ANZSNM RADIOPHARMACY SIG

GUIDELINES FOR GOOD RADIOPHARMACY PRACTICE

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INTRODUCTION

Radiopharmaceuticals are a special group of pharmaceuticals which, in their final form, contain a radionuclide. They may be classified into three groups: preparations which are supplied as a radioactively-labelled product in a ready-to-inject form, inactive products which are made radioactive immediately prior to patient injection and radionuclide preparations that are combined with an inactive preparation to produce the final product for injection. Radiopharmaceuticals tend to differ from normal pharmaceuticals in that, because of the short half lives of the radionuclides used, preparation and quality control may have to be performed in the hospital immediately prior to injection into the patient. Preparative procedures may vary from simple aseptic addition of a solution to complex labelling of samples taken from patients for radioactive labelling and subsequent re-injection. In many cases, the need to provide radiation shielding to protect the operator makes manipulation more difficult.

The range of procedures utilised will vary with the size and nature of the institution concerned and will be influenced by the range of technical skills available. It is therefore important that organisational arrangements are appropriate for the complexity of the processes and procedures employed.

The present Guidelines are intended to provide a basis for the safe and efficient practice of radiopharmacy in a hospital or clinical environment. It can provide a basis for self-audit or peer review. The Guidelines were developed by the Radiopharmacy Special Interest Group of the Australian and New Zealand Society of Nuclear Medicine in collaboration with ARPANSA and the Radiopharmacy Speciality Practice Committee of the Society of Hospital Pharmacists of Australia. Overseas codes and guides were also utilised.

The Guidelines do not deal in detail with requirements for radiation safety. For this aspect of the work and for other regulatory requirements such as those relating to dangerous goods, poisons, occupational health and safety, quarantine, animal welfare, waste disposal and building codes, the relevant legislation must be known and complied with.
CHAPTER 1: QUALITY MANAGEMENT

GENERAL

100 The practice of radiopharmacy is part of the broader practice of nuclear medical diagnosis, which itself may be treated as a quality system. The aspect that is designed to ensure that radiopharmaceuticals are safely and reproducibly prepared and handled in hospitals to a standard appropriate to their intended use is commonly known as Good Radiopharmaceutical Practice (GRP).

101 The quality of radiopharmaceuticals may affect not only the safety of the patient but also the outcome of the diagnostic or therapeutic procedure. A GRP quality system should therefore be designed and documented to provide the prescribed radiopharmaceutical products of the required standard.

QUALITY ASSURANCE AND QUALITY CONTROL

110 The two facets of quality management are quality assurance and quality control. ISO 8402 defines quality assurance as "all those planned and systematic actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality", while quality control is concerned with analysis, documentation and evaluation of results to ensure that the product complies with the relevant standard.

111 A quality plan should be designed and implemented to include both facets and sufficient resources, including premises, equipment, personnel and training, should be provided to allow the quality system to operate. The preparation of a Quality Manual is strongly recommended.

VALIDATION

120 Validation involves "establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes" (US FDA guideline "General Principles of Validation"). More simply, it may be viewed as the provision of documented evidence that a process achieves its intended outcome.

121 In the development of a procedure for the manufacture of a radiopharmaceutical, all critical steps should be validated, including the development of raw material specifications. Consideration should be given to the need for in-process controls to ensure the compliance of the final product. This is of particular importance where the product is to be used before the completion of all quality control testing. Changes in manufacturing procedures should also be similarly validated. It should be noted that scaling up a process represents a change in manufacturing procedure.

122 Examples of critical steps in radiopharmaceutical manufacture include:

- The establishment of specifications for the radioactive raw material. This is particularly important for non-registered sources and may require a purchase agreement with the supplier.
- The need for nitrogen purging in the preparation of cold kits. The effects on the performance of the final product of changing flow rates, time of nitrogen purging and solutions purged should be investigated.
- The sensitivity and the specificity of a labelled antibody to such parameters as pH, temperature and the quantity of radioactive label incorporated.

Reconstitution of cold kits using sodium pertechnetate[99mTc]

123 For registered products which have been subjected to evaluation by the registering authority (the TGA), validation of procedures described in the package insert for the reconstitution of cold kits using sodium pertechnetate[99mTc] injection is normally not required. Nevertheless, some validation of the preparation procedure should be performed when the product is first introduced within an institution. This is of particular importance where the product is to be used before the completion of all quality control testing. Changes in manufacturing procedures should also be similarly validated. It should be noted that scaling up a process represents a change in manufacturing procedure.

124 For products which have not been evaluated by the TGA (including cold kits reconstituted by simple addition), the user should request documented evidence of the manufacturer's validation of the reconstitution procedure. If this is unavailable, validation should be performed by the user.
It is particularly important that users validate the use of reconstitution conditions that may occur beyond those contained in the package insert. Particular attention should be paid to any effect of the changes on the stability of the product. The following should be noted:

- Increases in radioactive concentration can produce significant changes in product stability due to radiolytic decomposition.

- Increased levels of $^{99}\text{Tc}$ may also produce deleterious effects. Effects due to $^{99}\text{Tc}$ may be distinguished from those due to radiolytic effects by the addition of carrier $^{99}\text{Tc}$ to the pertechnetate[$^{99m}\text{Tc}$] used for reconstitution. Levels of $^{99}\text{Tc}$ may be minimised by reducing the time between generator elutions and/or reducing the shelf life of the eluted pertechnetate.

- The stability of the final product when dispensed and stored in syringes will normally not have been investigated by the manufacturer and the use of syringes for storage should be validated by the user. Stability in the syringe may also be affected by the presence of lubricants in the syringe.

- Changes in the source of sodium pertechnetate[$^{99m}\text{Tc}$] from that recommended in the package insert should be validated. Some chromatographic generator sources of pertechnetate may contain chemical additives which interfere in some labelling systems.

Similar considerations apply to labelling with other radionuclides.

Note: "Fractionation"- the practice of reconstituting a cold kit with an inactive diluent such as saline and redispensing into a number of vials for subsequent use constitutes "manufacture" of cold kits.

**Changes in specifications and quality control testing procedures.**

New quality control methods may be validated by comparing their performance against reference methods. Where possible, data should be obtained on the specificity, accuracy and reproducibility of the new method for comparison with the reference method. Where possible, standards containing varying amounts of potential impurities should be prepared by standard addition for the method validation.

The following should be noted:

- It is preferable to measure radiochemical purity by determining the quantity of active component directly rather than by an indirect method which measures levels of impurities.

- It is usually not possible to prepare reference mixtures of $^{99m}\text{Tc}$- radiopharmaceuticals by standard addition. In these cases, degraded samples may be prepared by heating, oxidation etc. for comparison with the reference method.

- Changes in chromatographic support media, e.g. TLC strips and solvent systems, should be validated.

- It is not sufficient to run a new method in parallel with a reference method in the testing a number of production runs. Validation should cover the range of impurities and levels of impurities that may be found in practice.

**Sterilisation**

Validation of the aseptic processing of cold kits requires "media fill runs" as described in clauses 781-784. The validation of processes for terminal sterilisation is well described in the Australian Code of GMP - Medicinal Products, 1990 and Annex 1 of the European Union GMP Guide for Medicinal Products, 1997.

**Automated systems**

The user should obtain from the supplier details of the validation of any system purchased for use in manufacture or quality control. Attention should be paid to the requirements for maintenance and any effect of the operating environment on the successful performance of the system. Validation of the system in use within the institution is nevertheless required.
CHAPTER 2: RADIATION SAFETY

200 Radiation is energy emission from a source. The main type of radiation of interest in nuclear medicine practice is classed as ionising radiation, including X-rays, gamma rays, alpha particles, beta particles, positrons, neutrons and protons. The major objective of radiation safety is to reduce public and occupational exposure, whether internal or external, to a minimum, keeping in mind the "ALARA" (as low as reasonably achievable) principle.

201 Where it is either impossible or impracticable to isolate a radiation source, the following four factors should be considered in order to reduce exposure from the source:

1. Time of exposure: The dose accumulated by a person working with a radiation source is directly proportional to the time the worker spends in the vicinity of the source. Therefore, the time spent near radioactive material should be minimised.

2. Radioactivity of the source: The quantity of radioactivity used should be the minimum necessary to produce a satisfactory result. Low activity sources (kilobecquerel sources) often do not require shielding, whereas high activity sources (megabecquerel and above) should not be handled without shielding.

3. Distance from the source: The radiation dose rate from any point source varies inversely as the square of the distance from the source. For this reason, it is desirable, whenever practicable, to use forceps instead of manipulating large amounts of radioactive material directly with the hands.

4. Amount of shielding present: Generally, this is the preferred method of protection as it results in safe working conditions. The amount of shielding required depends on the radiation type and energy, the radioactivity of the source, the source dimensions and the dose rate that is considered acceptable for radiation workers. Gamma radiation can be effectively shielded by using lead bricks or lead pots. Alpha and beta radiations are effectively shielded with aluminium or perspex. (Note that it is good practice to avoid using lead or any other high atomic number shielding materials when using beta sources). Neutron radiation requires special shielding conditions. The use of lead bench shields with lead glass windows and lead or tungsten syringe shields in dose-drawing stations or in blood cell manipulations is extremely beneficial in reducing personnel exposure. Tables of the attenuation that may be achieved by using various thicknesses of lead for shielding purposes may be found in the package inserts of radiopharmaceuticals.

It is the combination of careful attention to all four factors together with the use of well-planned and rehearsed techniques and procedures which leads to the safest working conditions and lowest exposures.

202 Internal hazards arise when radioactive materials are free to enter the body by inhalation, ingestion or absorption through the skin or through a wound. To minimise internal hazards, care should be taken in the manner by which samples, or doses, are taken from the radioactive material. The radioactive material should be properly contained, for example by using fume cupboards and spill confinement trays. Good laboratory practice should also be observed, especially with respect to cleanliness.

203 The following rules should be observed in the radiopharmacy when working with radioactive materials:

- Laboratory coats and disposable gloves should be worn at all times. Safety glasses should be used if the work is of a hazardous nature. Gloves should be changed at regular intervals in order to minimise the spread of contamination.
- Personal film badges or thermoluminescent dosimeters (TLDs) must be worn at all times when handling radioactive materials or working in areas where they are handled or stored.
- All working surfaces should be covered with absorbent paper that has an impermeable plastic coating on the reverse side.
- Radioactive materials should be kept in closed, sealed vials within shielding containers at all times.
- All shielding containers and vials should bear a label identifying the radiopharmaceutical, the total radioactivity, the volume and/or the radioactive concentration and the time and date of calibration.
- Small spills that present no radiological hazard to persons should be cleaned up immediately. More serious spills may require evacuation of the area before cleanup is undertaken and should be reported. General reference should be made to Interim Australian Standard AS 2243.4 (Int.)- 1994- Safety in
• Eating, drinking, smoking, the administration of medication or the application of cosmetics should be prohibited in areas where radioactive materials are handled or stored.

• Foodstuffs, drinks or medication should not be stored in the same area as radioactive materials.

• In order to demonstrate confinement of radioactivity, a suitable electronic radiation detector should always be available when radioactive materials are manipulated.

• Appropriate radioactive waste management (storage and disposal) should be in place in accordance with individual State/Territory radiation control legislation.

• 204 Current occupational exposure limits can be found in State/Territory radiation control legislation and the joint NHMRC-NOHSC National standard for limiting occupational exposure to ionizing radiation.

A list of relevant authorities in each State/Territory is given in Appendix 1.
CHAPTER 3: PERSONNEL AND TRAINING

300 Personnel involved in the manufacture or use of kits, generators and radiopharmaceuticals should be suitably qualified, experienced and competent to perform the duties prescribed. Depending on the level of management or on the task, this may involve qualification, experience and competence in one or more of pharmacy, radiopharmacy, radiochemistry, microbiology, sterile technique, radiation dosimetry and other scientific disciplines and skills. Specific legal requirements may apply, for example the handling of controlled substances and the control of radioactive material.

301 Duty statements and job descriptions should be drawn up for key personnel and their responsibilities clearly defined. A record of qualifications and training for each person should be maintained.

It is the responsibility of the Head of Department or Head of Service to ensure that personnel are qualified and competent for the performance of their duties. Competency should be reviewed on a regular basis and any necessary training provided.
CHAPTER 4: PREMISES AND EQUIPMENT

REQUIREMENTS- GENERAL

400 The radiopharmacy facility and equipment should be located, designed, constructed and maintained to suit the operations to be carried out. The layout and design should be such as to minimise the risk of errors and permit effective cleaning and maintenance, avoid cross-contamination, build up of dust or dirt and any other influence that may adversely affect the quality of the radiopharmaceuticals. The facility should also be designed to give proper radiation and contamination protection to personnel and the environment.

401 The customary principles for the layout of radioisotope laboratories, designed to protect the staff and the external environment in the event of radioactive contamination in the laboratory, should be followed. The radiation hazard must be controlled in accordance with radioactive substances regulations and in such a way that full attention can be given to the sterility, toxicity and purity of the radiopharmaceuticals produced.

402 The layout of a laboratory and the allocation of space will be dependent on the type of work to be carried out and should follow the principles given below for different types of preparation or organised dispensing. The layout should allow preparation to take place in a logical order corresponding to the required sequence of operations.

403 An entrance lobby or area near the entrance, where protective clothing can be put on, taken off and stored when not in use, should be provided. Procedures for entering and leaving the radiopharmaceutical or hot laboratory should be defined and a copy posted as a reminder.

404 Steps should be taken to prevent access by unauthorised persons. The entrance to each laboratory must have an identification placard on the door or in the immediate vicinity to identify the laboratory, indicate the main potential hazards within, advise the nature of personal protection required and advise the names and telephone numbers of persons to be contacted in case of emergencies.

405 Storage areas should be of sufficient capacity to allow orderly storage of various categories of materials and products.

406 In-process controls may be performed within the preparation area, provided that they do not involve any risk to the preparation process.

407 Appropriate lighting, temperature, humidity and ventilation should be provided.

408 Pipe work, light fittings, ventilation points and other installations should be designed and situated so as to avoid the creation of recesses which are difficult to clean. As far as possible, these should be accessible for maintenance purposes from outside the preparation area. Where practicable, service machinery should be located outside the production areas.

409 Pipelines carrying services should be identified by colour or standard markings. "Dead legs", where circulation cannot occur, should be minimised.

410 The design of drains and connection to the sewage system should be in accordance with building and radioactive substances regulations.

411 Washbasins, fitted with hands-free taps, should be provided.

412 Premises should be kept in good order and carefully maintained. It should be ensured that repair and maintenance operations do not endanger the quality of products. Premises should be cleaned in accordance with detailed written procedures.

413 Air intakes and exhausts should not be sited near wet drains or sources of dust. Cleaning of filters should occur away from pharmaceutical areas. Air ducts should be verifiably clean by inspection or testing on a regular basis. The air flow pattern should afford adequate protection to the product as well as operator safety. A plan of the building showing air handling facilities, air quality standards, flow rate, proportions recirculated and relative pressures should be available.

414 Extraction ducts should be cleanable and prevent condensate and dust accumulation. There should be no recess that cannot be cleaned. Exposed pipes should not touch walls but be suspended or supported to allow cleaning. Openings in walls, floors or ceilings should be sealed or have removable covers that permit cleaning. Light fittings should be located or sealed so as to not collect contamination.

GOODS RECEIVAL AND STORAGE
420 Materials should not be stored unprotected outside buildings. Space should be provided as a receive area for temporary receipt of goods whilst they are recorded, examined and opened if necessary. Stored goods should be kept clean, dry and in an orderly condition. Storage should be off the floor and away from walls to permit cleaning. All materials should be stored as recommended by the manufacturer.

421 Controlled storage environments, e.g. freezers and refrigerators, should be monitored using suitable temperature-recording devices and records reviewed and filed. Radioactive material should be suitably labelled. Refrigerators and freezers should be fitted with alarms to indicate refrigeration failure. Temperatures and humidity in other areas should be monitored and results tabulated to demonstrate the suitability of these areas in relation to product quality.

422 Stock rotation should be practised i.e. oldest stock used first.

**RADIOPHARMACEUTICAL DISPENSING**

**Dispensing of individual patient doses**

430 The reconstitution of kits is normally a closed procedure performed in a single step and the product administered within a few hours of preparation. The requirements governing premises for this operation are therefore similar to those for the dispensing of ready-for-use radiopharmaceuticals.

431 Where the reconstitution of kits involves more complicated procedures, such as boiling, microwave heating, chemical reaction or treatment with ultrasound to ensure dissolution, a more detailed planning of the working area should be undertaken, taking into consideration the procedures to be performed and the equipment to be used. A contained work station may be required.

432 Patient dose preparation should be performed with a low risk of microbiological contamination; separately from other work and in a sufficiently clean area. Material of patient origin should not be handled in the same room.

433 Local shielding must be considered for the drawing of doses.

434 Radioactivity meters should be available for the following:
   - received radiopharmaceuticals (surface contamination i.e. survey monitor);
   - background monitoring; and
   - dose calibration.

435 Storage facilities should be separate from radioactive waste.

**Laboratory design**

436 The design of the laboratory should comply with Australian Standard AS 2243.4 in relation to radiation safety of low or medium level laboratories.

437 The laboratory should be isolated from other laboratories and the work area allocated on a generous scale compared with normal laboratories: 10 m² overall room area per worker is desirable. Wall and door shielding may be required. Floors should have continuous vinyl coving (curved smooth joins) extending up the walls and welded joints. Rooms should contain a minimum of furniture and excess equipment and consumables should be stowed away to facilitate daily cleaning of surfaces.

438 Taps should be elbow, foot or beam-operated.

439 Surface materials, including bench tops, should have a minimum of joints and seams and be non-shedding and easy to clean. Doors and windows should have a hard, smooth, impervious finish and should close tightly. Doors and windows should fit flush with surrounding walls.

**Apparatus and equipment**

440 The laboratory should contain shielded containers, cabinets for short, intermediate and long term storage, a refrigerator and freezer, a lead glass dispensing shield, a contamination monitor, and an area monitor. The floor units should be made movable on castors.
450 Usually, a separate radioisotope laboratory is not present but is part of the general hot lab layout. The following principles should be applied with this in mind:

1. The radionuclide generator should be placed in a room with a good hygienic standard but, where the risk of release of airborne radioactive contamination is low. It need not always be placed in contained work station. In particular, a technetium generator should not be placed in a fume cupboard, since air quality is poor. Care should be taken to allow easy elution even when additional, stationary radiation shielding is used. If a contained work station is used for the generator, it should be of the vertical flow type to avoid the risk of aerosol contamination of the surroundings (see also "Technetium Generators").

2. If large amounts of radiopharmaceuticals containing volatile radionuclides such as iodine-131 are handled, it may be necessary to install fume cupboards, suitably designed for work with radionuclides, or closed glove boxes dedicated to the purpose. (See also "Radiolabelling- Iodination").

Storage of radioactive waste

451 Radioactive waste should be stored in adequately shielded containers or in a secure shielded room according to dose rate limitations set by the relevant regulatory authority. The radiation safety officer must be responsible for the safe handling, storage and disposal of radioactive waste.

452 Radioactive waste should be segregated at its source into appropriate categories. Examples of such categories are:

- Short-, medium- and long-lived radionuclides.
- Combustible and non combustible.
- Sharps and syringe needles.
- Carcasses and putrescible wastes.

453 Disposal of radioactive waste should be performed according to the NHMRC Code of Practice for the Disposal of Radioactive Wastes by the User (1985) and in accordance with any other applicable regulations, codes or hospital guidelines such as the NHMRC National guidelines for the Management of Clinical and related Wastes (1988). Individual State or Territory radiation control legislation must also be observed.

454 Needles and sharps should be treated as such but also with radiation protection in mind.

LABORATORIES FOR PREPARATION OF RADIOPHARMACEUTICALS OF PATIENT ORIGIN

460 Preparation of radiopharmaceuticals of patient origin can involve a wide range of operations, from simple labelling procedures to complicated chemical and biological synthesis. It may involve separation and subsequent radioactive labelling of cells from blood samples taken from patients, a process which may take several hours. The quality of the final product is dependent on the way in which all the steps in the procedure have been carried out.

461 When setting up the procedure for labelling autologous blood components or other material of patient origin, it is of the utmost importance for the quality of the radiopharmaceutical that the equipment used, the design of the working area and the laboratory facilities have been evaluated with regard to both pharmaceutical hygiene and radiation protection aspects. The labelling procedures should take place in areas where the product is protected against microbial contamination and against cross-contamination from other biological materials. In practice this can be achieved by using sterile starting materials and utensils and by applying aseptic techniques in work stations fitted with HEPA filters, e.g. contained work stations.

462 In order to avoid biological cross-contamination, only one labelling operation should be performed at a time and other radioactive labelling or dispensing procedures should not take place simultaneously in the same room. A small, separate room or at least a contained work station should therefore be reserved for these operations. A detailed guide to the room requirements for radiolabelling of blood products may be found in Chapter 9.

PHARMACEUTICAL CONTAINMENT ISOLATORS

Design principles

470 All isolators are accessed by a glove port comprising a gauntlet or glove/sleeve arrangement designed to maintain the aseptic environment within the isolator. The transfer of materials should take place via an interlocked isolation chamber that will not compromise the integrity of the work zone. All internal surfaces should be accessible to cleaning and decontamination. The air quality should be Class 3.5 and air should be swept away from the work and transfer zones.
Type 1 isolators should operate at positive pressure and Type 2 isolators should operate at negative pressure with respect to the background environment. Air supply may be laminar, turbulent or a combination of the two. Pressure differentials and air flow should be monitored. Isolators for radiopharmaceuticals should incorporate radiation protection. Discharge air should be handled in accordance with Australian standards. To ensure integrity of the background environment in the event of a breach of a Type 2 isolator, the exhaust fan should be capable of maintaining inward air flow with one gauntlet removed.

Siting of isolators

471 Isolators should be sited in a dedicated room with a high standard of hygiene. Interim Australian Standard AS/NZS 4273(Int): 1995 "Guidelines for the design, installation and use of pharmaceutical isolators" should be consulted.

Control and monitoring

472 Containment is a function of isolator design and maintenance. Standard operating procedures should be prepared for the operation, maintenance, operator training and performance monitoring of isolators.

ASEPTIC SUITES FOR COLD KIT MANUFACTURE

Design criteria and general principles

480 Since protection of the operator from radiation is not of concern for cold kit manufacture, the design of the cleanroom should follow the principles for product protection only. In this mode, clean (first) air is directed over the product so that it is not subjected to contamination. A laminar flow cleanroom complying with AS 1386.2, or a laminar flow workstation complying with AS 1386.5 and installed in accordance with AS 1386.7 in a Class 350 cleanroom will provide this degree of protection.

481 A minimum specification for environmental design and control is given in Annex 1 of the EU GMP Guide for Medicinal Products. Air quality is specified in terms of Australian Standard AS 1386-1989: Cleanrooms and clean workstations. This should be used as a reference for guidance on clean space control and on the design, installation, operation and inspection of clean work stations and cleanrooms generally. The grades of air quality can be found in the EU document. The minimum grade of air quality for particular operations should on pages 62 and 63 of that Guide. Further cGMP references are shown as < >.

482 Processing should be conducted in a cleanroom suite constructed and operated in accordance with AS 1386 parts 1, 3, 6 and 7. Cleanrooms should be effectively flushed with air supplied under positive pressure, delivered through HEPA filters <1204> and directed to obtain the cleanest air at the critical work areas. As contaminants are entrained, they are then conveyed downstream of work zones in the room for dilution or removal or both. These criteria generally result in the introduction of large quantities of air at low velocities into the clean space and in a unidirectional movement, usually downward or across the room, prior to removal.

483 Cleanrooms should be provided with suitable anterooms or equivalent separation facilities through which staff or articles may enter or leave. Separate rooms for the compounding of bulk solutions are preferred <1206>.

484 Facilities for changing into sterile garments should be structured on the black/grey/white principle as discussed in AS 1386 <1207>.

485 Sterilised articles for use in the cleanroom should preferably enter via a pass-through hatch between the cleanroom and anteroom. The hatch should be arranged so that only one of its doors may be opened at any one time <1212>.

486 Pressure differentials between rooms of specified overpressure should be maintained to at least a 15 Pa difference. This can be monitored by the use of appropriate manometers which are clearly visible <1215>. Readings taken at the beginning and end of sessions should be logged.

487 Cleanrooms and clean work stations should be certified for compliance with AS 1386 before commissioning and thereafter be inspected at least 3-monthly to determine the need for maintenance <1217>.

CENTRALISED DISPENSING

490 The requirements for laboratory and radioisotope laboratory design mentioned above also apply to this type of operation but, as other requirements will also have to be taken into account, a centralised dispensing operation will require premises specially designed for the purpose.
The total area should be large enough to ensure safe handling of both the actual dispensing operations and the paperwork involved. When planning the layout it may be advantageous to divide the area available according to the specific tasks to be performed. For example, this may be achieved by establishing:

- A separate room for aseptic work. Elution of generators, reconstitution of kits and dispensing of radiopharmaceuticals should take place in this room. The room should be provided with a pass-through hatch for introduction of materials and the room should be entered through an airlock with change of clothing facilities.

- A room for measurement of the activity of dispensed products and for labelling and packing dispensed products for distribution inside the hospital or for despatch to departments outside the hospital. This room may also be used to store non-radioactive materials, such as preparation kits, syringes, needles etc. If the room is large enough, it may also be used for the paperwork and for files and records.

- A room for storage of radioactive material. If only small amounts of radioactivity are handled, a store may be satisfactorily placed in the aseptic area. If larger amounts are handled, a separate storage area for radioactive materials should be provided to minimise the exposure of personnel to radiation.

ENVIRONMENTAL SPECIFICATIONS

The premises in which radiopharmacy is practised should meet the following specifications.

**Laboratories**

- Code of Practice for the Design of Laboratories using Radioactive Substances for Medical Purposes (1981), National Health and Medical Research Council, Canberra, ACT. The laboratory will either be a Type B (medium level) or Type C (low level) laboratory.


**Aseptic dispensing suites**

- Australian Code of Good Manufacturing Practice for Therapeutic Goods, Medicinal Products (August 1990), Therapeutic Goods Administration, GMP Audit and Licensing Section, Department of Community Services and Health, Canberra, ACT, Australia.

**Standards for cleanrooms and isolators**

The Australian Standards to be followed for non-laminar cleanrooms are:

- AS 1386.1 through AS 1386.6-1989. Cleanrooms and clean workstations.


- AS 1217-1985. Acoustics - Determination of sound power levels of noise sources.

- AS/NZS 4273 (Int.):1995. Guidelines for the design, installation and use of pharmaceutical containment isolators.

**Standards for laminar flow cabinets**

**Horizontal laminar flow cabinets**


- AS 1217-1985. Acoustics - Determination of sound power levels of noise sources.

• AS 1807.4 through 1807.25-1989. Cleanrooms, workstations and safety cabinets.
• AS 1217-1985. Acoustics - Determination of sound power levels of noise sources.

Cleanroom garments

• AS 2013.1-1989 Cleanroom garments product requirements.
• AS 2013.2-1989. Cleanroom garments processing and use.
• AS 1807.19-1989. Sizing and counting of particulate contaminants in and on cleanroom garments.
CHAPTER 5: INSTRUMENT CALIBRATION AND TESTING

GENERAL

Autoclaves and ovens

500 The sterilising efficiency of autoclaves and hot air ovens should be verified using biological, physical or chemical indicators and temperature-time graphs at appropriate intervals.

Analytical balances

501 The accuracy of analytical balances should be tested periodically using standard masses and the results recorded. Regular maintenance and servicing should be performed.

Survey meters

502 Contamination from radioactive substances throughout the workplace may lead to personnel exposure resulting from external exposure and/or internal exposure arising from inhalation, ingestion or entry through surface wounds. Survey meters should be used to monitor such contamination. Prior to use, the performance of the meter should be checked against a long-lived reference source.

Guidelines on the evaluation of surface contamination and recommendations on the selection of the type of monitor to be used may be found in the NHMRC publication: Recommended limits on radioactive contamination on surfaces in laboratories (1995), RHS No. 38.

Dose-rate meters

503 Dose-rate meters should be used to monitor the radiation exposure arising from radiation sources. The calibration of these meters should be checked annually by comparing their response with those of meters which have been calibrated against a national or secondary standard. Performance of the monitor can be tested by measuring its response to a known activity of 99mTc in a standard geometrical arrangement.

pH meters

504 pH meters and electrodes should be routinely tested with standard buffers before use and the results recorded.

505 pH electrodes should be inspected periodically to ensure that the specified level of internal electrolyte is maintained. Before use in the preparation of products for injection, pH electrodes may be disinfected by immersion in 70% v/v ethanol.

Nitrogen gas supply

506 Nitrogen should be filtered through a 0.2 micron pore size filter before use in order to remove possible microbial contamination and particulate residues from the cylinder. On procurement of each nitrogen cylinder, it is recommended that the gas be tested for the presence of anaerobic bacteria using Sterility Medium No. 1 (see Australian Code of Good Manufacturing Practice, Appendix C). All samples should be incubated for 14 days at 32 ± 2°C.

DOSE CALIBRATORS

Introduction

510 The radionuclide dose calibrator is the primary instrument used for the measurement of the radioactivity in radiopharmaceuticals and is an essential instrument in any clinic or department. BP/USP and other standards usually require that the radioactivity administered to patients must be measured to within ± 10% of the actual value. The instrument normally used for the measurement is a well-type ionisation chamber. This section is restricted to the use of this type of apparatus for the assay of total radioactivity and describes procedures that may be used for acceptance testing and ongoing quality control.

Location of calibrator

511 The ionisation chamber should be located in a stable, vibration-free, low-background area. For stable operation, temperature changes should be kept to a minimum. For this reason, the calibrator should be located away from air conditioning and heating outlets and not in direct sunlight. High humidity should also be avoided.
Measurement of sample geometry and material effects

512 The observed reading for a radioactive source inside an ionisation chamber is affected by the position of the source inside the well, the shape and size of the source (geometric effects) and the amount of self-absorption that takes place in the source itself and in the container. As attenuation is highly dependent on photon energy, these effects should be established for each type of sample container (vial and syringe) and for each radionuclide to be measured in that container.

Procedures:

Sample volume effect

513 Proceed as follows:

- Dispense 1 mL of a radionuclide sample into a clean sample container. Either measure the background activity or adjust the background reading to zero. Measure the activity at the appropriate calibrator setting.

- Add 1 mL of saline to the sample, gently swirl the vial to distribute the radioactivity and measure the activity.

- Repeat this process until a volume equal to or greater than the largest volume to be measured is reached.

- If a variation with volume is observed, prepare a plot of correction factor vs sample volume.

Note: After each measurement, the container should be removed from the sample holder and then replaced for measurement. If the discrepancy is greater than 1% the process should be repeated until concordant results are obtained.

Sample position effect

514 The sample holder should be designed to ensure a reproducible measurement position. The effect of measurement position may be studied by displacing the source horizontally in increments of about 1 cm and remeasuring. Low energy X-ray and gamma emitters are more sensitive in this regard. For this reason, the study should be performed using these radionuclides. If the calibrator is found to be sensitive to slight displacement of the source, steps should be taken to ensure a reproducible measurement position.
Sample container effect

515 The sample container can have a significant effect on the calibration of beta emitters and low energy X-ray and gamma emitters. When new sample containers are introduced, the effect on the calibration should be determined by dispensing measured aliquots of radionuclide solutions into the new vial and a reference vial. The effect of sample volume should also be determined.

The sample container may also have a marked effect on the measurement of radionuclides which emit significant quantities of low energy X-rays, e.g. 123I. In these cases, a filtration device such as copper should be used to reduce the effect of these X-rays on the observed reading.

Shielding effect

516 Backscatter from shielding around the chamber can alter the response to a source inside the detector. The effect of any change in location of a chamber or its shielding should be established by measuring radionuclide sources in the chamber before and after the introduced change. The chamber should be recalibrated with standard sources which are traceable to the Australian National Standard of measurement.

Linearity of response

517 The accuracy of a dose calibrator should ideally be independent of the quantity being measured. Variations may be observed at the high and low ends of the range of the calibrator.

518 Linearity of response may be measured by monitoring the decay of a high activity, high radionuclidian purity 99mTc source. This method, however, may require measurements to be made during the night and also requires the 99Mo content to be estimated so that corrections can be made to the readings obtained at the bottom end of the scale.

The following procedure enables the test to be completed on the same day and does not require any measurement of the 99Mo content. It should be performed using the first eluate of a new 99mTc generator, with careful attention to radiation safety when manipulating the larger activities expected from the first elution of a generator. All weighings should be performed using an electronic balance which may be read to one milligram and which should be located behind a lead glass screen to minimise radiation exposure. Transfer of solution should be made using a 1 mL automatic sampler with disposable plastic tips, taking care to ensure that complete transfer of solution takes place.

The procedure is as follows:

Solution A: Transfer the eluate to a tared vial and dilute the sample to 11 mL with saline. Reweigh the vial and measure the total activity in an ionisation chamber.

Sample 1. Ensure that Solution A is uniformly mixed by gently passing the solution in and out of a 1 mL disposable pipette. Remove 1 mL of Solution A for the preparation of Sample 2 and reweigh the vial. The remaining solution constitutes Sample 1.

Sample 2. Transfer 1 mL of Sample A to a tared vial. Reweigh the vial. Add 10 mL of saline and weigh the vial to determine the quantity added. Ensure that the solution is uniformly mixed by passing the solution in and out of a 1 mL disposable pipette tip. Remove 1 mL of the solution for the preparation of Sample 3 and reweigh the vial. The remaining solution constitutes Sample 2.

Repeat the process of consecutive dilution until the final solution contains about 30 kBq/mL. It should also be noted that only 9 mL saline should be added to the final solution to maintain the sample volumes at 10 mL.

Ensure that the background measurement is zero prior to making measurements on samples. Measure all samples using the 99mTc setting.

Calculate the expected activities of Samples 2 onwards using the measured activity of Sample 1. If deviations of greater than 5% are found, repeat the preparation of all samples to confirm that the discrepancy has not arisen from a dilution error in the preparation of the standards. Variations in excess of ± 5% usually indicate the need for adjustment or repair.

Notes

1. Departures from linearity may be intrinsic to the instrument. At the high end of the scale, departures may be
...
2. It should be noted that the maximum activity that can be assayed with a given ionisation chamber is radionuclide-dependent. If measurements are to be made with other radionuclides at the activities comparable to or greater than that measured for 99mTc, the linearity of response should also be measured for those radionuclides.

Accuracy

519 Where possible, instrument calibration should only be performed using standards traceable to the Australian National Standard*. As the ionisation chamber reading can vary with the type of measurement container, particularly with low energy gamma emitters, standards should be obtained in the container used for laboratory measurement of activity. For standards obtained in this form:

1. Place the standard in the ionisation chamber using the appropriate radionuclide setting and measure its activity. Record the measured activity and time.

2. Repeat the measurement five times, each time removing and then replacing the standard in the sample holder before making the measurement.

3. Calculate any discrepancy between the dose calibrator reading and the calculated activity as a percentage of the quoted activity. If this discrepancy is greater than 0.5%, adjust the ionisation chamber setting to give the correct result.

4. Measure the long-lived reference standard at the new setting.

* Maintained by the Radiation Standards Project at ANSTO, Private Mail Bag 1, Menai NSW 2234, Australia.

520 If the standard has been obtained in a non-standard container, measure the activity in the non-standard container as in steps 1-4 above. Then accurately transfer a weighed aliquot of the standard solution to an appropriate container and again proceed as in steps 1-4 above. Suppliers of reference standards should provide the activity per gram of the reference solution.

521 Standards are not readily available for all radionuclides in use in nuclear medicine. Where they are not available, a long-lived source should be measured at each radionuclide setting.

Note: Simulated sources should not be used for measuring accuracy. They may, however, be used as a routine check source for the instrument.

Reproducibility

522 Daily: A measurement of at least one long-lived reference source should be made daily using the setting used for the most commonly used radionuclide. Variations of more than ±3% from the expected value should be investigated.

The expected value should initially be the mean of at least the first ten measurements.

The source used should have negligible short term decay and have a gamma energy between 100 and 1000 keV. The activity should be high enough to produce an adequate ionisation current, e.g. for $^{137}$Cs, 10 MBq; or for $^{226}$Ra, 2 MBq. The use of sealed, solid sources will prevent accidental spillage.

523 Quarterly: Place the long-lived source in the ionisation chamber and record the measurement at one radionuclide setting. Remove and replace the source and if the reading is unchanged record the reading at each of the radionuclide settings. If repeated measurement gives deviations exceeding ±5% at any setting, the instrument must be recalibrated or repaired. An abnormally high reading may indicate contamination of the source and a wipe test should be performed. Discrepancies at one setting may be the result of an incorrect setting, an instrument fault or radioactive contamination.

Acceptance testing

524 Initial testing should confirm that the manufacturer's specifications for accuracy, reproducibility and linearity of response are achieved. Sample geometry effects for all radionuclides for all container types should be established. In addition, the quarterly reproducibility test should be performed. These readings form the basis for ongoing quality control. Acceptance tests should also be applied to calibrators immediately after they are repaired, again using standard sources for the accuracy tests.
The calibration factors provided by the manufacturer of a dose calibrator are unlikely to be traceable to the Australian National Standard and will often not correspond to the actual geometries being used. Standard sources should be used to calibrate the instrument. These sources should be in the same form as the solutions typically being measured (i.e., same container and same volume of solution).

525 Recommended testing frequencies for quality control:

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproducibility check</td>
<td>Daily</td>
</tr>
<tr>
<td>Linearity of response</td>
<td>Quarterly</td>
</tr>
<tr>
<td>Sample geometry As part of effects</td>
<td>Acceptance and then if change in geometry occurs</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Annually</td>
</tr>
<tr>
<td>Battery</td>
<td>Quarterly</td>
</tr>
</tbody>
</table>

**Documentation**

526 The documentation system should be designed to demonstrate that calibration can be traced to the Australian National Standard and that this calibration is maintained throughout the life of the instrument. Records which demonstrate the constancy of calibration may be kept either as tabulated data or in the form of a graph. Actual readings, with times and dates, should be recorded or plotted; it is not acceptable to record that the reading of the long-lived standard lies within a standard range.

527 Records should be kept of all instrument service and maintenance, reported faults, instrument relocation and any alterations made to shielding. All records should be retained for the life of the instrument.

528 Sources for use in calibration and quality control of dose calibrators
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Photon Energy (keV)</th>
<th>Photon abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{57}$Co</td>
<td>271d</td>
<td>122</td>
<td>85.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>137</td>
<td>10.6</td>
</tr>
<tr>
<td>$^{133}$Ba</td>
<td>10.7y</td>
<td>81</td>
<td>33.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>303</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>356</td>
<td>62.1</td>
</tr>
<tr>
<td>$^{137}$Cs</td>
<td>30y</td>
<td>662</td>
<td>89.8</td>
</tr>
<tr>
<td>$^{60}$Co</td>
<td>5.27y</td>
<td>1173</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1332</td>
<td>100</td>
</tr>
</tbody>
</table>

References:


GAMMA COUNTERS

530 Gamma counters are used in a nuclear medicine department for a range of applications. Typical uses include the counting of radioimmunoassay samples, specimen counting, counting of swabs taken as part of a contamination monitoring program and counting of quality assurance samples e.g. strips from a thin layer chromatogram (TLC). As the counter may be required to measure a number of different radionuclides over a wide range of activities, careful consideration should be given to the required uses when selecting the type of gamma counter for a radiopharmacy.

531 Most gamma counters use a sodium iodide (thallium activated) crystal as a scintillation detector, usually in the form of a well counter. Crystal sizes vary depending on the gamma energies of the radionuclides to be counted and sometimes large crystals are used because of a need to count high volume samples. Some gamma counters are designed for the counting of iodine-125 radioimmunoassay samples and may be unsuitable for counting high energy gamma emitters. Essentially all gamma rays with energies less than 200 keV are detected by 2.5 cm of sodium iodide surrounding the sample. If higher gamma energy samples are to be counted, then larger detectors should be considered.

532 Gamma counters used in nuclear medicine are usually single channel or dual channel pulse height analysers. The following procedures for acceptance testing and ongoing quality control may be used to assure the satisfactory performance of both manual and automatic gamma counters. It should be noted that instrument design may prevent the performance of some of these tests.

Acceptance testing

533 The following tests are recommended:

- Performance of scaler and/or ratemeter with 50 Hz or 60 Hz test facility.
- Energy calibration using a reference $^{137}$Cs source.
- Linearity of energy response using $^{137}$Cs and $^{129}$I and a range of reference radionuclides which cover the energy range to be used.
- Counting efficiency of a long lived reference source e.g. $^{137}$Cs.
- Precision by repetitive counting of reference source.
- Radiation shielding effectiveness by measuring the effect of a high activity source on the counting of a background tube. The effect of this source in sample counting positions close to the tube should be determined and measured in positions increasingly remote from the background tube being counted.
until the effect on the background counting rate is negligible. This effect should be determined for all radionuclides to be counted in the system.

- Integral background above a fixed threshold e.g. 20 keV.

- Linearity of count rate. This may be achieved by counting 1 mL aliquots of a series of reference $^{99m}$Tc solutions prepared as in 518. It is suggested that the radioactive concentration of the initial solution be no more than 1 MBq/mL.

Note: The count rates over which the system remains linear must be established if high activity samples are to be counted e.g. counting of TLC strips obtained in QC of $^{99m}$Tc cold kits.

- Dependence of count rate on sample volume and counting position (where it is adjustable). These effects should be determined for every type of sample container to be used and for every radionuclide to be counted in the system.

- Confirmation of the accuracy of any preset counting conditions by determining the counting efficiency of a reference source and comparing it with instrument specifications.

- Energy resolution by measuring the full width at half maximum (FWHM) of a reference 137Cs source.

**Performance monitoring**

534 The following test schedule is recommended:

<table>
<thead>
<tr>
<th>Test frequency</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirm background for radionuclide setting being used.</td>
</tr>
<tr>
<td>Monthly Scaler and/or ratemeter performance.</td>
<td>Energy calibration.</td>
</tr>
<tr>
<td></td>
<td>Integral background.</td>
</tr>
</tbody>
</table>

Reference:

CHAPTER 6: DOCUMENTATION

GENERAL

600 A carefully prepared and maintained documentation system is a central feature of an effective quality management system.

601 The objectives of the documentation system are:

- to define the operations of the operating unit and the control system;
- to minimise the risk of misinterpretation and error inherent in oral or casually written communication;
- to provide unambiguous procedural methods;
- to provide evidence of product performance and administration;
- to allow calculations to be checked; and
- to allow complete traceability of the history of each material, including checks, tests and disposal.

DOCUMENT GENERATION, ISSUE, RETRIEVAL AND STORAGE

610 The system should include a written procedure for the generation, issue, retrieval and storage of controlled (authorised) and working documents. Documents should be kept up to date. A copy of superseded documents should be filed for reference.

611 Records should be kept for 6 years from the date of manufacture or, for dispensed materials, for the period determined by hospital policy or relevant legislation. Records of clinical work may require retention for 7 years and those associated with clinical trials, 15 years.

GENERAL PRINCIPLES OF DOCUMENTATION

620 Documents should clearly indicate their source (hospital, department, etc.) and, where relevant, authorising person(s) and the date of authorisation. Authorisation should usually include the person responsible for quality assurance.

621 Documents should contain all necessary, but no superfluous, data. The level of detail in a document which gives instructions or procedures should be commensurate with the level of skill, qualifications and training of the person(s) normally expected to perform the activity. Instructions should be clear, unambiguous and easy to follow. Documents which require data entry should:

- clearly indicate what is to be entered;
- provide sufficient space for the entry;
- provide for signature and date of the entries; and
- allow adequate space between entries and space for comments.

622 Where possible, documents in routine use should be prepared as masters and issued as photocopies or printouts. Corrections or amendments should be initialled and dated and should permit the reading of the original information.

RECORD KEEPING- GENERAL

630 Complete records of all aspects of radiopharmaceutical procurement, preparation, utilisation and disposal should be maintained. The following aspects of radiopharmacy should be comprehensively documented:

- Radionuclide acquisition, in particular the documentation of the histories of radionuclide generators from receipt to disposal.
- Acquisition and quality control of reagents and cold kits and manufacturing records of in-house cold kit production, as detailed below:
- Chemical assays of starting materials.
- Supplier, supplier's batch number, purchase date.
- Formulation master sheet, quality control testing schedules.
- Date of manufacture, batch number.
• Date of release, expiry date, sample of label.
• Operator or authorised signatory who released the batch.
• Radionuclide, radiochemical and radiopharmaceutical quality of generator eluates, reconstituted cold kits, purified radiopharmaceuticals, etc. For commercial materials, these records are normally retained by the manufacturer. The tests may be repeated at the discretion of the user.
• Retrospective sterility and pyrogen testing, where indicated, of radiopharmaceutical residues.
• Individual patient doses, including patient identifying name and file or unit record number.
• Acquisition and quality control of reagents and cold kits, including records of any quality control results from the manufacturer.
• Records from in-house manufacturer
CHAPTER 7: MANUFACTURE OF STERILE COLD KITS

INTRODUCTION

700 This section sets out requirements relating to the manufacture of cold kits which are intended to be sterile in their finished usage form. The manufacture of these kits involves special requirements to avoid the risk of microbial, pyrogen and particulate contamination.

701 The guidelines in this section are based upon the Annex 1 of the EU GMP Guide for Medicinal Products (1997) and should be read in conjunction with this document.

ENVIRONMENTAL CONTROL

710 The design criteria and general principles for environmental control are given in clauses 480-487 and 492. Important details are highlighted below:

- Clean, sterilised protective garments should be provided at each work station.
- Access to cleanrooms should be restricted to the minimum number of authorised personnel.
- Microbial and particulate contamination should be controlled and monitored by a comprehensive standard operating procedure.
- Cleanrooms and related areas should be cleaned frequently and thoroughly.
- Where disinfectants are used, the choice of these agents and the way they are used should be as described in clauses. These agents should be supplied sterile.
- Cleanrooms and related areas should be monitored at planned intervals:
  (a) for airborne and particulate contamination and
  (b) for microbiological contamination, using a combination of air sampling, "settle plates" and surface sampling techniques.

711 Laminar flow workstations should comply with the requirements of AS 1386.5 and 1386.7: Cleanrooms and clean workstations; and those used for aseptic dispensing should be fitted with visual and/or audible warning devices to indicate the failure of the air supply.

712 Isolators should be designed, sited and controlled in accordance with AS/NZS 4273(Int): 1995- Guidelines for the design, installation and use of pharmaceutical isolators (see also clauses 470-472).

EQUIPMENT

720 Equipment for the manufacture and quality control of radiopharmaceutical cold kits should be designed, located and maintained to suit its intended use.

721 Equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed written procedures and stored only in a clean condition.

722 Ultraviolet lamps should not be used for air disinfection.

723 Freeze driers should be well instrumented and provision made to load and unload them under clean air conditions.
PERSONNEL, TRAINING, HYGIENE AND CLOTHING

730 Overall responsibility for sterile manufacturing in a radiopharmacy should rest with a radiopharmacist or a suitably trained radiopharmaceutical scientist, preferably with experience in sterile manufacturing and access to a hospital pharmacy and to microbiological expertise.

731 Personnel required to work in clean and aseptic areas should:

- be properly trained in cleanroom procedures and in disciplines relevant to correct manufacture of sterile products, including hygiene and the basic elements of microbiology; and
- maintain high standards of personal hygiene and cleanliness and be instructed to report any condition which may cause shedding of abnormal numbers or types of contaminants.

732 Clothing should be appropriate to the work zone environment in which the personnel will be working and should conform to AS 2013-1989: Cleanroom Garments <1406>.

DOCUMENTATION AND RECORDS

740 Appropriate documentation should be prepared for sterile manufacturing of cold kits based upon the requirements outlined in the cGMP. Specifications should be prepared for all starting materials, packaging materials, intermediate products and final products. Standard operating procedures for all aspects of cold kit production should be prepared in accordance with the cGMP, be updated whenever necessary and be reviewed annually.

741 For cold kit production, an ingredient "unique identifying number" and a product batch number system should be used. Records should provide a history of each starting material and batch of cold kits including preparation, quality control procedures, labelling and release specifications.

742 A log book of sterile operations should be kept. Every sterile operation should be logged, showing as much detail as is available, including dates, times, process checks, batch numbers and operator's name.

743 All temperature control charts for autoclaves should be retained as part of the processing records.

MANUFACTURING PROCEDURES

750 Except where safety considerations require that initial preparatory steps be carried out in a biohazard cabinet or other safety apparatus, all processes involving the manufacture of sterile cold kits, including the fractionation of cold kits, should be carried out inside a pharmaceutical laminar flow work station situated in a Grade C cleanroom. Air quality inside the cabinet should be no less than Grade A as specified in Annex 1 EU GMP.

751 Where an isolator is used for the manufacture of sterile cold kits, this unit should be located at least in accordance with AS/NZS 4273(Int): 1995- Guidelines for the design, installation and use of pharmaceutical isolators, but preferably inside a room supplied with air through filters certified to have a peak arrestance of at least 80% when tested by AS 1132-1973 using No. 1 dust <115>.

752 The chemical identity of starting materials should be verified according to methods specified in the BP or USP, where available. However in most instances methods will have to be sourced from other references, e.g. The Merck Index, or other sources such as manufacturers' data. These materials should be tested for chemical purity and the presence of heavy metal contaminants. All materials should be handled as outlined in starting materials control <640-653>, in such a way that identity, potency and purity are guaranteed.

753 All water used for cold kit preparation must be at least of the quality of Water for Injections BP: other requirements may also apply.

754 All saline used for cold kit preparation should be of the quality of 0.9% w/v Sodium Chloride for Injection, BP or USP.

755 Where stannous salts are used in cold kit manufacture, bulk solutions should be maintained under filtered ultra-high-purity nitrogen during preparation. Failure to do so may result in reduced stability of the final product.

756 Methods of sterilisation of all equipment, containers, closures etc. for aseptically processed products should follow accepted standards and procedures.
The method of choice for the sterilisation of bulk solutions used in the preparation of sterile cold kits is by filtration. All filters should undergo a filter integrity test, using a calibrated bubble-point apparatus after the filling cycle is complete. The result should be logged.

757 General procedures may be found in the cGMP Section 16.

**LABELLING**

760 The label on the container should comply with the Therapeutic Goods Order "General Requirements for Labels for Drug Products" and should therefore include:

- the approved name of the product (and any product identification code)
- the (quantitative) composition
- the name of the manufacturer
- instructions for reconstitution or a reference to the location of these instructions
- storage conditions
- the batch number
- the expiry date.

Where applicable the ARTG number must appear on the label of the primary pack.

Additional information may be required to meet regulatory and user requirements. Regulatory requirements for products to be administered parenterally may be found in the "Australian Guidelines for the Registration of Drugs".

**QUALITY CONTROL**

**Test for sterility**

770 A sterility test as outlined in the BP/EP: “Guidelines for Using the Test for Sterility” should be carried out on samples of each batch of sterile cold kits. Results should be attached to the appropriate batch manufacturing record.

**Test for pyrogens**

771 Pyrogen testing should be carried out routinely on each batch of cold kits where products of human/biological origin are used as starting materials (e.g. human serum albumin) or where the label states that a product is apyrogenic. Routine pyrogen testing is not required for other cold kits where the total volume administered is below 15 mL. However, a pyrogen test should be carried out on each batch where new starting materials are being used.

**Other tests**

772 The following tests should be performed on a representative sample from each batch of product as outlined in Chapter 10:

- pH.
- Stannous/total tin assay.
- Radiochemical purity of the labelled product.
- Particulate characteristics (where appropriate).
- Quantitative physiological biodistribution.

**QUALITY ASSURANCE**

**Batch and release specifications**

780 A product specification is the specification that a radiopharmaceutical must meet at the time of administration to the patient. Specifications given in monographs in the BP or EP are product specifications and should be the minimum acceptance standard for the product except that if the product is not the subject of a BP or EP monograph, then a USP monograph, if available, should be used. Any adoption of a less stringent specification should be documented and the rationale for the amendment established. For other products, appropriate specifications should be established based on the requirements of the diagnostic or investigational procedure. In establishing these specifications, consideration should be given to the effect of both radiochemical and radionuclidic purity on the radiation dosimetry of the product.
Release specifications should be written in the light of information on product stability so that appropriate allowance is made for any decomposition that may occur between the time of product release and the time of product expiry.

The decision to release a batch of sterile cold kits for use should take into account not only the above criteria, but also the cumulative test records and information gathered before and during its manufacture from the monitoring of the environment, personnel, equipment and processes. Release should be a formal, documented step.

**Validation of aseptic processing**

781 Aseptic processing and filling procedures should be validated for their overall performance (and environmental controls verified) at the time of qualification and at regular intervals using appropriate test runs <1635>.

782 Test runs should be carried out as outlined in the cGMP. A predetermined number of vials should be filled with a suitable culture medium, exactly mimicking the manufacturing procedure for cold kits. The vials should then be incubated for at least 14 days at 32 ± 2°C and examined for signs of microbial growth. Full microbiological test controls should be carried out.

783 Due to restricted batch sizes of cold kits produced in hospital radiopharmacies, a smaller number of containers than the 3000 prescribed in the cGMP may be used in each run to avoid an exaggerated and atypical fill period. The results of small runs are not additive statistically but together add to sterility assurance.

784 Revalidation should occur at least once per year. The nature and duration of the run should be sufficient to cover all manipulations that are normally performed in actual processing.

**GAMMA STERILISATION**

790 Cold kits may be sterilised by gamma irradiation. Where this method of sterilisation is to be used, the effects of the irradiation on the kit components should be studied. This may be achieved by subjecting the kit to at least three times the sterilising dose and examining the effect of this irradiation on both the chemical purity of the kit and on the behaviour of the reconstituted radiopharmaceutical prepared using the kit.

Residual moisture in freeze-dried products may have an adverse effect on the stability of kit components during irradiation. Moisture content should thus be carefully controlled in lyophilised kits that are gamma sterilised. It should also be noted that very few preservatives will survive gamma irradiation in the liquid state. The effect of gamma irradiation on preservatives used in kits to be stored in the frozen state should therefore be studied.

Additional requirements for sterilisation by gamma irradiation may be found in clauses 1627-1629 of and in Appendix A to the Australian Code of Good Manufacturing Practice- Medicinal Products.
CHAPTER 8: HOT LAB PROCEDURES

DISPENSING- GENERAL

800 Radiopharmacy practice can be assigned to one of the following four levels:

1. Dispensing of individual patient doses from ready-for-use radiopharmaceuticals.

2. Reconstitution of radiopharmaceuticals from radionuclide generators and reagent cold kits and blood cell labelling.

3. Centralised radiopharmacy (reconstitution and dispensing).

4. Manufacture of cold kits and other radio-pharmaceuticals.

801 Each preparation should be performed in accordance with an approved written procedure which should be safe, straightforward and reliable. Where possible, methods should be devised in which all the components required are contained in presterilised vials with the only manipulative procedure being aseptic transfer between vials using syringes. Methods requiring manipulation in open containers should be avoided. The number of cap punctures should be kept to a minimum to prevent coring and shedding of particles. Closures should be swabbed with an appropriate bactericide each time an entry is made.

802 Each finished preparation that is to be distributed outside the hospital should carry a label showing:

- that the contents are radioactive
- the Approved Name of the radiopharmaceutical
- the (quantitative) composition
- (for liquid radiopharmaceuticals) the total radioactivity (in SI units) or the radioactive concentration per mL at a stated date and time; or (for capsules) the radioactivity of each capsule (in SI units) at a stated date and time and the number of capsules in the container (for liquids) the total volume in the container
- the route of administration
- (for radiopharmaceuticals to be administered parenterally) the name and concentration of any antimicrobial preservatives
- the manufacturer's name
- the batch number
- the expiry date.

Additional information may be required to meet regulatory and user requirements. Regulatory requirements for products to be administered parenterally may be found in the "Australian Guidelines for the Registration of Drugs".

Where the preparation is to be administered within the hospital, it may be appropriate to omit certain of these items but addition of dispensing information such as hospital department and contact number may be required.

803 Careful attention to technique should be given to prevent cross-contamination between products during reconstitution or dispensing procedures.

804 Contingency plans for dealing with any foreseeable emergency situation involving radioactivity should be written down, displayed and known by personnel.
HOT LAB PROCEDURES

Consignment arrival

810 On arrival, packages containing radioactive materials should be inspected for signs of damage and monitored with a survey meter for leakage. A wipe test should be performed to determine radioactive contamination on the surface of any shipment container and any leakage should be reported to the supplier. Serious spills may require evacuation of the area before any cleanup is undertaken and should be first reported to the radiation safety officer.

Daily schedule

811 A qualified and responsible person should be designated to review the schedule of diagnostic and therapeutic procedures to be performed in the nuclear medicine department and ensure that appropriate radiopharmaceuticals are available. The following steps should be taken.

Selection of appropriate agents

812 Radiopharmaceutical cold kits (commercial or in-house) or individually formulated products should be selected for the procedures.

813 Diluents used to adjust the concentration of radiopharmaceuticals should be of BP or USP specification or better.

Preliminary activities

814 The work area should be prepared and set up by covering surfaces with plastic-backed absorbent material and laying out needles, syringes, shields, forceps, diluents, gloves and other necessary items.

815 Radionuclides, kits and diluents should be checked for identity, expiry time/date and appearance.

816 Identifying labels with a dated batch number should be affixed to reagent vials and shielding containers prior to the addition of radioactive material.

817 A radiopharmaceutical record sheet should be maintained for each batch of material. The record should include batch numbers, manufacturer, date received, expiration time/date, preparation procedure, quality assurance, and calibration results. Each dose from this batch should be recorded with the time, activity, dose volume and patient's name/file number.

818 Appropriate shielding should be selected.

819 Components, labels and equipment should then be rechecked.

Elution of generator

820 Before preparing radiopharmaceuticals with generator-produced radionuclides, the generator should be eluted and processed as follows:

821 An appropriate sterile/pyrogen-free vial for receipt of eluate and an appropriate lead pot or shielding container should be selected and both are labelled.

822 The generator should be eluted in accordance with the manufacturer's instructions, using aseptic technique.

823 Where the manufacturer guarantees the sterility of the eluate, appropriate precautions should be taken to maintain sterility.

824 Where the manufacturer does not guarantee the sterility of the eluate, the eluate should be sterilised by autoclaving (according to BP specifications or their equivalent) or filtration through a 0.2 micron filter into a sterile vial. The integrity of the filter should be checked by a calibrated bubble-point apparatus.

825 The total radioactivity should be measured and volume and calibration time noted. These data should be recorded on a daily worksheet, or similar. A test for parent breakthrough should be carried out.

Reconstitution of radiopharmaceuticals

826 The amount of radiopharmaceutical required for each procedure should be calculated and the quantity adjusted.
diluted if necessary. The withdrawal of the required activity and subsequent reconstitution of the kit should be performed either using a shielded syringe or behind a lead glass screen. Calculations should be checked, and the activity, volume and time recorded.

827 Using aseptic technique, the eluate should be used to reconstitute the radiopharmaceutical in accordance with the established protocols or manufacturer's instructions.

828 A visual inspection of the preparation through a lead glass shield or a shielded polarised light box should be performed to confirm that the appearance complies with specification. The total activity of the vial should be measured and the activity, calibration and expiry times calculated and recorded.

**Dosage levels**

829 Dosage levels should be determined based on patient history, age, weight, sex and surface area.

**Aseptic dispensing**

830 Dispensing procedures or labelling of blood components should be carried out in an aseptic environment (refer Chapter 9).

831 Each dose should be calculated, aseptically withdrawn and measured prior to administration.

832 Care should be taken to ensure even distribution of particulate radiopharmaceuticals prior to withdrawal.

833 Unless otherwise indicated, care should be taken to prevent, as far as possible, ingress of air into products containing stannous ion or any other reducing agent.

834 Most guidelines recommend random retrospective sterility testing on radiopharmaceutical residues in order to monitor aseptic operations involved in reconstitution of cold kits and withdrawal of patient samples. However, there are two serious restrictions to this kind of testing: the results may engender a false sense of security unless the test is performed at once, i.e. under "hot" conditions and small numbers of samples will not yield statistically significant results. Operator training and qualification are more important. Pyrogen testing will seldom be necessary in view of the small volumes usually involved.
Correct administration

835 Appropriate steps should be taken to ensure that the intended agent, in the intended dose, in the intended dosage form is received by the intended patient at the intended time via the intended route of administration.

836 Safe work practices ensuring that there is no possibility of re-use of syringes or needles should be followed.

TECHNETIUM-99m GENERATORS

840 Technetium generators should be sited in a clean area away from general traffic. Additional lead shielding may be required to reduce the external dose rate to acceptable levels (see also clause 450).

841 On arrival, the package should be inspected for obvious signs of damage during transit. The surface dose rate should be measured with a dose-rate meter. An external dose rate above 2 mGy/hr may indicate internal damage or leakage of radioactive solution.

842 The generator should be installed according to the manufacturer's instructions. It is recommended that an elution be performed as soon as practicable so as to limit $^{99}\text{Tc}$ in subsequent elutions.

843 All elutions should be performed according to the manufacturer's instructions. $^{99}\text{Mo}$ breakthrough should be measured on all eluates. The lead pot method is the simplest method of measurement of this breakthrough. It should be noted that the presence of $^{132}\text{I}$ in the eluate can give falsely elevated readings for $^{99}\text{Mo}$ breakthrough. An unacceptable breakthrough reading cannot be attributed to $^{132}\text{I}$ unless confirmatory evidence is obtained, preferably by gamma spectrometry or half life determination.

844 Records should be kept of all generator elutions. Records should include:

- Dose calibrator setting where the isotope is manually dialled.
- Reading of long-lived reference source.
- Time of elution.
- Volume of eluate.
- $^{99m}\text{Tc}$ activity.
- $^{99}\text{Mo}$ breakthrough reading.

845 Sudden changes in $^{99}\text{Mo}$ breakthrough or elution efficiency may indicate generator problems and should be investigated.

846 At periodic intervals, after the completion of the generator working life, an elution should be performed and the eluate subjected to a sterility test to provide an assurance of satisfactory operator technique.

RADIOLABELLING - IODINATION

850 Radioiodination reactions ($^{123}\text{I}$, $^{125}\text{I}$ and $^{131}\text{I}$) should be performed in a centralised facility and by procedures approved by a radiation safety officer. State regulations relating to handling, storage and disposal of radioactive waste must be followed. Additional information is provided in the NHMRC "Code of Practice for the Disposal of Radioactive Wastes by the User: 1985".

851 Iodine labelling is usually performed with a reductant-free solution of radioactive sodium iodide supplied in a small volume of 0.1 M sodium hydroxide. A small fraction of the radioactivity is almost always present in a volatile form and escapes when the vial is opened. For this reason, all labelling operations must be performed either in a hot cell, in a well ventilated fume cupboard or in a small Perspex labelling hood in which the air is continually recirculated through an activated charcoal filter. With this latter system, the effectiveness of the charcoal filter should be regularly monitored and the filter replaced whenever necessary.

852 Because of the long physical and biological half lives of the iodine radionuclides, operators should take precautions to minimise exposure, skin contamination and inhalation. Gloves, gowns etc. should be checked for contamination. Thyroid gland activity should also be monitored. Standard operating procedures should exist for the handling of spills and contamination.

853 Radiation shielding must be designed to minimise the radiation exposure of the operator and to preserve the integrity of the labelling operation. Preparation of $^{131}\text{I}$ therapy doses has the potential to result in high radiation doses to the operator. Techniques should be developed using either non-active or low activity preparations. Low activity preparations should be used to assess the potential radiation hazards of the procedure.

POSITRON EMISSION TOMOGRAPHY (PET)
Many radiopharmaceuticals used in positron emission tomography (PET) are prepared using the short-lived radionuclides fluorine-18 (t1/2 = 10 min), carbon-11 (t1/2 = 20 min), nitrogen-13 (t1/2 = 10 min) and oxygen-15 (t1/2 = 2 min). With the exception of $^{18}$F, because of the very short half lives involved, the preparation of the radiopharmaceutical must take place either in the medical institution or nearby. This section refers to the preparation and quality control of short-lived radiopharmaceuticals at such institutions. PET radiopharmaceuticals prepared using longer-lived radionuclides should be treated in the same manner as conventional radiopharmaceuticals and the criteria set out in other parts of this document apply.

861 In general, the principles set out in other parts of this document apply also to radiopharmaceuticals prepared using short-lived radionuclides. As it is not possible to fully test these preparations prior to patient administration, the preparation process and its controls must be thoroughly validated.

Starting material specifications and testing

862 Written specifications, testing procedures, suitable storage conditions and expiry dates should be established for all materials and components used in the manufacture and testing of the product. As the quality of the target material directly affects radionuclidic purity, acceptance testing must be performed by the PET centre. The reliability of all suppliers, particularly suppliers of critical components, should be established. Where possible, critical components e.g. target materials, should be purchased only from a single reputable source.

863 Where possible, certificates of analysis, performance testing etc. should be obtained from the supplier. If these are not available, testing should be made to full specification.

Product and release specifications

864 Release specifications are the criteria for supply of the product for patient use. Because of the short life of the product, release may be based on a limited number of tests. Other tests may be performed subsequent to patient use to confirm the suitability of the product. Release specifications must be written in the light of information on product stability so that appropriate allowance is made for any decomposition that may occur between the time of product release and the time of administration to the patient.

865 For radiopharmaceuticals labelled with a radionuclide for which the half life is greater than 20 minutes, it is recommended that the following release tests be performed on every batch of product:

- pH.
- Appearance.
- Radiochemical purity.
- Specific activity (where there are toxicity concerns or where the localisation is mass-dependent).

866 For radiopharmaceuticals labelled with a radionuclide for which the half life is less than 20 minutes, it is recommended that the above tests be performed on the first preparation of each day.

867 It is recommended that a sterilising filter integrity test be performed for each batch prior to patient administration. In cases where there are several preparations passed through the filter on the same day, the filter integrity test should be made after the final preparation of the day has been passed through the filter.

868 Sterility, apyrogenicity, chemical, radionuclidic and radiochemical purity should be determined as part of the final quality control testing during the validation of the preparation procedure and for the initial production batches. If the product remains within satisfactory limits during this time, the testing frequency may be reduced. A documented sampling program of testing for sterility, pyrogenicity, chemical purity and radionuclidic purity should be established and reviewed periodically.

Reasons should be sought for any failure to meet specification. In the event of a critical failure e.g. for sterility or radiochemical purity, an investigation should be carried out. Where such an investigation leads to amendment of procedures, revalidation should be considered.

Preparation

869 Written procedures should be prepared for all stages of the preparation of all radiopharmaceuticals. These should be supported by validation studies which demonstrate that they lead to radiopharmaceuticals which meet all acceptance criteria. Particular attention should be paid to the irradiation conditions to establish the effect of changes in any parameter on the radionuclidic, radiochemical or chemical purity of the final product. Critical parameters include beam current, threshold energy, particle energy, isotopic composition of target material, target alignment, irradiation time, composition of backing material and chemical purity of target.
870 Tests should be established to ensure the satisfactory performance of automated equipment. The requirements for computer software may be found in Chapter 12.

871 Where possible, each PET preparation intended for parenteral administration should be subjected to terminal sterile membrane filtration (0.2 micron). Preparations for inhalation should be passed through a 0.45 micron filter to remove larger particulates.

872 Radiation stability should be established for all components subjected to high radiation exposures and appropriate replacement and maintenance schedules established.

Quality control

873 Written procedures should be prepared for all raw material, in-process and final quality testing of the product. All procedures should be supported by documented validation studies.

874 The correct operation of all analytical equipment should be confirmed, using internal and external standards, upon initial installation, repair, change of columns or solvent systems. Guidelines on the use of dose calibrators are given in Chapter 5.

References

2. FDA: Guide to inspections of liquid injectable radiopharmaceuticals used in Positron Emission Tomography (PET), November 1993.

PREPARATIONS FOR THERAPY

880 Because of the physical nature of the radionuclides used and the activities required for therapy, the processes of preparing and dispensing therapeutic radiopharmaceuticals have a greater potential to expose operators to radiation than do the same procedures for diagnosis. Operations should therefore be performed in a controlled area with entry restricted to essential staff only. Careful consideration should be given to the amount of shielding required and the measures to be taken to avoid exposure resulting from internal contamination.

881 Laboratories used for preparation of therapeutic radiopharmaceuticals should meet the requirements set out for hot labs (see Chapter 4) and conform to the following design standards:

- Code of Practice for the Design of Laboratories using Radioactive Substances for Medical Purposes (1981), National Health and Medical Research Council, Canberra, ACT.

882 Additional requirements are similar to those for diagnostic radiopharmaceuticals. However, the following points may need to be considered:

- The introduction of shielding may interfere with laminar flow in a cabinet. Only items of equipment which are needed for the preparation to be performed should be present in the cabinet. Validation of the cabinet should therefore be performed with shielding in place.
- Totally enclosed systems should be considered where there is a risk of airborne contamination of the operator.
- For routine preparations, remote handling equipment should be considered.
- The interaction of high energy beta particles with high atomic number materials will lead to the production of high energy X-rays (bremsstrahlung). Materials of low atomic number e.g. plastic or aluminium may be more effective for shielding of pure beta emitters.
- Operators should be aware of the high dose rates near the surface of open solutions of beta emitters. Where possible, tongs should be used for handling.
- Because of the risk of airborne contamination, labelling with 131I should be undertaken only in a fume cupboard or hot cell designed for that purpose. All operators should also be regularly monitored for the presence of thyroid radioactivity.
When $^{131}$I-labelled human serum albumin was introduced as an agent for cisternography, there were many reports of aseptic meningitis. Many of these reactions were shown to be the result of the presence of bacterial endotoxins in the preparation. Similar reactions have also been reported following the use of $^{99m}$Tc-DTPA and $^{111}$In-DTPA preparations. In the latter case, the cause of the reaction was traced to pyrogen contamination of the buffer used in the manufacture.

Special precautions are thus required for the manufacture of preparations which are to be injected intrathecally. Additional attention should be paid to the depyrogenation of glassware, equipment etc., and reagents to be used in the manufacture should be tested for the presence of bacterial endotoxins using the limulus test.

Preparations which are to be injected intrathecally should be tested for the presence of bacterial endotoxins using the BP test. The maximum allowable endotoxin concentration is $14/V$ Units per mL, where $V$ is the volume of the maximum dose of the preparation to be administered. It should be noted that, unless a commercially available product is registered for use in cisternography, the user should demonstrate that the above endotoxin limit is not exceeded.

Careful attention should be paid to the chemical composition of the preparation. Osmolarity and pH can affect nerve function and it is important that these parameters be carefully controlled. The possibility for chelation of the small amount of calcium in the CSF, which may lead to a patient reaction, must also be considered. For this reason, the calcium-DTPA complex should be used for the preparation of cisternography agents containing DTPA.

NOTE: the only registered radiopharmaceutical for cisternography at the time of writing is indium$^{111}$In pentetate injection.

References:

CHAPTER 9: RADIOLABELLING OF BLOOD CELLS AND BODY SUBSTANCES

INTRODUCTION

900 This Chapter describes the laboratory practices and environmental conditions necessary for the safe manipulation of blood or other body substances and the preparation of radiolabelled blood cells for patient re-injection. The procedures described here do not cover all aspects in detail and should be read in conjunction with related documents.

901 During cell manipulation and radiolabelling for clinical diagnosis, it is necessary to maintain both cell viability and sterility and to avoid operator exposure to biological and radiation hazards.

902 Manipulation of cells or body fluids for in vitro diagnosis requires strict attention to operator technique and should be performed in a Biological Safety Cabinet Class I (BSC I) or its equivalent.

903 Radiolabelling of patient cells for re-injection requires, in addition to approved techniques, the use of biological containment devices, which include the following:

- Biological Safety Cabinet Class II (BSC II).
- Biological Containment Device Class III (BCD III), as developed for work with high-risk microorganisms.

Both these biological containment devices provide product sterility and operator protection without prohibitively slowing the cell radiolabelling procedure. Further details on the construction and operation of these devices may be found in the relevant Australian Standards. However, the use of these cabinets must not instil a false sense of security, which may promote sub-standard technique.

904 The inclusion of appropriate shielding within the BSC II reduces operator radiation exposure.

905 A senior staff member experienced in the manipulation of cells and body fluids or cell-labelling methodology should fulfil the roles of operator, trainer and organiser of the blood cell radiolabelling laboratory.

Key factors

906 The following aspects of labelling of cells with radionuclides are covered in this chapter:-

- Appropriate staff health program.
- Adequate operator training.
- Use of standard laboratory safety techniques.
- Use of a BSC II, BCD III or equivalent device.
- Use of protective clothing and gloves.
- Safe transport of specimens.
- Substitution of plastic mixing cannulas for needles where practicable.
- Effective emergency spill procedures.
- Safe disposal of infected or radioactive waste.

BIOLOGICAL HAZARDS AND Routes OF TRANSMISSION

907 Operator protection is of paramount importance. Universal blood and body substance precautions must be followed at all times. The Occupational Health Department of each hospital should be consulted when setting up a suite for the radiolabelling of body substances. As all biological specimens are potentially dangerous, strict adherence to safe laboratory practice is essential.

908 Biological hazards are encountered primarily in the handling of blood. However breast milk, saliva, CSF, pus, menstrual fluid, urine, faeces and semen should also be considered as potentially infectious biological substances.

909 Biological exposure principally occurs at the workplace by absorption through:

- The respiratory system, via inhalation of aerosols from centrifuging or from opening pressurised containers, or when adding or withdrawing blood specimens to or from closed containers under pressure, or during cell re-suspension.
• Ingestion from contaminated hands or food.
• When sharps contaminated with infected blood or body substances penetrate the skin.
• When infected blood or body substances splash into the eye or other mucous membranes, onto broken skin or into a cut.

910 Accidental self-inoculation may be minimised by providing an adequate, uncluttered environment and by utilising approved techniques in a controlled manner. The use of needles should be minimised where possible and replaced by use of plastic mixing cannulas or similar devices. Where syringe needles are recapped, a recapping needle device must be used utilising one-handed technique.

STAFF HEALTH PROGRAM

911 All personnel involved in the handling, manipulation or radiolabelling of cells or biological substances should be vaccinated against Hepatitis B.

912 Radiolabelling of cells for patient re-injection should not be performed by operators who:

• suffer from bacterial or viral infections; or

• have frank exudate lesions or weeping dermatitis. Direct patient contact should be avoided until the lesions have healed.

WHOLE BLOOD COLLECTION AND TRANSPORT

913 Patient whole blood should be collected by trained personnel skilled in venepuncture technique, with gloved hands and protected by a hospital gown or its equivalent.

914 To prevent cell haemolysis during blood collection, 21 gauge needles and butterflies (or larger) should be used where practicable. All blood specimens must be clearly labelled with patient name, unique identifying number and date. The syringe containing patient blood should be transported to the blood cell radiolabelling laboratory (hereinafter referred to as the laboratory) according to hospital policy and by gloved personnel. Generally this involves the utilisation of a rigid sterile container (syringe/needle) enclosed by a waterproof bag or outer container.

915 For transport between institutions, patient blood or biological substances should be placed in a sealed container (syringe with syringe cap attached) surrounded by absorbent padding within a plastic bag. Appropriate labelling must be utilised to prevent mixing up of patient blood cells or biological samples. The transport of radioactive blood or biological substances requires additional protective shielding, as specified by local regulations.

MANIPULATION OF BLOOD CELLS OR BODY FLUIDS FOR IN VITRO RADIOLABELLING

Maintenance of operator protection

916 The manipulation of blood cells or body fluids for in vitro clinical diagnosis requires attention to the maintenance of operator protection only, as blood cells or body fluids are not re-injected. The operator should be gowned and gloved at all times, utilising safe laboratory practice procedures (see clauses 943-962). Under ideal circumstances, individual samples should be manipulated in a BSC II located in a low-traffic room. Although the room requirements are less stringent, clause 930 on general principles of room design should be consulted. It is not a requirement to locate the BSC II in a sterile pressurised room. Further relevant details may be found in clauses 926-931.

Maintenance of product sterility and operator protection

917 Radiolabelling patient cells for re-injection requires a controlled sterile environment utilised by trained operators. Excessively time-consuming cell manipulations should be avoided where possible. The use of an open or closed vial system on a laboratory work bench is NOT an acceptable alternative to a controlled sterile environment. Product sterility is compromised when biological fluids are added to or removed from open vials and the operator is exposed to aerosols when vial lids are removed or cells are resuspended.

918 The closed vial system is based on the use of needles (increasing the risk of needle-stick injuries) and may expose the operator to aerosols when biological fluids are added or withdrawn under pressure. Sterility is
Retrospective sterility testing (based on an aliquot of the radiolabelled cell injectate) can be performed with both systems. This, however, requires incubation of a radioactive biological sample with nutrient media and is subject to the statistical limitations of interpretation of results from small sample sizes.

Maintenance of product integrity in the BSC II

The BSC II is designed primarily for use with the open vial system, where sterile vertical laminar flow air bathes the work bench, allowing the operator to perform manipulative procedures without compromising sterility. A horizontal or vertical laminar flow cabinet is NOT an acceptable alternative device and must not be used. Strict aseptic technique by gownned operators using gloved hands must be used at all times.

If a closed vial system must be used, the BSC II provides maximum operator protection from generated aerosols.

Because the BSC II operates at a low air velocity (0.5 m/sec), it provides practically no resistance to the ingress of air propelled by passers-by, opened doors etc. and so must be positioned away from rapid air movements.

Maintenance of operator protection with the BSC II

To ensure adequate operator protection, all steps must be performed within the BSC II by gownned personnel with gloved hands.

Although the air barrier at the front of the cabinet is intended to prevent the egress of potentially contaminated air from within the BSC II to the outside environment, rapid hand movements within the work space should be strictly avoided, while biological and/or radioactive spills should be contained within the cabinet.

Operator radiation protection may be in the form of an "L" shaped lead shield, as this shape does not interfere with the laminar air flow of the BSC II.

ENVIRONMENT FOR BLOOD CELL RADIOLABELLING

Utilisation of a sterile room to locate the BSC II is not fully compatible with the performance of cell radiolabelling as multiple transfers are required to and from the centrifuge and there is a need to minimise radiolabelling time.

The BSC II should be located in a low-traffic room separately from the radiopharmaceutical preparation area. Its exhaust air (which undergoes prior high efficiency (HEPA) filtration) may be released directly into the room. In the absence of a separate dedicated room, therefore, careful delineation of surrounding activities should be made.

Optionally, some institutions may prefer that the room be operated at negative pressure and/or that air from the room and/or BSC II undergoes continuous exhausting.

Every effort should be made to reduce air particulate and microbial contamination within the laboratory, so that the efficiency of HEPA filters is not compromised. This will ensure that Class 3.5 conditions are maintained across the work bench of the BSC II.

Room requirements

The laboratory should act as a secondary barrier (where the primary barrier is the BSC II). To achieve this:

- The internal wall surfaces of the room should be of a durable paint to facilitate decontamination and regular cleaning.
- The floor should be impervious and easy to clean e.g. vinyl with welded seams and coved at the wall junction.
- Bench tops should be impervious to water and resistant to acids, alkalis, organic solvents and moderate heat.
- There should be sufficient bench space to enable cleaning of equipment and unpacking of biological specimens.
• It is preferred that doors have clear glass window panels so that occupants can be clearly seen from the outside. Windows must remain permanently closed.

• Adequate shielding should be provided for areas where radiation is manipulated or radioactive materials are stored.

• Provision should be made for hand washing facilities with foot, beam or elbow-operated taps.

• Provision should be provided for exhausting formaldehyde into the atmosphere when the BSC II is decontaminated, which should be annually or after a major biological spill.

**Exhaust air**

931 HEPA filtered exhaust air from a BSC II is usually exhausted directly into the laboratory. However, concern regarding exhaust HEPA filter integrity (as leaks may develop between routine challenge tests) and their inability to remove viruses has led to the concept of indirectly discharging the exhaust air into the outside environment.

This provides a convenient method of maintaining the room at negative pressure when in use and is achieved by a capture hood principle (soft-coupled exhaust outlet), as specified in AS 2647-1994. This can be applied to a BSC II located in either a controlled or uncontrolled environment. However, under no circumstances should exhaust air from the BSC II be connected directly to ventilation ducts, air conditioning or exhaust systems which discharge directly into the atmosphere as this may lead to uncontrollable variation in cabinet air flow velocity and pressure due to windage.

**RECOMMENDED EQUIPMENT**

932 Additional equipment necessary for cell radiolabelling procedures includes:

• BSC II or III (in the following sections, a BSC III is of course a suitable replacement for a BSC II).
• Fixed or angled sealed centrifuge.
• Refrigerator.
• Lead glass shield for use within the BSC II.
• Protective clothing.

**Centrifuge**

933 Sealed rotor centrifuges offer superior operator protection from breakage or aerosol production when biological specimens undergo centrifugation. The sealed rotor should be autoclavable and have a transparent lid to allow the operator to see any breakages. In the event of vial breakage, the sealed rotor should be autoclaved and the lid not removed until the autoclave process is completed.

934 Centrifuges should be mounted on a firm work bench and operators instructed in their correct use, with particular attention to balancing. If the centrifuge is not fitted with a lock to prevent it being opened while spinning, operators must ensure that the rotor has completely stopped turning before opening the lid.

935 Centrifuge buckets should be disinfected with 2% glutaraldehyde or 1% sodium hypochlorite on a regular basis.

**Radiation detector**

936 A radiation contamination monitor should be available for regular checks of possible bench and work space contamination. Dose rate monitors may also be considered for monitoring operator exposure.

**OPERATOR TRAINING**

937 The Head of Department or Head of Service is responsible for ensuring that:

• personnel receive adequate instruction in the handling of biological material, in aseptic technique and in radiation protection before commencement of cell radiolabelling. The utilisation of established procedures by each staff member should be validated; and

• all personnel are instructed in the function, operation and limitations of the BSC II. In particular, personnel should be made fully conversant with the controls, alarms and air flow systems of the BSC II.
Personnel must be aware that the BSC II may be ineffective in preventing the ingress of contamination onto the work bench when inappropriate techniques are used. The operator must carry out the aseptic process in a manner designed to effectively use the HEPA filtered air above the work bench.

It should be recognised that gloved hands are not sterile or particle-free, as their surfaces become contaminated within minutes after gloving, due to exposure to ambient air and from touch contamination.

Personnel should be aware that operator techniques designed for horizontal laminar flow cabinets are not applicable to the BSC II, although some basic principles remain the same.

The Radiopharmaceutical Scientist must ensure that personnel are safety-conscious and are aware of the biological risks involved during cell radiolabelling procedures. Safety and emergency spill procedures must be documented, adhered to and made available to each staff member. The Radiopharmaceutical Scientist and Hospital Radiation Safety Officer (HRSO) must be notified promptly of all accidents and/or spills involving operator exposure to radioactive material. Other requirements for notification may apply in the case of spillage of biological material.

Gloves should be carefully removed and changed when they accidentally touch contaminated surfaces or are visibly contaminated, at the completion of the radiolabelling procedure and when leaving the laboratory. Hands should be washed between glove changes and when leaving the laboratory.

**SAFE LABORATORY PRACTICE**

Only one blood radiolabelling procedure should be performed at a time. Where this is impractical, it is imperative to institute an effective sample identification and coding system to prevent accidental cross-contamination of samples or equipment.

All procedures which generate aerosols, droplets and spills should be avoided where possible. In this regard, an open system is preferred to a closed system.

The labelling procedure should be designed around the use of plastic mixing cannulas (rather than needles) to minimise the possibility of needle-stick injuries during manipulation, particularly recapping of needles.

Surfaces should be decontaminated with an appropriate sanitising agent e.g. 70% isopropyl alcohol/ethanol or benzalkonium chloride (35:1000 dilution), or 0.25% chlorhexidine gluconate in 70% ethanol prior to use, after all procedures are completed and whenever surfaces are overtly contaminated. The floor should be similarly decontaminated, after cleaning, at suitable intervals.

The work surface should be monitored for radionuclide contamination after completion of the radiolabelling procedure.

Prompt decontamination of spills should be standard practice.

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

Operators should keep hands away from eyes, nose and mouth during cell radiolabelling to prevent accidental exposure of mucous membranes and contamination of gloves.

Smoking, drinking, eating, storage of food and beverage containers or utensils and the application of cosmetics should be prohibited within the laboratory.

Office work should not be done in the laboratory, although specific areas should be set aside for record keeping.

Access to the laboratory should be limited to times when work is being conducted and only to authorised personnel.

**Needles and syringes**

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

In the event of a needle-stick or other injury due to sharps potentially contaminated with body substances, or the splashing of mucosal surfaces, operators should follow the recommended hospital policy for
in 70% ethanol should be applied to skin wounds but not to mucosal surfaces. If the sharps injury involves the hands, the torn glove should be removed immediately and the above procedure followed.

**Clothing**

956 Gloves should be worn when taking or handling patient blood and in the transfer of blood specimens to the laboratory. Protective clothing, including safety glasses, should be donned on entering the laboratory and prior to performing cell radiolabelling. After gowning up, the operator's hands should be gloved and the gloves doused with 70% isopropyl alcohol or other sanitising agent to remove exterior talc and to sanitise the gloves.

957 Suggested attire includes clean non-linting continuous-fronted gowns that are snug-fitting at the wrists. These garments protect the operator's whole body and aid in reducing the particulate load when working with the BSC II. Normal laboratory coats are unsuitable for this purpose. Gowns should be for single use (although recyclable) and should be discarded when they become soiled. They should not be worn outside the laboratory. Commercially-available Tyvek sleeves may be used.

958 Reusable garments that are visibly soiled with potentially infectious material should be separated from other used garments prior to re-processing. Alternatively, the garments may be disposed of in accordance with hospital/institution policy. Gloves and protective clothing should be worn when transferring infectious garments into leak-proof bags.

**Hand washing**

959 Hands should be washed thoroughly with a suitable sanitising agent (e.g. 5% chlorhexidine gluconate) when the operator de-gowns and removes gloves after radiolabelling or after handling blood or other biological fluid.

**Waste disposal**

960 Used disposable syringes, needles, mixing cannulas and other sharp items should be placed in hospital-approved puncture-resistant containers, which should be located as close as practicable to the point of use. They must be disposed of in accordance with hospital policy. Biological waste must not, under any circumstances, be left unsealed or left lying around in the laboratory, where it may be inadvertently removed by cleaning staff.

961 Samples that are radioactive must be labelled appropriately, placed in sealed containers and stored behind adequate shielding until deemed safe for disposal. Other approved methods of storage are permissible, as specified by the HRSO and Radiopharmaceutical Scientist.

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

**SPECIFIC LABELLING PROCEDURES AND PRECAUTIONS**

**In vivo cell labelling (e.g. \(^{99m}\)Tc-RBC)**

963 As this technique is performed in vivo, it does not utilise the laboratory. However, the operator should be suitably attired with protective clothing (standard hospital gowns are acceptable) and gloves, utilising a syringe re-capping device when needles are used and syringe shields to reduce radiation exposure during each radiolabelling step.

**In vitro RBC labelling (e.g. \(^{99m}\)Tc-RBC, \(^{51}\)Cr-RBC)**

964 The in vitro RBC radiolabelling technique should be carried out in the BSC II when either an open or closed vial system is used. For example the addition of pertechnetate[\(^{99m}\)Tc] to pre-tinned whole blood must be performed using adequate shielding in a safe manner with aseptic technique. Stannous tin-treated blood and pertechnetate[\(^{99m}\)Tc] may be mixed on a rotor mixer positioned behind adequate shielding.

"In vivitro" RBC labelling (e.g. \(^{99m}\)Tc-RBC)

965 There is no requirement to perform this technique in the cell-labelling laboratory. The operator should be suitably attired with protective clothing and gloves. Absorbent sheets should be used where practicable. Typically, the addition of pertechnetate[\(^{99m}\)Tc] to pre-stannous-treated whole blood is performed using syringe shields or other adequate shielding in a safe manner with aseptic technique. Stannous tin-treated blood and pertechnetate[\(^{99m}\)Tc] may be mixed on a rotor mixer positioned behind adequate shielding.
966 In vitro WBC radiolabelling technique should be carried out in the BSC II irrespective of whether an open or closed vial system is used. The isolation of WBC from whole blood in the BSC II reduces operator biological exposure and maintains product sterility. The addition of $^{111}$In-oxine or $^{99m}$Tc-exametazime to isolated WBC should be performed using adequate shielding and aseptic technique.

**In vitro $^{99m}$Tc-WBC labelling (phagocytic method)**

967 In vitro $^{99m}$Tc-WBC radiolabelling technique should be carried out in the BSC II when an open vial system is used. When a closed system utilising a syringe and modified centrifuge is used, there is no requirement to perform this technique in the BSC II. However, care should be exercised to eliminate unwanted aerosols when centrifuging radioactive plasma.

**In vitro platelet labelling (e.g. $^{111}$In- or $^{99m}$Tc-platelets)**

968 In vitro platelet radiolabelling should be carried out in the BSC II irrespective of whether an open or closed vial system is used. For example, platelet isolation from whole blood in a BSC II reduces operator biological exposure and maintains product sterility, whilst the addition of $^{111}$In-oxine or $^{99m}$Tc-exametazime to isolated platelets should be performed using adequate shielding and aseptic technique.

**Re-injection of radiolabelled cells**

969 Prior to re-injection, radiolabelled cells should, where possible, be diluted to their normal clinical concentration using patient plasma, 0.9% w/v Sodium Chloride BP or other specified medium.

970 Before injection, the syringe should be checked for aggregation or clumping of cells.

971 After verification that the patient is to receive his or her own radiolabelled cells, the syringe should be inverted several times to re-suspend the cells. The person taking the blood should perform the re-injection. Radiolabelled cells should be injected slowly.

**Assessment of cell viability post radiolabelling**

972 Prior to introducing a new cell labelling procedure into clinical use, studies of post-radiolabelling cell viability should be carried out. Cell viability studies may be conducted at regular intervals at the discretion of individual hospitals.

**PRE-OPERATIONAL PROCEDURES**

973 Before using the BSC II, the following procedures should be carried out:

- Remove dust cover from BSC II.
- Turn BSC II on. The low pressure audible alarm should sound and the fan should commence to operate.
- Clean inside of BSC II with an appropriate sanitising agent, e.g. 70% alcohol, using non-linting cloth and taking care not to spray sanitising solution onto ceiling HEPA filter. Note: Alcoholic solutions may pose a fire hazard, while hypochlorite solutions corrode stainless steel.
- Sanitise all utensils, stands, etc. within the BSC II.
- Remove or re-arrange unnecessary items within the BSC II to preserve laminar air flow.
- Cover the work zone with a new, non-particle-shedding sterile containment sheet.
- Ensure viewing window is firmly closed.
- Leave BSC II running for at least 10 minutes before use.

The following procedures are optional.

- Record main and exhaust HEPA filter pressure readings before each procedure.
- Record radiation detector reading after each procedure.
The following procedures must be observed during cell radiolabelling:

- Assemble all required materials and equipment in close proximity to the BSC II. A movable trolley is useful.
- Sanitise all items (70% alcohol) before entry to the BSC II and place to the front and sides of the work bench, leaving the centre area clear for the radiolabelling procedure.
- Minimise the number of entries and exits of gloved hands from the BSC II. (Gloves must be re-sanitised prior to entry into the work bench).
- Perform all critical operations about 100-150 mm above the work bench surface, anywhere in the BSC II. Under no circumstances may critical areas be touched.
- Keep all non-sterile items, including gloved fingers, forceps etc. downstream from critical sites, ensuring that critical sites are always bathed with sterile HEPA-filtered air.
- Make syringe connections etc. perpendicular to the air stream, keeping gloved hands below critical sites.
- Sanitise insertion surfaces before needle insertion into closed containers.
- Do not use centrifuges within the BSC II.
- Do not rush procedures.
- Always manipulate radioactive material behind shielding.
- Inspect the finished product for clumped cells, cell adherence to the inside of the tube, cell lysis etc.
- After completion of the radiolabelling procedure, remove the radiolabelled cells from the BSC II and calibrate activity.
- Record syringe activity and relevant patient data. Label syringe shield and carrier lead pot with patient name and code, dose and date.

Between consecutive procedures

If more than one procedure is to be carried out in the BSC II, the following procedures must be followed:

- Clean BSC II with sanitising agents using non-linting cloth.
- Replace containment sheet if contaminated and preferably on each occasion.
- Allow the BSC II to run for a minimum of 5 minutes before use in order to establish stability.

BSC II shutdown

The procedure should be as follows:

- Wipe all items over with a sanitising agent before removing equipment from the BSC II.
- Monitor the radioactivity and dispose of absorbent liners in the contaminated waste bag if levels are acceptably low. If not, store in accordance with the radiation protection policy.
- Thoroughly clean with a sanitising agent any equipment that is left in the BSC II (including the work bench).
- Monitor work bench for radionuclide contamination.
- Allow the BSC II to remain operating for at least 5 minutes to purge air spaces.
- Replace dust cover.
• Record pressure reading on manometer gauge and radiation reading on detector (optional).

Cleaning

977 Cleaning and sanitisation of the BSC II work bench should be performed at the beginning and end of each radiolabelling procedure or when spillage occurs. When the BSC II is not in use, the dust cover should be used to prevent the ingress of contamination, the UV light should be turned on and the BSC II turned off.

978 Thorough physical cleaning of instruments is essential before disinfection or sterilisation. Splashing should be avoided when rinsing or cleaning. Cold water and detergent should be used to assist the removal of blood, serum etc. from instruments. Hot or boiling water should be avoided as protein may be precipitated, preventing adequate removal.

979 Benches on which specimens are handled should be covered with a containment sheet.

980 Special receptacles should be provided in the laboratory for the collection of contaminated material.

981 The sump of the BSC II should be cleaned regularly and following any spillage. After sanitisation, the work bench may be removed (while the cabinet is operating) and the undersurface and sump floor cleaned with an appropriate sanitising agent.

Monitoring of BSC II pressure gauge

982 An excess pressure reading indicates the need for filter replacement or further maintenance, while a sharp reduction in the pressure indicates a blower system malfunction or major leakage somewhere in the filter or hood. In order to monitor the performance of the BSC II, pressure readings may be recorded after each use of the cabinet.

Monitoring of radionuclide contamination

983 The work zone within the BSC II should be monitored for radionuclide contamination and the result recorded after completion of each radiolabelling procedure. An excessive radiation reading indicates that free radionuclide has been released during the radiolabelling procedure. Both the Radiopharmaceutical Scientist and the HRSO must be informed immediately. Steps must be taken to ascertain the break in the radiolabelling technique, while the Radiopharmaceutical Scientist and the HRSO will decide whether the contaminated BSC II can be used.

PROCEDURES FOR BIOLOGICAL AND RADIOACTIVE DECONTAMINATION

984 All spills and breakages within the BSC II and laboratory must be cleaned up immediately by appropriate procedures (as specified by the Radiopharmaceutical Scientist and HRSO), taking into consideration their potential biological and/or radiation hazard. Broken glass etc. should be carefully removed using forceps and placed in an appropriate sharps container or, if radioactive, in an appropriate shielded sharps container. The area should be monitored after decontamination of a radiation spill.

985 To reduce the possibility of cross-contamination, overt biological contamination of gloves and gowns should be treated immediately either by dousing the gloves with a sanitising agent or complete removal of the affected glove or garment. When direct skin contact is involved, the skin area should be immediately washed with cold water for at least 5 minutes, followed by thorough washing with a sanitising agent. If gloves are contaminated, they should be removed first.

986 If radiation contamination is suspected, garments should be monitored and, if contaminated, carefully removed and stored until safe.

987 In the event of any of these accidents occurring the Head of Department or Head of Service, Radiopharmaceutical Scientist and HRSO must all be notified.

Decontamination of BSC II

988 Formaldehyde vapour decontamination may be considered when serious spillage has occurred. Before decontamination can be effectively performed, visible residues must be removed from all external surfaces. The BSC II must also be monitored for radionuclide contamination.

BSC II breakdown
If the BSC II stops running and/or the alarm sounds during radiolabelling of blood cells, the following steps must be taken:

- Check the manometer gauge for retention of pressure, as the alarm may indicate that the HEPA filter requires changing. If failure is confirmed by failure to achieve the set pressure differential, stop all work and re-seal open vials or tubes.
- Turn off all services within the cabinet.
- Close the work access opening with the dust cover.
- Turn off power supply to the cabinet.
- Contact Radiopharmaceutical Scientist.

**INSPECTION AND TESTING**

Inspection and testing should be performed by a NATA-registered authority in accordance with AS 2252, Part 2 (BSC II). It should be conducted at the designated installation site post delivery, then at least annually and after each modification or relocation of the cabinet and whenever HEPA filters are replaced. Prior to testing (or carrying out maintenance work) the cabinet must be monitored for radionuclide contamination levels, thoroughly sanitised and decontaminated with formaldehyde vapour. Where BSC IIs are operated frequently with high particulate air or where mechanical faults are suspected, the user should consider more frequent testing.
CHAPTER 10: QUALITY CONTROL

GENERAL

1000 A quality control system should be established for each radiopharmaceutical to be prepared. Quality Control should take and test samples of starting materials (including packaging materials), relevant intermediate products and finished products for conformity to specifications and to determine their release for use or rejection on the basis of the test results.

1001 The quality control program should also include procedures for verifying the correct operation of equipment used in production and testing as well as testing of both the production and storage area environments.

1002 Appropriate statistical techniques should be used to monitor and control radiopharmacy operations.

ROUTINE QUALITY CONTROL PROCEDURES

Goods receipt

1010 On arrival, packages containing radioactive materials should be inspected for signs of damage and monitored with a survey meter to check for leakage. A wipe test should be made to determine radioactive contamination on the surface of any shipment container and any leakage should be reported to the supplier. Serious spills may require evacuation of the area before any cleanup is undertaken and should first be reported to the radiation safety officer.

1011 The contents of all shipments should be checked both against the delivery date and the order form. Labels and other documentation should be checked for batch number, activity, calibration date and time, expiry time and other relevant data and the details recorded. Raw material (including radioactive materials) to be used for the preparation or testing of radiopharmaceuticals should be quarantined until approved for use by Quality Control.

1012 Prior to release for use, the activity of ready-for-use products should be measured and compared to the quoted activity on the accompanying documentation. If there is any significant discrepancy, the radiopharmaceutical should be withheld from use until the reason for the discrepancy is determined.

Radionuclidic purity

1013 Radiopharmacies and nuclear medicine clinics usually do not have access to equipment for measuring the radionuclidic purity of a radiopharmaceutical. For this reason, it is essential that all radiopharmaceuticals that are purchased in the ready-to-use form are purchased from a registered manufacturer who is subject to a GMP audit.

1014 On occasions, radiopharmacies either purchase or are provided with radioactive materials for use in the preparation of radiopharmaceuticals for either routine medical use or for research. In these cases, unless the institution has a facility to measure radionuclidic purity, a specification should be established with a manufacturer who is subject to a quality audit. As part of the contract, the supplier should be requested to provide a certificate of analysis with each batch provided.

1015 Through use of an ionisation chamber, radiopharmacies are able to make an estimate of the content of molybdenum-99 in technetium-99m. This measurement should be made on all eluates from a technetium-99m generator and is discussed in the section dealing with generators (840-846).

Radiochemical purity

1016 Radiochemical purity may be determined by a variety of techniques including chromatographic separation, solvent extraction, electrophoresis and precipitation. The range of techniques available is usually dependent on the size of the institution and the complexity of the radiopharmaceutical preparations. As a minimum standard, all institutions should have developed the capability of performing simple paper and thin layer chromatographic separations.

1017 Except in cases where there is a requirement in the package insert, routine measurement of radiochemical purity of radiopharmaceuticals reconstituted from registered cold kits with registered sources of sodium pertechnetate[\(^{99m}\)Tc] injection, using the reconstitution procedure outlined in the package insert, should not be necessary. The test may be of value when new staff are introduced or in eliminating a cause of any abnormal patient scan.
1018 In cases where radiochemical purity is not routinely measured, a protocol should be developed for the measurement of radiochemical purity in batches showing abnormal behaviour. The protocol should be validated by testing a number of initial batches. Periodic measurements should be made to maintain skills in the performance of the test so that it may be performed with confidence when unexpected results are obtained.

**Chemical contamination**

1019 In general, there is no need to test registered radiopharmaceuticals for chemical contamination. However, in some preparation procedures, trace metals have been shown to have an effect on product labelling e.g. high Al\(^{3+}\) levels in pertechnetate may affect the preparation of \(^{99m}\)Tc-sulphur colloid. Trace metals also can affect labelling yields by competing with the radionuclide for binding sites e.g. \(^{111}\)In labelling of monoclonal antibodies. \(^{99m}\)Tc can be regarded as a trace metal contaminant and can have an effect on the preparation of some products e.g. \(^{99m}\)Tc-RBC or \(^{99m}\)Tc-exametazime.

**Particulate radiopharmaceuticals**

1020 In general, there is no need to test registered radiopharmaceuticals for particle size, distribution and number. However, visual inspection by the user is recommended to ensure absence of macroscopic contamination.

**Stannous tin content**

1021 Many cold kits for the preparation of \(^{99m}\)Tc-radiopharmaceuticals depend for their labelling on the reduction of pertechnetate\([^{99m}\)Tc\] by a stannous salt within the preparation. Oxidation of the stannous salt may occur during the preparation of the cold kit: any release testing of a cold kit containing a stannous salt should therefore include a specification for stannous tin content.

Any quality control procedure should be validated. Simple titration with iodine or N-bromosuccinimide is often suitable, but as these titrimetric procedures are subject to interference by other reducing agents such as added stabilisers, alternative procedures such as polarography may need to be developed.

**Retrospective test for sterility**

1022 This subject is discussed in clause 834.

**Physiological distribution**

1023 For some radiopharmaceuticals, the physiological distribution test is the best indicator of the quality and expected performance of the radiopharmaceutical. The actual procedure for performing an animal biodistribution test and the animals to be used will vary for different radiopharmaceuticals. The procedures for a number of established radiopharmaceuticals may be found in the Pharmacopoeia monographs.

1024 A typical procedure involves the injection of the required volume and radioactivity of the radiopharmaceutical into a specified number of animals. Any injection in which extravasation occurs should be discarded. The exact radioactivity injected may be determined by measurement of the radioactivity in the syringe before and after injection or by the measurement of the injected animal in an ionisation chamber.

1025 After dissection of the animal, the radioactivity in the specified organs should be measured in an ionisation chamber or other suitable device taking care, as far as possible, to maintain a constant geometry. For some radioisotopes, the different extent of absorption of the emitted radiation by the various organs may need to be taken into account.

1026 The pass values for the biodistribution of radioactivity in an animal and the number of animals required to pass the test should be clearly stated. Criteria to allow for the test to be repeated and the specification to be used to constitute a pass for the repeat test should also be clearly stated.

**PRODUCT SPECIFICATIONS**

1030 Where possible, regulatory specifications, e.g. BP, USP, should be the minimum requirement for the final product. However, in many cases no regulatory specification exists. In these cases, it is therefore necessary to draw up a specification for internal use. The following should be a minimum requirement. Some product uses may require a more stringent specification to be applied.

- Physical properties
  - Particle size limits for colloids and macro-aggregates should be established. For macroaggregates to be
• Chemical purity
  The chemical toxicity of all excipients including the radionuclide carrier should be established. Heavy metal contamination should be no greater than that allowed for similar pharmacopoeial products. Limits should be set for all excipients.

• Radionuclidic purity
  Radionuclidic purity limits are available for most of the common radionuclides used in nuclear medicine. Where these are unavailable, the effects of any radionuclidic contaminant on radiation dosimetry and scan quality must be established.

• Radiochemical purity
  Requirements will vary with the application, but, in general, radiochemical purity should be greater than 95%. Pharmacopoeial limits may apply.

• Radioactive concentration
  Radioactive concentration may fall as the result of adsorption onto container walls and stopper. The radiochemical purity of the product may be affected by radiolysis and consequently the product shelf life may be decreased. Stability data should exist to demonstrate the product stability over the range of radioactive concentration used.

• Sterility, pyrogenicity
  BP requirements should be followed.

1031 When radiopharmaceuticals or gases are sterilised by final filtration, all filters should undergo a filter integrity test using a calibrated bubble-point apparatus.

1032 Specifications and quality control procedures for registered radiopharmaceuticals may be found in the Australian Radiation Laboratory Report ARL/TR093 "Quality Assurance of Radio-pharmaceuticals-Specifications and Test Procedures".

USE AND CARE OF EXPERIMENTAL ANIMALS

1040 The use of animals for scientific purposes, whether for research or product testing, places major responsibilities on the Radiopharmaceutical Scientist or animal technician. These responsibilities are given in the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, NHMRC/CSIRO/AAC, 1997. A major tenet of this Code is that all animal experiments must be fully justified, scientifically valid and conducted so as to cause the minimum possible pain or distress to the animal. The extent of testing or experimentation should be kept to the absolute minimum and techniques that replace or complement animal testing should be used wherever possible. These principles are especially relevant to radiopharmacy because the sacrifice of the animal is the usual test endpoint.

1041 All institutions which use animals for scientific purposes must establish one or more Animal Experimentation Ethics Committees (AEECs) which are to be directly responsible to the governing body of the institution or its delegate. The responsibilities, membership and mode of operation of an AEEC are described in the Code. It is the responsibility of the institution, through the AEEC, that all experiments comply with legislation and the institution must, on the advice of the AEEC, discipline investigators who contravene the Code or the decisions of the AEEC.

1042 The AEEC must have terms of reference which include provisions to monitor the acquisition, transport, production, housing, care, use and disposal of animals. All proposed radiopharmaceutical quality control tests or research experimentation involving the use of animals must be approved by an AEEC. State legislation may also require licensing of operators.

1043 The radiopharmacy must hold records of the acquisition of all animals, the purpose for which animals were used and details of the method of sacrifice or disposal of each animal.
CHAPTER 11: STABILITY TESTING

1100 For all purchased products, stability information should be available from the manufacturer. For "in-house" preparations, stability studies should be performed on a minimum of three production batches. If discordant results are obtained between the three batches, further batches should be examined.

1101 As many products show a sudden onset of instability, data should be obtained at intermediate points up to and beyond the planned shelf life of the product. As a guide the test period should extend to 125% of the planned shelf life.

1102 In the testing program, the product should be tested to full specification at preparation. At intermediate points, parameters that are likely to change should be measured. Typical parameters include:

- Physical stability e.g. particle size.
- Chemical stability e.g. pH, benzyl alcohol content.
- Radioactive concentration.
- Radiochemical purity.
- Biodistribution.
- Stannous tin content (for $^{99m}$Tc cold kits).

1103 In the stability study, particular attention should be paid to storage conditions. It is desirable that storage conditions be carefully controlled for the study- a room temperature study in non-air conditioned premises may give different results in winter and summer. If the product is to be stored under refrigeration without the warning "Do not freeze", then stability, particularly physical stability (e.g. no precipitate formation, no denaturation of protein) at about -5°C should be demonstrated.

1104 If the product is to be transferred to a second container prior to patient administration e.g. a syringe, then stability for the storage time in that container should be demonstrated.

1105 In the case of cold kits, the effect of kit age on the stability of the product after reconstitution should be demonstrated. It is sufficient to perform this study at batch preparation and at batch expiry. Reconstitution should be performed using the extremes of the reconstitution conditions and measurements should be made both at the time of reconstitution and at or after the time at which the reconstituted product expires. If the product is to be transferred to a secondary container for storage or distribution, stability in that container should be demonstrated.

1106 Additional stability data should be available covering the claimed shelf life of the inactive product when reconstituted with both the highest and lowest activities of $^{99m}$Tc to be used for preparation of the $^{99m}$Tc-labelled radiopharmaceutical in the minimum and maximum reconstitution volumes. This study should be performed at a number of time intervals up to and beyond the claimed shelf life after reconstitution. Stability data should also be available for the shelf life of the product in its final packaging form e.g. a syringe. The data should be available for the highest radioactive concentration to be used for reconstitution. If the final packaging form is to be changed, stability data should be regenerated.
CHAPTER 12: COMPUTERS AND COMPUTER SOFTWARE

1200 Where a computer is used in connection with any procedure or process associated with the production of radiopharmaceuticals, the computer system should meet the requirements of these Guidelines for those manual functions that it replaces. General requirements are described in Chapter 9 of the Medicinals Code. The following points may be noted:

- Software development by the vendor or user should follow the principles of Australian Standard 3563: Software Quality Management System or at least those of ISO9001: Model for Quality Assurance in design/development, production, installation and servicing. Where a source code is purchased, vendors should be asked to certify in writing that software development or modification has followed this standard or its equivalent.

- A hierarchy of permitted access to enter, amend, read or print out data should be established according to user need. Suitable methods of preventing unauthorised access should be available.

- Entry of critical master data into a computer by an authorised person should require independent verification.

- The validation of the system should be documented.
CHAPTER 13: PRODUCT REGISTRATION AND MANUFACTURER LICENSING

1300 This section is intended as a guide to the requirements for registration of radiopharmaceuticals and licensing for their manufacture under the Australian Therapeutic Goods Act, 1989 (the Act). However, as this section is necessarily brief and as it includes some legal aspects subject to interpretation, it should not be regarded as definitive.

1301 Wherever the Act applies, supply of unregistered goods or manufacture without a licence is illegal.

1302 Note also that independently of Therapeutic Goods requirements, prior quarantine clearance must be obtained to import any substance subject to the controls of the Quarantine Act, 1908. Broadly, this applies to any material of biological origin, whether human, animal, plant or bacterial and whether drug or device. Application forms to import biological materials may be obtained from the Chief Quarantine Officer in all capital cities. Applications will not be accepted by the Australian Quarantine and Inspection Service unless this application form is used.

In addition, an import permit is required under the Customs Act for any radioactive material. Permits for this purpose are issued by the Australian Radiation Laboratory. Their issue is facilitated if the product is registered in Australia.

Attention is also drawn to the legislation of the various statutory authorities (see Appendix 1) relating to:

- obtaining a licence/registration to possess, sell, purchase, dispose of or use radioactive material;
- transporting radioactive material by air, sea, rail or road; and
- sending radioactive material through the post (currently not permitted).

1303 The Therapeutic Goods Act has very wide "definitions" (interpretations) of "therapeutic goods" and of "manufacture" so that, to limit its application to areas of greater importance, it is necessary to provide, by regulation:

(a) general exclusions from its application, by Ministerial Determination;
(b) exclusion of many goods from the requirement for registration; and
(c) exclusion of certain persons or classes of products from the requirement for licensing to manufacture.

1304 Additionally, there are limitations to the applicability of the Act deriving from constitutional considerations, although these are to be redressed by complementary State legislation now in place (Victoria, NSW) or being drafted. In order to gain familiarity with the operation of the Act, it is important to understand the current exclusions and limitations and to understand that the constitutional limitation operates independently of the goods and persons exclusions mentioned above; each must be considered separately.

1305 The Act requires that:

(a) unless exempt, therapeutic goods to which the Act applies must be included in the Australian Register of Therapeutic Goods (the ARTG) in relation to their importer, manufacturer, supplier (excluding a wholesaler) or exporter; and
(b) unless an exempt person or a person making exempt goods, the manufacturer in Australia of therapeutic goods to which the Act applies must hold a licence to manufacture ("person" here includes a corporation).

1306 To determine whether the Act applies, one looks firstly at whether goods are "therapeutic goods" as "defined", and whether, although therapeutic goods, they have been excluded from the operation of the Act. Next, one looks at whether (in brief) the person who as a sponsor or manufacturer is a trading corporation (as are many hospitals) or is a person trading interstate, importing, exporting, or supplying as Benefits (or otherwise to the Commonwealth) the goods. The Act applies presently only to such persons or corporations except where complementary legislation has taken effect.

1307 Next, one must consider whether the goods are specifically exempted from registration. Finally, one examines whether "manufacture" as "defined" (bringing the goods to their final state) is being undertaken and whether the goods or the person making them may be specifically exempt from licensing to manufacture. This is a separate question to registration.
The specific exemptions for registration do not include radiopharmaceuticals as a general class, but there are exceptions in the circumstances given below.

The goods specifically exempt from licensing to manufacture do not include radiopharmaceuticals.

The persons specifically exempt from licensing do include pharmacists and radiochemists in public hospitals who are making radiopharmaceuticals for supply in hospitals or public institutions in the same State or Territory as the hospital or public institution which employs them.

Many, if not most or all hospitals in which radiopharmaceuticals are "manufactured" ("bringing the goods to their final state" is "manufacture") meet one or more of the criteria for licensability but, under a Commonwealth/State administrative arrangement, only those which supply interstate are licensed at present. To clarify this situation, cold kit manufacture within the hospital has recently been specifically exempted by regulation. For hospitals engaged in manufacture but not supplying interstate, the manufacturing sections of these guidelines presently have only advisory and "professional standard" status.

The "person" who imports, exports, or makes radiopharmaceuticals (or has them made) for supply or supplies them (the "sponsor") must have them included in the ARTG, ie register them. In this case, however, there is no corresponding administrative arrangement with the States, though there are many exclusions which in fact cover most cases. Radiopharmaceuticals to which the Act applies are expected to be registered unless they are:

(a) specifically made for a particular person (Schedule 5 to the Regulations, item 6); or
(b) for clinical trials (subject to conditions) or for use within the hospital in the absence of a substantially similar product that is registered (also subject to conditions; refer to Schedule 5A); or
(c) for critical situations (refer to section 19 of the Act and to Regulations 12A and 12B); or
(d) made in a hospital pharmacy for patients within that hospital or its satellite hospitals (Federal/State policy decision); or
(e) cold kits manufactured by a radiopharmacist in a public or private hospital or a radiochemist in a public hospital for use in the same State hospital system (Regulation 12, Schedule 5, item 13).

The ARTG number of registered products must be included on the product label. Other requirements are given in the current Therapeutic Goods Order for labelling of drug products.

There is no legislative constraint on the use of a registered radiopharmaceutical by a medical practitioner for purposes different to those accepted for registration: this is an ethical matter.

Applications for licensing or registration should be made to the Therapeutic Goods Administration. Guidelines to the operation of the Act and for registration are available and external consultants are also available to assist. If questions or doubts arise that cannot be answered from the guidelines, it may be advisable to contact the TGA's Drug Safety and Evaluation Branch before completing the application.
CHAPTER 14: ADVERSE REACTIONS AND ABNORMAL BEHAVIOUR

1400 The incidence of adverse reactions to the administration of radiopharmaceuticals is low. However, any suspected adverse reaction should be reported to

Adverse Drug Reactions Advisory Committee (ADRAC)
TGA
PO Box 100
WODEN ACT 2606

Tel : (02) 6232 8386
Fax : (02) 6232 8392

1401 "Blue card" prepaid mailer forms are available for this purpose and may be obtained from ADRAC or the TGA’s website. Details of the origin of the radiopharmaceuticals, batch numbers of all components, dose administered and any patient medication should also be provided. A copy of the report should also be provided to the Australia and New Zealand Society for Nuclear Medicine (ANZSNM) office for its register and to the manufacturer of the preparation for information.

1402 Any instances of abnormal radiopharmaceutical behaviour, such as an abnormal patient scan or a failure to meet product specification, including package labelling, should also be reported, with the same details, to the ANZSNM register and the manufacturer. As the altered radiopharmaceutical distribution may be the result of a drug-radiopharmaceutical interaction, details of any patient medication should also be reported.

If the circumstances indicate that recall of a (purchased) manufactured product may be appropriate, the Recalls Section of the TGA, Telephone (02) 6232 8636, should be notified.

1403 Administration of an unintended product or dose may be reportable under State legislation. Careful records of such an event should be kept, an investigation commenced and corrective action instituted.

1404 For registered products, it is a condition of registration under the Therapeutic Goods Act that the Sponsor must forward copies of "adverse reactions or similar experiences" to the Therapeutic Goods Administration. Serious unexpected reactions should be notified "immediately" i.e. within 72 hours. Other reactions should be reported using the "blue card" system.

1405 Adverse reactions arising during clinical trials should be handled according to the Australian Guidelines: Clinical Trials Exemption Scheme (CTX Scheme) for Drugs, 1992.

1406 In all cases, batch records should be examined to ensure that the product met specification. Retrospective testing may be indicated to assist in identifying the cause of the problem.

1407 A Standard Procedure for documenting and reviewing all deviations from expected test results or expected in vivo behaviour should be in place and followed.
ABBREVIATIONS

The following is a selected list of abbreviations used in the text:

AEEC
Animal Experimentation Ethics Committee
ANSTO
Australian Nuclear Science and Technology Organisation
ANZSNM
Australian and New Zealand Society of Nuclear Medicine
ARTG
Australian Register of Therapeutic Goods
BSC
Biological Safety Cabinet
BCD
Biological Containment Device
HEPA
High Efficiency Particulate Arrestance (filter)
NATA
National Association of Testing Authorities
NHMRC
National Health and Medical Research Council
NOHSC
TGA
Therapeutic Goods Administration.
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APPENDIX 1: RADIATION SAFETY AUTHORITIES

COMMONWEALTH

ARPANSA
Lower Plenty Road
YALLAMBIE VIC 3085
Tel    (03) 9433 2211
Fax    (03) 9432 1835

AUSTRALIAN CAPITAL TERRITORY

Radiation Safety Section
ACT Dept. of Health & Community Care
GPO Box 825
Canberra, ACT 2601
Tel:    (02) 6207-6946
Fax:    (02) 6207-6966

NEW SOUTH WALES

Radiation Control Section
Environmental Protection Authority
PO Box A290
SYDNEY SOUTH NSW 1232
Tel:    (02) 9995-5482
Fax:    (02) 9649-4470

NORTHERN TERRITORY

Radiation Health Branch
Territory Health Services
GPO Box 40596
CASUARINA NT 0811
Tel:    (08) 8999-2983
Fax:    (08) 8999-2530

QUEENSLAND

Radiation Health Branch
Dept. of Health
450 Gregory Terrace
FORTITUDE VALLEY QLD 4006
Tel:    (07) 3406-8006
Fax:    (07) 3406-8030
SOUTH AUSTRALIA

Radiation Section
Department of Human Services
PO Box 6, Rundle Mall
ADELAIDE SA 5000
Tel: (08) 8130 0702
Fax: (08) 8130 0777

TASMANIA

Health Physics Branch
Dept. Of Community & Health Services
GPO Box 125
HOBART TAS 7001
Tel: (03) 6222-7241
Fax: (03) 6222-7257

VICTORIA

Radiation Safety Unit
Dept. of Human Services
GPO Box 4057
MELBOURNE VIC 3001
Tel: (03) 9637-4860
Fax: (03) 9637-4508

WESTERN AUSTRALIA

Radiation Health Section
WA Health Department
Locked Bag 2006
NEDLANDS WA 6009
Tel: (08) 9346-2260
Fax: (08) 9381-1423.
APPENDIX 2: ACKNOWLEDGEMENTS

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