival curve, activity of the blood samples over time can be plotted on a semilog paper to linearise the curve. The patient's RBC effective half-life is calculated from the curve, the normal being 25 to 35 days. In case of a significant splenic sequestration of RBCs, a significant and progressive increase in splenic uptake relative to the other expected site of RBCs, like blood pool or liver, may be present. ^{51}Cr-RBC uptake is monitored using thyroid uptake probe positioning over spleen, liver and heart.

The usual administered activity of ^{51}Cr-RBC for RBC mass and volume determination is 0.8 – 1.5 MBq and 2.0 - 4.0 MBq for survival and sequestration studies.

Leucocytes and platelets

White blood cells (WBCs) or leukocytes are cells of the immune system defending the body against both infectious disease and foreign materials. Several different and diverse types of WBC exist. They are all produced and derived from a multipotent hematopoietic stem cell in the bone marrow. WBCs are found throughout the body, including the blood and lymphatic systems. One primary technique to classify WBCs is to look for the presence of granules, which allows the differentiation of cells into two categories: granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (lymphocytes, monocytes and macrophages) [4].

Platelets or thrombocytes are blood cells involved in the cellular mechanisms of primary haemostasis leading to the formation of blood clots [4].

Radiolabelling of WBCs and platelets

Non-selective lipophilic ^{111}In and ^{99m}Tc complexes, which label all cells indiscriminately are used for radiolabelling of WBCs and platelets. Generally radiolabelling efficiency is higher when ^{111}In complexes are used (80-90%) compared to ^{99m}Tc-HMPAO, where radiolabelling efficiency is normally 50-80%. Availability, low radiation exposure and better imaging characteristics are major advantages when ^{99m}Tc-HMPAO is used for radiolabelling. The clinical results using ^{111}In or ^{99m}Tc-HMPAO WBC are similar. However when ^{99m}Tc is used for radiolabelling, scans can be completed sooner, because imaging takes place at 1 hour and at between 4-6 hours [2,12].

Neutral lipophilic complexes rapidly diffuse across cell membranes. Once inside the cell, the complex either dissociates and allows ^{111}In to bind to intracellular proteins (^{111}In-oxine) or breaks down to a more hydrophilic complex which is unable to cross the cell membrane and is thus trapped in the cell (^{99m}Tc-HMPAO). In the case of radiolabelling with ^{111}In-oxine, ^{111}In also binds to transferrin present in the plasma. Therefore the cells have to be washed thoroughly to remove plasma before radiolabelling. In the case of radiolabelling with either ^{111}In-tropolone or ^{99m}Tc-HMPAO, radiolabelling can take place in the presence of small amounts of plasma.

Because of the non-selective approach, the cells need to be separated prior to radiolabelling. The separation of WBCs and platelets from RBC in the blood can be achieved by sedimentation of anticoagulated blood. 30-50 ml of blood is taken into a 60 ml syringe containing an anti-coagulant. The anti-coagulant of choice is acid-citrate-dextrose (ACD) in concentration 1.5 parts of ACD to 8.5 parts of whole blood. Erythrocyte sedimentation may be accelerated by the use of sedimentation agents such as 6% hydroxyethyl starch (Hespan). Alternatively 6% dextran or methylcellulose may be used. Normally 3 ml of Hespan per 30 ml of whole blood is used. Hespan may be added to ACD in a syringe before blood is taken. Sedimentation time is generally 45-60 min and may be affected by different factors such as number of cells and certain disease states. Sedimentation may be carried out in the syringe placed

upward in a suitable holder or in a universal tube. After sedimentation, the upper layer containing WBCs and platelets is transferred into a sterile universal tube. To separate WBCs from platelets, the plasma is spinned at low speed e.g. 150 g. Platelet rich plasma is removed before the radiolabelling agent is added to the pellet containing WBCs and small amounts of RBCs. The mixture is incubated at room temperature. Incubation time varies depending on the radiolabelling agent used. Generally it is longer when ^{99m}Tc-HMPAO is used. After radiolabelling, the cells are re-suspended in saline; and free fraction of radiolabel is washed away by centrifugation. Radiolabelled cells are re-suspended before re-injection with saline or diluted plasma. Plasma is prepared from plated rich plasma by centrifugation at higher speed e.g. 500-700 g.

To ensure optimal viability of radiolabelled cells, the labelling should be completed as quickly as practical; and the cells should be injected within 3 hours of removal.

Platelet rich plasma removed from the WBCs may also be used for separation of platelets. This is achieved by an additional centrifugation step at higher speed where the platelets are spinned in the pellet and plasma can be removed. The radiolabelling procedure of the platelets is the same as for leucocytes.

The recommended dose for ^{111}In-WBCs is 18.5 MBq; and for ^{99m}Tc-HMPAO-WBCs, it is 400 MBq (range of 185-450 MBq). For children the activity may be adjusted according to body weight, with a minimum activity of 40 MBq of ^{99m}Tc-HMPAO-WBCs in order to obtain images of sufficient quality [8]. Breast feeding should be interrupted and the expressed feeds discarded when ^{99m}Tc-HMPAO-WBCs is used for imaging [9]. Cell radiolabelling could be affected by a patient drug therapy. For more detailed information see [2,5].

Radiolabelling efficiency

The percentage of radioactivity incorporated into the cells is usually described as radiolabelling efficiency. It should be determined as the last step before radiolabelled cells are re-suspended and re-injected: the radiolabelled cells are separated from the labelling medium by centrifugation. The activity of the labelled cells is measured before and after separation. Labelling efficiency is then calculated:

$$\% \text{ Radiolabelling efficiency} = \frac{\text{radioactivity on separated cells}}{\text{total activity before separation}} \times 100\%$$

Nevertheless a high radiolabelling efficiency is not necessarily indicative of a good labelling procedure or viable cells. Regardless of the radiolabelling efficiency, it is important to obtain a viable population of cells for reinjection.

Cell viability

It is essential that radiolabelled cells remain viable when they are re-injected to the body. They may be damaged from the harvesting and/or radiolabelling procedures. Cell viability is most frequently assessed by Trypan blue exclusion assay. Trypan blue is a stain which is incorporated into dead cells, whereas live cells are not coloured. Equal volumes (0.1 – 0.2 ml) of radiolabelled cell suspension and 0.4% Trypan blue are gently mixed in an appropriate tube and incubated at room temperature for 5 minutes. The mixture is applied on a haemocytometer slide and cells counted under a light microscope. The percentage of viable cells is the number of viable cells divided by the number of dead and viable cells. Usually it should be >95%.

Chapter 6 – Radiopharmacy

Record Keeping and Administration

Brendan McCoubrey

Historical legislative framework

Council Directive 65/65/EEC (1965) dealt with the use of radionuclide generators, their storage and elution and the production of radiopharmaceuticals thereof for the purpose of administration to patients.

Council Directive 75/319/EEC (1975) dealt with the placing on the market of radiopharmaceuticals and the conditions for authorising the manufacturing and marketing of these radiopharmaceuticals.

Council Directive 87/21/EEC and Council Directive 83/570/EEC amended the two above Directives respectively with regard to additional provisions laid down for radiopharmaceuticals.

Council Directive 89/343/EEC issued in 1989, extended the scope of both Council Directive 87/21/EEC and Council Directive 83/570/EEC particularly with regard to the incorporation of the provisions of 84/466/Euratom (patients) and 84/467/Euratom (staff and public).

Current legislative framework

Council Directive 91/356/EEC (1991) details the principles of Good Manufacturing Practice (GMP) for Medicinal Products for human use.

Directive 96/29/Euratom (Basic Safety Standard Directive) lays down provisions for the protection of personnel.

Directive 97/43/Euratom (Medical Exposures Directive) lays down provisions for the protection of patients.

Legislative rationale

The principal concerns of existing legislation and guidelines with regard to radiopharmacy record keeping and documentation are:

Quality Assurance: The implementation of standards and frequencies of quality control testing and of equipment monitoring within the radiopharmacy to ensure continued compliance with the relevant legislation regarding radiopharmaceutical standards.

Training of personnel: The professional competence of the staff in the implementation of the working practices and the documented procedures in the facility. This has a large part to play in ongoing radiation protection within the radiopharmacy. The training should be appropriate to the tasks performed by the individual. Ability and competence of staff should be assessed initially and reviewed regularly by the person managing the facility. A detailed description of the training process and a record of completion should be maintained.

Transport: The packaging, movement, and transport of radioactive material. This includes transport of radionuclides to the facility and where relevant, the dispensing service from the facility.

Records of waste disposal: Waste storage of all radioactive products and material, and their subsequent waste disposal. Under the terms of the holder's licence, records must be kept of each manipulation of radioactive substances as provided for under the terms of the licence.

Therefore, the record must identify the date of acquisition of all unsealed radioactive substances, their radioactive content then and at the subsequent time of disposal, along with the date and method of disposal. For sealed radioactive sources, a record must be kept, detailing acquisition date, source classification, results of wipe tests and the method and date of disposal. When radioactive waste has decayed and is ready for final disposal all radioactive warning signs must be removed.

Environmental and microbiological monitoring: Adequate environmental and microbiological monitoring procedures are a requirement of Good Manufacturing Practice (GMP). This necessitates regular adherence to a suitable protocol of testing of environmental and microbiological standards with set warning and action limits and the keeping of documented records of compliance.

Local rules

These should contain clearly defined procedures for working with radioactive materials and should include:

a) Names of those on the Hospital Radiation Safety Committee.
b) Specification of controlled and supervised areas.
c) Systems of work for controlled areas.
d) Details of storage of radionuclides.
e) Details of where and how radionuclides are handled.
f) Routine monitoring procedures.
g) Records to be kept.
h) Action to be taken in the event of a spill.
i) Date when local rules were drawn up / superseded.

Record keeping and documentation

The keeping of adequate records is a standard requirement of a radiopharmacy to ensure continued good radiopharmacy practice. These records may be classified according to the following main areas of responsibility.

- Patient medical examinations
- Calibration and testing of monitors
- Maintenance of equipment
- Inventory of sources and equipment
- Movement of sources and equipment
- Source material accounting, including receipt and disposal details
- Leak tests and area monitoring
- Staff dosimetry
- Accidental or emergency exposure

Specifically these records pertain to the continued optimised operation of all areas within the radiopharmacy and should provide systematic retrospective evidence that each area continues to meet performance criteria laid down by both legislation and guidelines at national and European levels.

Healthcare quality management documentation

The holder of a manufacturing authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, that they comply with the requirements of the marketing authorisation, and that they do not place patients at risk due to inadequate safety, quality or efficacy. To achieve this, a comprehensively designed and correctly implemented system of Quality Assurance, incorporating Good Manufacturing Practice (GMP) and Quality Control (QC), must be in place. It should be fully documented and its effectiveness monitored. All aspects of the Quality Assurance (QA) system should be adequately resourced with competent personnel, suitable and sufficient premises, equipment and facilities. Accurate and complete record keeping is essential so that it will be possible to trace the source, composition and activity of all radiopharmaceuticals administered to patients.

Quality assurance documentation

Due to short half-lives it is not possible to rigorously test before administration. QA is retrospectively achieved through strict adherence to written procedures. Accurate records must be maintained and kept up to date. The working environment must be suitably monitored to ensure that microbiological, particulate and radioactive contamination levels comply with established standards. All equipment must be subject to regular performance checks and calibrated against suitable standards where appropriate. Operator techniques must also be regularly monitored.

Quality Assurance documentation should originate with the purchase of materials for use as radiopharmaceuticals; and the audit trail should extend to the administration of individual patient doses. The receipt of all materials by the facility should be documented and checked for correctness. These records should be capable of tracing all materials from source and up to final delivery. A system of documentation must be in operation such that the history of each preparation can be adequately traced.

EANM reporting scheme

The European Association of Nuclear Medicine has established two central European Databases for the reporting of possible defective products and for the reporting of adverse reactions to administered radiopharmaceuticals. Adverse incidents involving the preparation or administration of radiopharmaceuticals should be notified to the relevant local authority in the first instance; and details should also be forwarded to the EANM. A link to the EANM website is provided below.

EANM Adverse Reactions Report 2002
http://www.eanm.org/committees/radiopharmacy/adverse_reactions.pdf

Inventory of radiopharmacy records and documentation

To ensure a complete systematic recording and documentation process, it is necessary to first separate the operation of the radiopharmacy facility into its component elements.

A detailed Standard Operating Policy (SOP) concerning record keeping and documentation should be drawn up for each of the following areas, specifically listing the required data fields to be completed for each separate operation within the radiopharmacy.

General radiopharmacy operative records

- Standard Operation Protocols (SOPs)
- Records of workstation performance
- Records of microbial and particulate levels in the lab and workstation
- Data on starting materials and ingredients
- Data on the production process
- Data on distribution of the final product to allow recall or halting
- Disposal of radioactive waste
- Emergency procedures
- Risk assessment forms
- Minor / major spill incident forms

Radiopharmacy generator/s records

- Date
- Generator lot no.
- Generator expiry
- Elution activity
- Elution time
- Elution volume
- Mo breakthrough test
- Radiopharmaceutical lot no.
- Radiopharmaceutical expiry
- Reconstitution time
- Reconstitution volume
- Reconstitution activity
- Personnel at all stages

Radiopharmaceutical reconstitution records

- Name of the preparation
- Route of administration
- Activity in Becquerel's
- Volume
- Time / Date measured
- Batch no.
- Radiation warning trefoil
- Applicable special storage conditions
- Expiry date
- Applicable special preparatory instructions
- Address of radiopharmacy
- Transport index of the packaged product
- Personnel at all stages

Gamma Camera/s Records

- Date
- Personnel
- Camera peaking
  - Peaked
  - Window
  - Dead time
- Co^{57} flood source
  - % UFOV result
  - % CFOV result
- Ionisation chamber
  - Constancy test Cs^{137}
  - Calibration test Tc^{99m}
  - Ionisation chamber self test

Patient Records

- Patient name
- Medical record no.
- Patient source
- Consent

- Examination type
- Examination no.
- Date of exam
- Radiographer
- Radiopharmaceutical kit
- Radiopharmaceutical expiry
- Activity
- Time of injection
- Administrator
- Administrator route
- Patient incident forms

Workload statistics
- Exam type
- GA
- Sedation
- Demographics

Personnel dosimetry records
- Personnel readings
- Extremity readings
- Contamination levels
- Background readings

National authority records
- Correspondence
- Certificates of compliance:
  - Camera
  - Dose calibrator
  - Contamination monitor
  - Dose rate meter

External Suppliers' Records
- Manuals
- Repairs and logbooks
- Kit ordering
- Generator ordering and delivery
- Accessories
- Software upgrades

Internal hospital supply records
- Pharmacy
- Stores
- CSSD
- Technical services

Release or failure of preparations

In accordance with GMP, procedures must be put in place whereby a final product is subject to release/failure assessment. For the holder of a manufacturing authorisation, there should be a written procedure detailing all production and quality control data, which should be reviewed before the batch is dispatched. The procedure should also describe the measures to be taken by the facility if unsatisfactory test results are obtained after dispatch. Recall operations should be shown to be operable within a short space of time. Conditions for the release/failure of preparations should include:

a) A formal recorded decision of approval taken by an authorised person prior to release of preparations.
b) A written release procedure, effected only if:
   i) The product has been prepared in accordance with GMP;
   ii) The product complies with the release specifications.
c) A written procedure which should take effect where a failure to meet the required

standard is recorded. The event should be documented and investigated.

d) A written procedure should exist for the recall of defective radiopharmaceuticals.

Transport of Radioactive Materials

All of the regulations and codes of practice covering the transport of radioactive material are based on the safety standard publications of the IAEA. Responsibility for transport must be clearly allocated; and adequate records of dispatch and receipt should be kept. All containers should be suitably labelled; and these labels should be removed from empty containers. Procedures for transport should be laid down in the Local Rules. These should take account of any hazardous situations that may arise during transport and of detailed procedures for dealing with those. Links to the International Atomic Energy Agency (IAEA) Transport Regulations 2005 may be found on the following websites:

- The International Atomic Energy Agency (IAEA) Regulations for the Safe Transport of Radioactive Material: http://www.iaea.org/
- Information Sheet at World Nuclear Transport Institute http://www.wnti.co.uk/UserFiles/File/public/publications/factsheets/wnti_fs-2.pdf

External Transport of Radioactive Materials

Packages for external transport from the radiopharmacy must be labelled with the correct international transport labels showing the radionuclide, activity and transport index. Criteria for these labels are strictly prescribed by the IAEA. Figure 1 gives an example of the criteria pertaining to the dimensions and ratios of radiation warning labels. Figure 2 demonstrates the criteria for the classification of packages. Figure 3 gives an example of a Category II package warning label. Transport documents must also be completed as required by national legislation.

Figure 1: Basic trefoil symbol with proportions based on a central circle of radius X. The minimum allowable size of X shall be 4 mm (1).

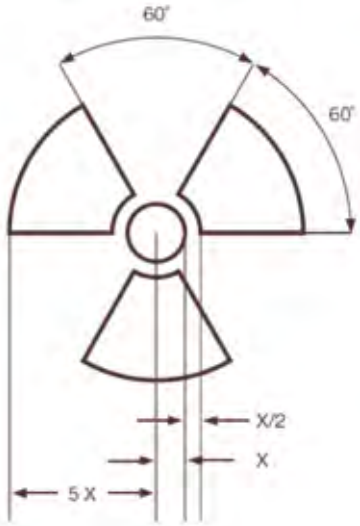


Figure 2: Categories of packages and overpacks (1).

Conditions		
Transport index	Maximum radiation level at any point on external surface	Category
0*	Not more than 0.005 mSv/h	I-WHITE
More than 0 but not more than 1*	More than 0.005 mSv/h but not more than 0.5 mSv/h	II-YELLOW
More than 1 but not more than 10	More than 0.5 mSv/h but not more than 2 mSv/h	III-YELLOW
More than 10	More than 2 mSv/h but not more than 10 mSv/h	III-YELLOW†

* If the measured *TI* is not greater than 0.05, the value quoted may be zero in accordance with para. 526(c).
† Shall also be transported under *exclusive use*.

Figure 3: Category II Yellow Label. The background colour of the upper half of the label shall be yellow and the lower half white, the colour of the trefoil and the printing shall be black, and the colour of the category bars shall be red (1).

Process for the creation of records

All entries should be computerised where possible or in clear, legible indelible handwriting. The use of block letters should be mandatory. Record keeping should be completed at the time each action is taken by the person responsible for the action. Alterations to the record should be signed and dated with a reason for the alteration where relevant. The data in the record should be retained according to national data laws. Where computerised systems are utilised for the creation of records, authorised access by means of individual passwords or codes should be employed. Data should be backed up regularly and stored at a separate secure location. Sensitive data should be encrypted in accordance with Na-

tional Data Protection legislation. Alternative arrangements should be in place in the event of a breakdown; and these temporary records should be incorporated into the permanent log as soon as possible after the re-establishment of normal service.

Control of documents

A Master Document should be created and the number and location of approved copies recorded. Every document should contain a version number and a review date. A system should be in place to prevent the inadvertent use of superseded documents.

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Technologist Committee and Technologist Education Subcommittee
Hollandstrasse 14, 1020 Vienna, Austria
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E-mail: info@eanm.org
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