<825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging

Type of Posting	Revision Bulletin
Posting Date	22–Nov–2019
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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance—Postponement

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, USP is postponing the official date of Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging <825> pending resolution of an appeal related to this chapter.

After publication of <825> on June 1, 2019, USP received an appeal related to the chapter. In accordance with USP's Bylaws, the responsible Expert Committee (Chemical Medicines Monographs 4) worked with a sense of urgency to consider the information raised in the appeal and issued a decision on the appeal (see Decision on Appeal to USP <825>). In accordance with USP's formal appeals process, the appellant has requested further review by an appointed Panel.

USP's Bylaws provide that the official date of a standard under appeal must be postponed while an appeal is pending. Therefore, USP is postponing the official date of <825> until further notice.

USP's General Notices permit early adoption of revised standards in advance of their official date, as follows:

> 3.10 Applicability of Standards:
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> Early adoption of revised standards in advance of the official date is allowed by USP unless specified otherwise at the time of publication. Where revised standards for an existing article have been published as final approved "official text" (as approved in section *2.10 Official Text*) but have not yet reached the official date (6 months after publication, unless otherwise specified; see "official date", section *2.20 Official Articles*), compliance with the revised standard shall not preclude a finding or indication of conformance with compendial standards, unless USP specifies otherwise by prohibiting early adoption in a particular standard.

It is the decision of individual entities regarding whether to implement <825> in advance of the official date. Regulatory authorities and enforcement bodies also may issue requirements or recommendations on this point. USP plays no role in enforcement.

Should you have any questions, please contact Ravi Ravichandran, Principal Scientific Liaison (301-816-8330 or rr@usp.org).

Change to read:

▲⟨825⟩ RADIOPHARMACEUTICALS—PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING

The official date for this chapter is postponed until further notice. When the official date is reestablished, the period allowed for implementation will not be less than six months.

1. INTRODUCTION

Radiopharmaceuticals, as defined in this chapter (see *Glossary*), are a subset of radioactive materials (RAMs) falling under the control of the US Nuclear Regulatory Commission (NRC) or NRC-contracted agreement state agency. Radiopharmaceuticals are also a subset of prescription drugs falling under the control of the US FDA for manufacturing and marketing. Other federal regulatory authorities (e.g., Department of Transportation) have control over certain activities related to radiopharmaceuticals. Compliance with these regulations, as applicable, must be ensured in addition to compliance with the standards described in this chapter. [NOTE—Users outside the US must comply with equivalent regulations, as applicable, pertaining to radiopharmaceuticals.]

This chapter is intended to provide uniform minimum standards for the preparation, compounding, dispensing, and repackaging of sterile and nonsterile radiopharmaceuticals for humans and animals that occur as part of state-licensed activities (e.g., the practice of pharmacy and the practice of medicine). These standards apply to all radiopharmaceutical processing activities, including those with radionuclides that emit a single photon, a positron, or a therapeutic particle. Furthermore, these standards apply to sterile intravascular radioactive devices (e.g., radioactive microspheres for intravascular brachytherapy).

This chapter does not apply to the following activities:

- Manufacturing of approved radiopharmaceuticals (e.g., NDA, ANDA, BLA) in FDA-registered manufacturing establishments
- Manufacturing of radiopharmaceuticals as investigational agents (e.g., IND, RDRC)
- Compounding of radiopharmaceuticals in a registered FDCA §503B outsourcing facility
- Preparation/compounding of positron emission tomography (PET) drugs that are not manufactured as approved drug products (e.g., NDA, ANDA, BLA) and conforms with *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses* ⟨823⟩
- Administration of radiopharmaceuticals to patients

In each of these scenarios except for patient administration, the further processing and manipulation of the drug product after release falls within the scope of this chapter.

This chapter does not apply to the preparation of non-radioactive drugs, including those used as pharmacologic adjuncts for certain nuclear medicine procedures. These drugs must be prepared following standards described in *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ and *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩.

This chapter applies to all practice settings where radiopharmaceuticals are prepared, compounded, dispensed, or repackaged. Practice settings consist of state-licensed nuclear pharmacies, federal nuclear pharmacy facilities, and other healthcare facilities, including, but not limited to: nuclear medicine departments in hospitals and clinics, nuclear cardiology clinics (fixed site or mobile), and other specialty clinics.

This chapter applies to all individuals who prepare, compound, dispense, or repackage radiopharmaceuticals. Applicable individuals consist of authorized nuclear pharmacists (ANPs) and authorized user (AU) physicians, as well as individuals working under their supervision. This includes, but is not limited to, student pharmacists, nuclear pharmacy technicians, nuclear medicine technologists and students, and physician residents and trainees.

US federal and state radiation regulatory authorities require limiting radiation exposure to personnel who handle radiopharmaceuticals, which necessitates special provisions for radiation protection. The principles of radiation safety involve time, distance, shielding, and radioactive contamination control. Moreover, the use of radiation detection and measuring devices is a necessary component of radiopharmaceutical handling procedures. Strict adherence to all typical aseptic handling practices is not possible in many scenarios where radiopharmaceuticals are handled. Thus, it is necessary to balance aseptic handling practices (patient safety) with radiation protection practices (worker safety). This chapter describes appropriate strategies that provide assurance of maintaining patient safety, while also ensuring the safety of individuals performing these activities. Because radiopharmaceuticals represent a unique class of prescription drugs, the use of technologies, techniques, materials, and procedures other than those described in this chapter are not prohibited so long as they are documented to be equivalent or superior to those described herein.

1.1 Nonsterile Radiopharmaceuticals

Examples of nonsterile radiopharmaceuticals include oral capsules and oral solutions. For conventionally manufactured products or compounded preparations obtained from 503B-registered outsourcing facilities, dispensing can proceed as described in *12. Dispensing*. For prepared or compounded preparations, such preparations must comply with applicable identity, quality, and purity standards, as described in manufacturer labeling, *USP* monographs, or other appropriate sources (e.g., documented, peer-reviewed materials). They can then be dispensed as described in this chapter.

1.2 Sterile Radiopharmaceuticals

Examples of sterile radiopharmaceuticals include injectables (e.g., intravenous, intrathecal, intraperitoneal, subcutaneous, and intradermal), inhalations, ophthalmics, and intra-organ instillations. For conventionally marketed products, see *12. Dispensing*. For prepared or compounded preparations, such preparations must comply with applicable identity, quality, and purity standards. For compounded preparations involving one or more nonsterile components, a sterilization procedure (e.g., filtration with bubble point testing) must be performed prior to dispensing. For injectable compounded preparations involving one or more components that are not certified to be pyrogen-free, bacterial endotoxin testing, as defined in *Bacterial Endotoxins Test* ⟨85⟩, must be performed prior to dispensing.

The most important factor for maintaining sterility is the avoidance of touch contamination. Wipe the vial septum with sterile 70% isopropyl alcohol (IPA) prior to initial needle puncture. If the vial shield top is then closed, the septum must be disinfected again with sterile 70% IPA prior to another needle puncture. Some vial shields are constructed such that the vial septum is recessed and difficult to access. One approach for disinfecting the vial septum in this type of vial shield is to use right-angle forceps to hold a sterile 70% IPA wipe and apply direct contact with the vial septum. It is also acknowledged that such vial shields disrupt first air contacting the vial septum during certain handling conditions. Wipe the septum with sterile 70% IPA frequently whenever multiple punctures are occurring (e.g., removing several individual doses from a multiple-dose container).

2. RADIATION SAFETY CONSIDERATIONS

The handling of radiopharmaceuticals necessitates meeting the radiation regulatory agency requirements for worker safety. This involves licensing commitments to keep all exposure levels for the workers involved as low as reasonably achievable (ALARA) practices. Principles of radiation safety involve time, distance, shielding, and contamination control. Moreover, radiation detection and measuring devices are necessary. Aseptic handling practices must be balanced with radiation safety considerations, based on the following:

- Knowledge, training, experience, and professional judgment related to the type, abundance, and energy of the radioactive emissions
- The quantity of radioactivity, volume, handling steps, and timing
- Other factors, which can vary on a case-by-case basis

2.1 Time

Radiation exposure to personnel is directly proportional to the quantity of radiation handled and the time handling the RAM; minimizing handling time will minimize radiation exposure. Personnel handling radiopharmaceuticals may work quickly in a controlled and safe manner, including multiple hand movements in and out of the ISO Class 5 primary engineering control (PEC) during aseptic processes.

2.2 Distance

Radiation exposure follows the inverse square law; increasing the distance between the operator and the RAM will decrease radiation exposure to personnel by the square of the distance. Handlers of radiopharmaceuticals may utilize techniques to increase distance, such as using remote handling tools, including within an ISO Class 5 PEC.

2.3 Shielding

Radiation exposure to personnel decreases with the use of shielding materials. Therefore, handlers of radiopharmaceuticals may use various shielding materials (e.g., lead, tungsten) in various configurations. The use of shielding, such as L-block, torso, vial, and syringe shields, is usually required throughout the radiopharmaceutical handling process, including within an ISO Class 5 PEC.

2.4 Radiation Contamination Control

RAM contamination (e.g., spills, drips, sprays, volatility) is an important concern for radiation protection. Therefore, various techniques and materials may be used by handlers of radiopharmaceuticals to minimize radioactive contaminations. For example, container contents are maintained at neutral or negative pressure, because positive pressure in a container is a common cause of radioactive contamination. Disposable absorbent pads are commonly used to contain such radioactive contamination and, when used in an ISO Class 5 PEC, the pads must be clean and low-lint. Vertical air flow, not horizontal, in a PEC is used to control contamination. When exposure to blood and other potentially infectious material is reasonably anticipated, some engineered needlestick prevention devices may pose a radiation hazard to employees. Policies must be implemented for handling biohazardous radioactive sharps while minimizing contamination.

RADIATION DETECTORS AND MEASURING DEVICES

Radiopharmaceuticals require measurement with a suitable radiation measuring device (e.g., dose calibrator). These and other necessary equipment, (e.g., monitors, bar code scanner, label printer) may be placed inside an ISO Class 5 PEC but should be placed in a manner that minimizes disruptions of airflow.

As per RAM license requirements, individuals must wear body and, as required, extremity dosimeters (e.g., a ring worn on a finger) for long-term monitoring of personnel radiation exposure. The body dosimeter should be worn underneath the gown. Any extremity dosimeter must be worn underneath gloves and must not interfere with proper fit of gloves.

3. IMMEDIATE USE OF STERILE RADIOPHARMACEUTICALS

The preparation and dispensing of sterile radiopharmaceuticals in a patient care setting may be handled as an immediate use practice. The information below describes the appropriate handling requirements for immediate use sterile radiopharmaceuticals in an ambient environment that lacks primary and secondary engineering controls (SEC) when intended for a single patient. Strict aseptic technique and limited beyond-use date (BUD) must be adhered to given the lack of engineering controls.

- Appropriate for preparation (including minor deviations) and/or dispensing that is limited to use for a single patient.
- Preparation (including preparations with minor deviations) components must be sterile, conventionally manufactured drug products (e.g., NDA, ANDA).
- Dispensing of drug products produced under an approved IND or RDRC protocol is allowed.
- Manipulations for any unit doses (e.g., decreasing the dosage, needle changes) or dispensing for one patient (e.g., withdrawing a dose) is allowed.
- Must be administered within 1 hour of the first container puncture or exposure of any critical site involved (e.g., syringe tip, needle hub or needle) to ambient air, whichever is first.
- All components involved (e.g., Tc-99m sodium pertechnetate syringe or vial, final prepared radiopharmaceutical kit vial, diluent vial) must be discarded within 1 hour of being punctured or after use for a single patient administration, whichever is first.
- Dose pooling (combining doses from two or more syringes to meet one patient's need) may be performed as immediate use. Any residual activity that remains must be immediately discarded and not utilized for any other patient.
- Follow hand hygiene and garbing in *4.4 Hand Hygiene and Garbing for Immediate Use Preparations*.
- Follow *10.4 Preparation of Radiolabeled Red Blood Cells for Immediate Use* for red blood cell labeling.
- Follow *12.2 Labeling* for labeling.
- Area for sterile preparation and/or dispensing must be functionally separate from nonsterile compounding area (e.g., radiolabeling food) during the time of use.
- Does not require a segregated radiopharmaceutical processing area (SRPA), classified area, or PEC.
- The number of steps or punctures is not limited.
- Does not require personnel to complete the aseptic qualifications as detailed in *4.1 Aseptic Qualifications* (e.g., aseptic technique training with documented assessment, media fill challenge, gloved fingertip testing).
- While adding a non-radioactive, sterile and commercially manufactured pharmaceutical (e.g., lidocaine) to a unit dose is otherwise considered compounding, it is allowed for immediate use purposes as long as all of the above are adhered to.
- Dose splitting (splitting a unit dose for administration to more than one patient) may not be performed as immediate use; if performed, dose splitting must be done in an ISO class 5 PEC in either an SRPA or in an ISO class 8 or better buffer area.

4. PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE

Personnel must be trained to work with radiopharmaceuticals per the policies and standard operating procedures (SOPs) authorized by an ANP or AU physician. These individuals (e.g., nuclear medicine technologists or nuclear pharmacy technicians) must follow these policies and SOPs of the ANP or AU physician and work under their supervision. As appropriate, this should include blood-borne pathogens training.

Individuals entering a compounding area must be properly garbed and must maintain proper personal hygiene to minimize the risk of contamination to the environment and/or radiopharmaceuticals. Individuals who have a condition that may pose a higher potential of contaminating the radiopharmaceutical and the environment with microorganisms (e.g., rashes, sunburn, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection) must report these conditions to their supervisor. The designated person is responsible for evaluating whether these individuals should be excluded from working in sterile processing areas before their conditions are resolved.

4.1 Aseptic Qualifications

Personnel must prove competency, as applicable to their job functions, prior to performing radiopharmaceutical aseptic tasks that are beyond immediate use. These qualifications may be conducted at a different site if all SOPs are identical for the applicable job function. These qualifications must be completed and documented initially, and then successfully repeated at intervals described below in *Timing of Reevaluation and Requalification* under the observation of a designated person and include the following:

- Aseptic technique training with a documented assessment (written or electronic)
- Garbing and hand hygiene, as defined by the policies and SOPs
- PEC cleaning and disinfecting
- Gloved fingertip and thumb sampling
- Media-fill testing

GLOVED FINGERTIP AND THUMB SAMPLING

Appropriate garbing, including sterile gloves, is necessary for personnel who enter and perform tasks in an ISO Class 5 PEC (e.g., aseptic manipulations, cleaning the PEC). Personnel that perform such functions must prove their competency in this process. Gloved fingertip and thumb sampling must be performed initially on both hands, immediately following hand-hygiene and garbing. Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming unis (cfu) and subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu (total for both hands).

- The gloved fingertip and thumb sampling must be performed with touch plates or other devices (e.g., plates, paddles, or slides) that contain a general microbial growth agar [e.g., trypticase soy agar (TSA) soybean–casein digest media] supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this supports both bacterial and fungal growth
- Gloves must not be disinfected immediately before touching the sampling device, as this could cause a false-negative result
- Using a separate sampling device for each hand, a gloved fingertip and thumb sample from both hands must be collected by rolling finger pads and thumb pad over the agar surface
- The plates must be incubated in an incubator at 30°–35° for no less than 48 h, and then at 20°–25° for no less than 5 additional days

MEDIA-FILL TESTING

Media-fill testing is necessary for all personnel who prepare, compound, dispense, and repackage sterile radiopharmaceuticals. This testing must be reflective of the actual manipulations to be carried out by the individual and must simulate the most challenging and stressful conditions to be encountered in the worker's duties.

- Media-fill tests must be documented as defined by the facility's policies and SOPs.
- Media-fill tests should be performed at the end of a work session in the PEC.
- Media-fill tests must be performed with a commercial source of soybean–casein digest medium. Those performing sterile-to-sterile processing activities must start with sterile media. Those performing nonsterile-to-sterile compounding must use a nonsterile soybean–casein digest powder to make a solution. Dissolve nonsterile commercially available soybean–casein digest medium in nonbacteriostatic water to make a 3% nonsterile solution. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.
- The certificate of analysis (CoA) must include documentation of growth promotion testing for each lot of media used.
- Once the media-fill simulation is completed and the final containers are filled with the test medium, incubate media-filled containers in an incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to detect a broad spectrum of microorganisms. Failure is indicated by visible turbidity or other visual manifestations of growth in the medium in 1 or more container–closure unit(s) on or before 14 days.
- In the event of failure, results of the evaluation and corrective actions must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, and the results.

4.2 Reevaluation, Retraining, and Requalification

REQUALIFICATION AFTER FAILURE

Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique, gloved fingertip and thumb sampling, or media-fill testing must successfully pass reevaluations in the deficient area(s) before they can resume processing of sterile preparations. All failures, retraining, and reevaluations must be documented.

REQUALIFICATION PROGRAM

Personnel must successfully complete requalification in the core competencies listed in *4.1 Aseptic Qualifications*. Successful completion must be demonstrated through observation, written testing, and hands-on demonstration of skills.

TIMING OF REEVALUATION AND REQUALIFICATION

Visual observation: Personnel must be visually observed while performing hand hygiene, garbing SOPs, and aseptic technique procedures initially, and then at least once every 12 months.
Gloved fingertip and thumb sampling: Personnel must perform fingertip and thumb sampling 3 times initially, and then every 12 months (in conjunction with media-fill testing).
Media-fill testing: After initial qualification, conduct a media-fill test of all personnel engaged in sterile radiopharmaceutical processing at least every 12 months (in conjunction with gloved fingertip and thumb sampling).
Cleaning and disinfecting: Retrain and requalify personnel in the cleaning and disinfecting of sterile processing areas every 12 months or in conjunction with any change(s) in cleaning and disinfecting SOPs, whichever is sooner.
After a pause in sterile radiopharmaceutical processing: Personnel that have not performed radiopharmaceutical processing in more than 6 months must be requalified in all core competencies before resuming duties.

Sterile compounding using a nonsterile drug substance or components: Personnel who perform sterile compounding using a nonsterile drug substance or components (see *11.3 Sterile Compounding Using a Nonsterile Drug Substance or Components*) must be requalified in all core competencies every 6 months.

4.3 Ancillary Personnel

Personnel who are authorized to be within the sterile processing area and do not handle sterile preparations are not required to complete training on media-fill testing but are required to complete all other training and testing. Other personnel or visitors (e.g., auditors, regulators, student observers) must comply with garbing and gloving SOPs but do not need to prove competency.

4.4 Hand Hygiene and Garbing for Immediate Use Preparations

Radiopharmaceuticals may be prepared and dispensed as immediate use, and the precautions related to personal hygiene to be followed must include the following:

- Hand hygiene: Wash hands and arms to the wrists with soap and water or use a suitable alcohol-based hand rub with a time based on institution policies to reduce bioburden on the hands.
- Garbing: Immediately after hand hygiene, don a clean coat/gown that has not been exposed to a patient or patient care area, and either don sterile gloves or don nonsterile disposable gloves and then disinfect the gloves with sterile 70% IPA. [NOTE—A different lab coat must be worn to care for a patient than the coat/gown used for radiopharmaceutical preparation.]

4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area

In situations involving repackaging, dispensing, preparation, preparation with minor deviations, or compounding of sterile radiopharmaceuticals in an ISO Class 5 PEC, the following precautions related to personal hygiene are to be followed:

- Before entering the SRPA or buffer area, personnel must remove outer garments (e.g., bandanas, coats, hats, jackets, sweaters, vests); all cosmetics; all hand, wrist, and other exposed jewelry including piercings that could interfere with the effectiveness of the garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection). Nail products (e.g., artificial nails, polish, extenders) are prohibited. Natural nails must be kept neat and trimmed. Remove ear buds and headphones. Radiation dosimetry devices are allowed, as required by the RAM license.
- Do not bring electronic devices that are not necessary for compounding or other required tasks.
- Immediately before entering the SRPA or buffer area, remove visible debris from underneath fingernails under warm running water using a disposable nail cleaner. Personnel must wash hands and arms up the elbows with soap and water for at least 30 s and then dry hands using low-lint towels. Alternatively, hand washing may be performed after donning shoe covers, head/hair covers, and face mask, as described below.
- Personnel must don the following garb—shoe covers, head/hair/facial hair covers, face mask—in an order that eliminates the greatest risk of contamination, as defined in facility SOPs.
- If not already performed, remove visible debris from underneath fingernails under warm running water using a disposable nail cleaner. Personnel must then wash hands and arms up to the elbows with soap and water for at least 30 s and then dry hands using low-lint towels. Electronic hand dryers are not permitted.
- Personnel must then perform hand antisepsis cleansing using a suitable alcohol-based hand rub.
- Personnel must then don a low-lint gown with sleeves that fit snugly around the wrists and enclosed at the neck. Disposable gowns are preferred. If reusable gowns are used, a clean gown must be donned daily.
- Personnel must then aseptically don sterile, powder-free gloves. Gloves must completely and snugly cover the ends of the gown cuffs so that skin on the wrists and upper hands is completely enveloped.
- Because gloves may not remain sterile due to touching or handling potentially nonsterile materials, personnel must periodically apply sterile 70% IPA to gloves while balancing the risk of radioactivity contamination.
- Personnel must also routinely inspect the gloves that they are wearing for holes, punctures, radioactivity contamination, or tears. If a defect, radioactivity contamination, or malfunction is detected, personnel must immediately remove the gloves, repeat antiseptic hand cleansing using an alcohol-based hand rub, and don new sterile gloves.
- Direct personnel touch contamination is the most common source of microorganisms, so personnel must avoid touch contamination of container septa, needles, syringe and needle hubs, and other critical sites.

When personnel exit the buffer area or SRPA, shoe covers, head/hair covers, face masks, and gloves must be properly disposed of and new ones donned for each reentry into the buffer area or SRPA. Gowns may be re-used within the same shift if the gown is maintained in a classified area or in (or immediately outside of) the SRPA that minimizes contamination (e.g., away from sinks).

5. FACILITIES AND ENGINEERING CONTROLS

5.1 Facility Design and Environmental Controls

In addition to minimizing airborne contamination, sterile radiopharmaceutical facilities must be designed and controlled to provide a well-lighted and comfortable working environment (see *Physical Environments That Promote Safe Medication Use*

⟨1066⟩). The classified areas and SRPA must be continuously maintained at a temperature of 25° or cooler and should be continuously maintained at a relative humidity (RH) below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for personnel attired in the required garb. The temperature and humidity must be monitored in the classified areas each day that it is used, either manually or by a continuous recording device. The results of the temperature and humidity readings must be documented at least once daily or stored in the continuous recording device, and must be retrievable. The temperature and humidity readings must be reviewed as described in the facility's SOPs. Free-standing humidifiers/dehumidifiers and air conditioners must not be used within the classified area or SRPA. Temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The designated person is responsible for ensuring that each area related to sterile radiopharmaceutical processes meets the classified air quality standard appropriate for the activities to be conducted in that area. They must also ensure that the ISO Class 5 PECs are located, operated, maintained, monitored, and certified to have appropriate air quality.

TYPES OF SECONDARY ENGINEERING CONTROLS AND DESIGN

Due to the interdependence of the various areas or areas that make up a sterile radiopharmaceutical processing facility, it is essential to define and control the dynamic interactions permitted between areas. When designing doors, consider the placement of door closures, door surfaces, and the movement of the door, all of which can affect airflow. Tacky surfaces must not be used in ISO-classified areas.

The PEC must be located in a SEC, which may be either an ISO-classified buffer room with ante-room or an SRPA, in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a laminar airflow workbench (LAFW) or biological safety cabinet (BSC). The ISO-classified ante-room and buffer area must be separated from the surrounding unclassified areas of the facility with fixed walls and doors. Facility design and controls must be in place to minimize the flow of lower-quality air into the more controlled areas. Air supplied to the classified areas must be introduced through HEPA filters that are located in the ceiling. Returns must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate. A smoke study of the PEC must be repeated whenever a change to the placement of the PEC within the area is made. The classified areas must be equipped with a pressure-differential monitoring system. The ante-room must have a line of demarcation to separate the clean side from the less clean side. The ante-room is entered through the less clean side, and the clean side is the area closest to the buffer area. Required garb must be worn prior to crossing the line of demarcation (see *4. Personnel Qualifications, Training, and Hygiene*).

A PEC may be located within an unclassified area, without an ante-room or buffer area. This type of design is called an SRPA. Only sterile radiopharmaceutical preparation, preparation with minor deviations, dispensing, and repackaging may be performed in an SRPA. If the SRPA meets ISO Class 8 total airborne particle count specifications, it can also be used for storage and elution of non-direct infusion radionuclide generators (e.g., Tc-99m). The SRPA must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow which may adversely affect the air quality in the PEC. The impact of activities that will be conducted around or adjacent to the SRPA must be considered carefully when designing such an area. A visible perimeter must establish the boundaries of the SRPA. Access to the SRPA must be restricted to authorized personnel and required materials. An SRPA must not be located adjacent to environmental control challenges.

It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., ISO Class 8 ante-room to ISO Class 7 buffer area to ISO Class 5 PEC) to prevent the influx of contaminants. Airlocks and interlocking doors can be used to facilitate better control of air flow between areas of differing ISO classification (e.g., between the buffer area and ante-room), or between a classified area and an unclassified area (e.g., between the ante-room and an unclassified area such as a hallway) See *5.7 Environmental Controls* for a description of air pressure differentials. If a pass-through is used, both doors must never be opened at the same time, which may be achieved using interlocking mechanisms.

THE RADIOPHARMACEUTICAL PROCESSING ENVIRONMENT

The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 1*) and must be designed to minimize microbial contamination during processing of radiopharmaceuticals under dynamic operating conditions.

The airflow in the PEC must be unidirectional (laminar flow), and because of the particle collection efficiency of the filter, the "first air" at the face of the filter is, for the purpose of aseptic processing, free from airborne particulate contamination. HEPA-filtered air must be supplied in the direct processing area (DPA) (ISO Class 5; see *Table 1*) at a velocity sufficient to sweep particles away from aseptic processing areas and maintain unidirectional airflow as much as possible during operations, given the limitations added from the radiation shielding in the DPA. Proper design and control prevents turbulence and stagnant air in the DPA. In situ air pattern analysis via smoke studies must be conducted at the critical area to demonstrate unidirectional airflow and sweeping action under dynamic conditions.

Table 1. ISO Classification of Particulate Matter in Area Air[a]

ISO Class	Particle Count[b] /m³
3	35.2
4	352
5	3520
6	35,200
7	352,000

Table 1. ISO Classification of Particulate Matter in Area Air[a] *(continued)*

ISO Class	Particle Count[b] /m³
8	3,520,000

[a] Adapted from ISO 14644-1, Clean areas and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.
[b] Limits for number of particles ≥0.5 µm measured under dynamic operating conditions.

TYPES OF PECS AND PLACEMENT

Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for preparing radiopharmaceuticals. Placement of the PEC must allow for cleaning around the PEC.

A PEC provides an ISO Class 5 or better environment for sterile radiopharmaceuticals. The unidirectional airflow within the PEC helps protect the DPA from process-generated contamination of an aseptic processing environment. The unidirectional airflow within the PEC helps protect the DPA from process-generated contamination (e.g., opening wrappings of sterile containers, worker movement, etc.) as well as from outside sources.

Laminar airflow workbench (LAFW): An LAFW used for preparing radiopharmaceuticals must provide vertical unidirectional HEPA-filtered airflow. In cases where the LAFW is located within the segregated containment area of a hot-cell, it is acceptable for a horizontal unidirectional HEPA-filtered airflow pattern to be utilized.

Biological safety cabinet (BSC) Class II: A BSC Class II is a cabinet with an open front, inward airflow, downward unidirectional HEPA-filtered airflow, and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to biohazardous material and to provide an ISO Class 5 or better environment for preparing sterile radiopharmaceuticals.

Placement of PEC: The PEC must be located out of traffic patterns and away from area air currents that could disrupt the intended airflow patterns inside the PEC. If used only to prepare, prepare with minor deviations, dispense, or repackage sterile radiopharmaceuticals the ISO Class 5 PEC may be placed in an unclassified SRPA. If used to compound sterile radiopharmaceuticals, the PEC must be located within an ISO Class 7 or better buffer area with an ISO Class 8 or better ante-room. A dynamic airflow smoke pattern test must be performed initially and at least every 6 months to ensure that the PEC is properly placed into the facility and that workers understand how to utilize the unidirectional airflow to maintain first air as much as possible given the limitations added from the radiation shielding in the DPA.

AIR-EXCHANGE REQUIREMENTS

For classified areas, adequate HEPA-filtered airflow to the buffer area(s) and ante-room(s) is required to maintain the appropriate ISO classification during processing activities. Airflow is measured in terms of the number of HEPA-filtered air changes per hour (ACPH). The ACPH may need to be higher to maintain the required ISO classification and microbial state of control depending on these factors: the number of personnel permitted to work in the area, the number of particulates that may be generated from activities and processes in the area, the equipment located in the area, the area pressure, and the effects of temperature. The summary of ACPH requirements is listed in *Table 2*.

A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7 areas.

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 7 under dynamic operating conditions considering factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, increases the total HEPA-filtered ACPH to at least 30 ACPH
- If the PEC is used to meet the minimum total ACPH requirements, the PEC must not be turned off except for maintenance
- The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on certification reports

A minimum of 20 ACPH of HEPA-filtered air must be supplied to ISO Class 8 areas.

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- Ante-rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 8 under dynamic operating conditions
- The total ACPH must be documented on certification reports

Table 2. Summary of ACPH Requirements for Sterile Radiopharmaceutical Processing

Processing Area	ACPH Requirement
Unclassified SRPA	No requirement
ISO Class 7 area	≥30 ACPH
ISO Class 8 area	≥20 ACPH

5.2 Creating Areas to Achieve Easily Cleanable Conditions

CLASSIFIED AREAS

The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and non-shedding, so they can be cleaned and disinfected, and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Junctures between the ceiling and the walls and between the wall and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, each panel must be caulked or otherwise sealed and secured to seal them to the support frame.

Walls must be constructed of or covered with a durable material (e.g., epoxy-painted walls or heavy-gauge polymer) and the integrity of the surface must be maintained. Panels must be joined together and sealed to each other and the support structure. Floors must include coving to the sidewall or the juncture between the floor and wall must be caulked. Floors must include coving to the sidewall. Classified areas should minimize dust-collecting overhangs such as utility pipes and ledges such as windowsills. If overhangs or ledges are present, they must be easily cleanable. The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls must be sealed.

SRPA

The SRPA and all surfaces (e.g., walls, floors, counters, equipment) within the SRPA must be clean, uncluttered, and dedicated to sterile radiopharmaceutical processing activities. Surfaces in the SRPA should be smooth, impervious, free from cracks and crevices, and non-shedding, so they can be easily cleaned and disinfected, and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Dust-collecting overhangs such as utility pipes and ledges such as windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.

5.3 Water Sources

The facility where sterile radiopharmaceuticals are prepared must be designed so that activities such as hand hygiene and garbing should not adversely affect the ability of the PEC to function as designed. Sinks should enable hands-free use with a closed system of soap (i.e., non-refillable) to minimize the risk of extrinsic contamination. In facilities with an ante-room and buffer area, the sink used for hand hygiene may be placed either inside or outside of the ante-room. If the sink is located outside of the ante-room, it must be located in a clean space to minimize the risk of bringing in contaminants into the ante-room. If the sink is located inside the ante-room, it may be placed on either the clean side or the less-clean side of the ante-room. [NOTE—The order of hand washing and garbing would depend on the placement of the sink (see *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*).] The buffer area must not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)]. The ante-room must not contain floor drain(s). If installed, sprinkler systems in classified areas should be recessed and covered, and should be easily cleanable. In a facility with an SRPA design, the sink must be accessible but located at least 1 m from the PEC and generators, if present. The sink must not be located inside the perimeter of the SRPA.

5.4 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary are permitted in the classified area or SRPA and they should be low-shedding and easily cleaned and disinfected. Their number, design, location, and manner of installation must not adversely impact environmental air quality and must promote effective cleaning and disinfecting. No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the classified area or SRPA.

Carts used to transport components or equipment into classified areas must be constructed from nonporous materials with cleanable casters and wheels. All items must be wiped with low-lint wipers and an appropriate disinfectant by personnel wearing gloves before they are brought into the clean side of ante-room(s), pass-through(s), into an SRPA or into an ISO 5 PEC. However, constraints that would lead to excessive radiation exposure to radiation for workers and thereby be contradictory to following ALARA safety principles (e.g., the wiping of unshielded sources of radioactive material) might preclude this from occurring. In a classified area, carts must not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, is cleaned and disinfected.

5.5 Classified Areas

Activities and tasks carried out within the buffer area must be limited to only those necessary. Food, drinks, and materials exposed in patient care and treatment areas must not enter ante-rooms or buffer areas. When processing activities require the manipulation of blood-derived or other biological material (e.g., radiolabeling patient's or donor's blood cells), the manipulations must be clearly separated from routine material-handling procedures and equipment used in radiopharmaceutical preparation activities, and they must be controlled by specific SOPs to avoid any cross-contamination.

5.6 Remote Aseptic Processing Involving a Hot-Cell

A hot-cell device provides an inherent physical segregation for the ISO Class 5 aseptic processing area. If the hot-cell is located in an ISO-classified space, personnel must garb according to requirements listed in *4.5 Hand Hygiene and Garbing for Buffer*

Areas and Segregated Radiopharmaceutical Processing Area. In settings where tasks are carried out within the hot-cell enclosure not within an ISO-classified space by remote means (i.e., no direct intervention by personnel into the ISO Class 5 space), it is not necessary for personnel to don the garbing described in *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* to carry out these aseptic manipulations or to perform other routine tasks in the general area where the hot-cell is located. If hand and arm incursions into the interior of the hot-cell might be necessary for personnel to stage the required materials and supplies, the personnel must garb in relation to the contamination risk associated with the individual hot-cell/ISO Class 5 relationship.

For situations where a PEC device is located within a hot-cell, dynamic airflow smoke pattern tests must show that the staging of supplies and materials in the demarcated PEC area does not allow the influx of unclassified air into the PEC. Personnel may be garbed in nonsterile gloves and a low-particulate lab coat for interventions that are outside of the PEC. A failure of the airflow smoke pattern test requires personnel to garb in accordance with *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* for all incursions into the hot-cell.

For situations where the hot-cell is an integrated HEPA filtration system with a clear demarcated area that is a PEC, dynamic airflow smoke pattern tests must show that the staging of supplies and materials into the demarcated PEC area does not allow the influx of less than ISO Class 5 quality air into the PEC. Personnel may be garbed in nonsterile gloves and a low-particulate lab coat for interventions that are outside of the PEC. A failure of the airflow smoke pattern test requires personnel to garb in accordance with *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* for all incursions into the PEC.

Since other hot-cell/PEC configurations and technologies may exist, verification (either by airflow smoke pattern tests or other manufacturer specified methods) must ensure, upon each certification, that the staging of materials and supplies does not allow for the intrusion of less than ISO Class 5 air into the designated ISO Class 5 space. A failure of the airflow smoke pattern test requires personnel to garb in accordance with *4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area* for all incursions into the hot-cell.

5.7 Environmental Controls

All RAM users must comply with the conditions specified in their approved RAM license application and regulations, and RAM license conditions may supersede the following requirements for environmental controls described in this section. Pass-through enclosures for transferring radiopharmaceuticals from controlled handling areas (e.g., buffer area) should be designed to provide reasonable balance between maintenance of air quality and other worker safety concerns (e.g., radiation exposure, physical injury from lifting heavy shielded cases). At a minimum, there must be a mechanical system or SOP in place that ensures that both doors cannot be open at the same time. There may be both positive and negative air pressure within the facility; positive pressure to minimize the potential of microbial contamination in sterile drug preparation areas, and negative pressure to minimize potential radioactive contamination from volatile or airborne radiopharmaceuticals. Positive pressure environments must have a minimum differential positive pressure of 0.02-inch water column between each ISO-classified area (e.g., between the buffer area and ante-room). The pressure differential between the ante-room and the unclassified area must be no less than a positive 0.02-inch water column. Refer to the RAM license for negative pressure requirements. For preparation of sterile radiopharmaceuticals, consideration of both concerns could be addressed as follows:

1. Buffer area, if present, must be positive pressure compared to the ante-room
2. Ante-room, if present, must be positive pressure compared to unclassified portions of the restricted area
3. Restricted area, in the presence of volatile or airborne radiopharmaceuticals, must be negative pressure compared to the unrestricted area
4. SRPA must be negative pressure compared to unrestricted areas in the presence of volatile or airborne radiopharmaceuticals (e.g., I-131 sodium iodide and Xenon).

Various environmental controls for various preparation scenarios (see *Table 7* for maximum BUDs for differing environments) are described in the following sections. *Table 1* details the limits for particle counts for each specific ISO classification.

ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS

Any time a pressure differential is required, a pressure monitoring device is required. In a classified area, a pressure differential monitoring system must be used to continuously monitor the pressure differential between the ante-room(s) and buffer area(s) and between the ante-room and the general environment outside the classified area(s) or area(s). The results from the pressure monitoring system must be reviewed and documented at least daily on days the area is used. All pressure monitoring devices must be tested for accuracy and required performance at least every 6 months.

AMBIENT ATMOSPHERE FOR IMMEDIATE USE PREPARATIONS

The following requirements should be met in ambient atmosphere environments:

- Non-patient care space, functionally separate (not necessarily a different area) from the patient care area, such as a radiopharmaceutical handling space, or hot lab, in a hospital, clinic, or mobile coach
- A designated area for medication preparation that is clean and free from clutter
- Low traffic (i.e., limited number of people going in and out or moving around the area during times that radiopharmaceutical processing is being carried out)

SRPA WITH VERTICAL FLOW ISO CLASS 5 PEC(S) FOR RADIOPHARMACEUTICAL PREPARATIONS

An SRPA with vertical ISO Class 5 PECs must meet the following requirements:

- Area surrounding the PEC may be ambient (unclassified) atmosphere

- Area must be clean, uncluttered, and dedicated to the processing of radiopharmaceuticals
- Appropriate for preparation, preparation with minor deviations, repackaging, and dispensing of radiopharmaceuticals

An area that meets ISO Class 8 total airborne particle-count specifications may be used to store and elute non-direct infusion radionuclide generators (e.g., Tc-99m).

AN ISO CLASS 8 BUFFER AREA WITH VERTICAL FLOW ISO CLASS 5 PEC(S) WITH AN ADJACENT ISO CLASS 8 ANTE-ROOM

This environment is appropriate for all activities listed in *SRPA with Vertical Flow ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

AN ISO CLASS 7 BUFFER AREA WITH VERTICAL FLOW ISO CLASS 5 PEC(S) WITH AN ADJACENT ISO CLASS 8 OR BETTER ANTE-ROOM

This environment is appropriate for all activities listed in *An ISO Class 8 Buffer Area with Vertical Flow ISO Class 5 PEC(s) with an Adjacent ISO Class 8 Ante-Room* and sterile compounding.

HOT-CELL

This environment is appropriate for all activities listed in *SRPA with Vertical Flow ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

CERTIFICATION OF PECS AND ENVIRONMENT IN WHICH THE PEC IS LOCATED

Certification of the classified areas, including the PEC, must be performed initially and recertification must be performed at least every 6 months using procedures outlined in the current Controlled Environment Testing Association (CETA) certification guide for *Sterile Compounding Facilities*, or an equivalent guideline, and must include the following:

- Airflow testing: To determine acceptability of the air velocity, the air exchange rate, and area pressure cascade to ensure that air consistently flows from most to least clean areas, and that the appropriate quality of air is maintained under dynamic operating conditions.
- HEPA filter integrity testing: HEPA filters must be leak tested after installation and as part of recertification.
- Total particle counts testing: Conducted under dynamic operating conditions using calibrated electronic equipment.
- Smoke visualization studies: Performed under either simulated or dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

In cases where technologies exist for hot-cell and PEC configurations that are not consistent for certification by the current CETA standards, other equivalent means for certifying the PEC may be performed and documented per facility SOPs. In this case, the PEC must maintain the environmental equivalent for total particle counts and the protection of the ISO Class 5 area from intrusions of lesser controlled air.

DAILY MONITORING OF ENVIRONMENT

The temperature and humidity must be monitored in the SRPA or area containing a hot-cell, and if in a classified area the pressure must monitored, each day that preparations are made, either manually or by a continuous recording device. These include:

- Relative humidity should be kept at 60% or lower
- Temperature and relative humidity continuous readings must be confirmed daily to have remained within the acceptable range
- Excursions must be documented and, if applicable, appropriate corrective actions taken
- Temperature monitoring devices must be verified for accuracy every 12 months or as required by the manufacturer
- Monitoring of pressure differentials must be performed

See *Packaging and Storage Requirements* ⟨659⟩ for information on controlled area temperature and allowable excursions.

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective air and surface monitoring program provides information on the environmental quality of the classified areas where sterile radiopharmaceuticals are processed. The program identifies environmental quality trends over time, potential routes of microbiological contamination, and allows for implementation of corrective actions to prevent microbiological contamination of the radiopharmaceuticals. Facilities must develop and implement written air and surface monitoring procedures for all sterile radiopharmaceutical classified areas. Air and surface monitoring results and the corrective actions must be documented, and records must be readily retrievable as required by jurisdictional laws and regulations.

6.1 General Monitoring Requirements

The goals of an air and surface monitoring program are to determine whether microbiological contamination is present at unacceptable levels and to assess whether proper personnel practices are being followed, cleaning and disinfecting agents are effective, and environmental quality is maintained. The microbiological air and surface monitoring program must include viable impact volumetric airborne particulate sampling and surface sampling.

Air and surface sampling must be performed initially for classified areas in a facility to establish a baseline level of environmental quality. After initial sampling, the classified areas must be monitored according to the minimum frequencies described in this section to ensure that the environment remains in a suitable state for aseptic processing tasks.

The air and surface monitoring program involves the collection and evaluation of samples from various air and surface locations to detect viable microbiological contaminants. The data are then used to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfection techniques and agents specified in the facility SOPs. Regular review of the sampling data must be performed to detect trends such as elevated levels of microbial bioburden, elevated levels of nonviable particulates, or other adverse changes within the environment. Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified limits.

In addition, results must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Prompt corrective action in response to any adverse findings is required to maintain the necessary environmental quality for handling sterile radiopharmaceutical. Data must also be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required air and surface quality levels (see *Table 3* and *Table 4*).

Air and surface sampling must be conducted during actual or simulated dynamic operating conditions to confirm that the required environmental quality in classified areas is maintained. Due to radiation exposure concerns for the workers involved, it is permissible for sampling to be carried out at the conclusion of sterile radiopharmaceutical processing but prior to cleaning and disinfecting the surface area. In this case, simulated tasks that are reflective of the routine aseptic activities are performed. In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any modification of facilities or equipment
- In response to identified problems (e.g., positive growth in sterility tests of compounded radiopharmaceuticals)
- In response to identified trends (e.g., repeated positive gloved fingertip sampling results or failed media-fill testing involving more than one operator where a review of the operator technique shows no reasonable flaws in process; repeated observations of air or surface contamination)
- In response to changes that could impact the controlled area environments (e.g., significant change in cleaning process or the agents involved)

To obtain an air and surface sample that is representative of the typical aseptic operating conditions at the facility, air and surface sampling must be conducted under dynamic or simulated dynamic operating conditions in all PECs and classified areas. If conducted during actual sterile processing, the monitoring program must be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the sterile radiopharmaceutical(s) or the environment.

The air and surface monitoring program must be clearly described in the established SOPs of the facility and must include a diagram of the sampling locations, SOPs for collecting samples, frequency of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the classified areas, and action levels that will trigger corrective action. The locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible contamination risk to the sterile radiopharmaceuticals involved with the operation's processes and that are likely to be representative of the conditions throughout the area.

Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified limits.

It is important that personnel who operate the equipment be trained in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All air sampling devices must be serviced and calibrated as recommended by the manufacturer.

6.2 Monitoring Air Quality for Viable Airborne Particles

A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all classified areas.

VIABLE AIR SAMPLING: TIMING AND LOCATIONS

Volumetric active air sampling of all classified areas (e.g., ISO Class 5 PEC and ISO Class 7 and 8 areas) using an impaction device must be conducted during dynamic operating or simulated operating conditions at least every 6 months.

Air sampling sites must be selected in all classified areas. When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow if taken during actual sterile processing activities. Viable air sampling must include:

1. Follow the manufacturer's instructions for operation of the air sampling device, including placement of media.
2. Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
3. At the end of the sampling, retrieve the media plates/devices and cover.
4. Invert the media and incubate at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m^3 of air on an environmental sampling form based on sample type (i.e., viable air). Include sample location and date.
5. Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m^3 of air on an environmental sampling form based on sample type (i.e., viable air). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently. Both samples could be TSA or one sample could be TSA and the other fungal media [e.g., malt extract agar (MEA) or sabouraud dextrose agar (SDA)]. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample at 20°–25° for no less than 5 days. Fungal media samples must be incubated at 20°–25° for no less than 5 days. Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample.

Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air) and include the sample location, and sample date.

A general microbiological growth medium that supports the growth of bacteria and fungi must be used (e.g., TSA medium). CoA(s) from the manufacturer must verify that the medium meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in a temperature monitored incubator with a calibrated measuring device. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented. Incubators used for microbiological testing must be placed in a location outside of any classified area or SRPA and kept away from areas where compounding or sterile processing activities are carried out. All sampling activities must be performed by trained individuals.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 3* and in relation to previous data to identify adverse results and/or trends. If two pieces of media were collected at a single location, all recovered growth on each must be documented and action levels are applied individually to each plate/device (i.e., results from each cubic meter of air sampled must be compared to the action level for that area). If levels measured during the viable air monitoring program exceed the levels in *Table 3* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair, or reducing the BUD of the radiopharmaceutical during investigation and while carrying out the corrective action plan. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during viable air sampling exceed the levels in *Table 3*, an attempt must be made to identify any microorganism recovered to the genus level (see *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).

Table 3. Action Levels for Viable Airborne Particle Air Sampling[a]

ISO Class	Air Sampling Action Levels [cfu/m^3 (1000 L) of air per plate]
5	>1
7	>10
8	>100

[a] Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. US Department of Health and Human Services, Food and Drug Administration (FDA), September 2004.

6.3 Monitoring Surfaces for Viable Particles

Surface sampling is an important component of the maintenance of a suitably controlled environment for sterile radiopharmaceutical processing, especially because transfer of microbial contamination from improperly disinfected work surfaces (e.g., via inadvertent touch contact by personnel) is a potential source of contamination of the radiopharmaceutical(s). Surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as proper cleaning and disinfection. All sampling sites and procedures must be described in the facility's SOP.

SURFACE SAMPLING: TIMING AND LOCATIONS

Surface sampling of all classified areas and all PECs must be conducted at least monthly for the detection of microbial contamination. Each classified area must be sampled (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩). The DPA of the PEC, and any equipment permanently contained in the PEC, must be sampled. Staging or work surfaces in classified areas near the PEC, frequently touched surfaces in classified areas, and pass-through enclosure(s) for all classified areas are to be evaluated to determine the locations that pose the greatest risk of harboring microbial contamination.

Surface sampling must be performed at the end of the radiopharmaceutical aseptic activities or shift, but before the area has been cleaned and disinfected. However, radiopharmaceutical personnel must also consider the appropriate exposure and contamination prevention measures prior to and while collecting samples. If the worker assesses that the risk for exposure is not in conformance with ALARA safety standards, measures must be taken to eliminate the risk (e.g., implementation of appropriate shielding, performing the sampling at a later time or alternate day).

SAMPLING PROCEDURES

Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. CoAs from the manufacturer must verify that the media meet the expected growth promotion, pH, and sterilization

requirements. Surface sampling devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. If used, contact plates must have a raised convex surface. Sterile swabs wetted with sterile water or a sterile neutralizing buffer may be used when sampling irregular surfaces and difficult-to-reach locations, such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected.

Use the following procedures for surface sampling on flat surfaces:

1. Remove the cover from the surface sampling device. Firmly press, using a rolling motion, if possible, the media surface onto the surface to be sampled. The surface sampling device will leave a residue of growth medium on the sample site. After sampling, use sterile 70% IPA to remove residue. Cover each surface sampling device.
2. If using plates, invert the plates.
3. Incubate the surface sampling devices at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu/sample on an environmental sampling form based on sample type (i.e., surface). Include sample location and date.
4. Incubate the device at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location.

1. Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
2. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample at 20°–25° for no less than 5 days.
3. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
4. Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample. Record the results of the sampling.
5. Record the results of the sampling.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 4* and examine counts in relation to previous data to identify adverse results or trends. If two devices were collected at a single location, all recovered growth on each must be documented and action levels are applied to each piece of media individually (i.e., results from each sampling device must be compared to the action level for the area). If levels measured during surface sampling exceed the levels in *Table 4* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair, or reducing the BUD of the radiopharmaceutical(s) during investigation and while carrying out the corrective action plan. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during surface sampling exceed the levels in *Table 4*, an attempt must be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).

Table 4. Action Levels for Surface Sampling

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

7. CLEANING AND DISINFECTING

Cleaning and disinfecting are important because surfaces in classified areas and SRPAs are a potential source of microbial contamination of sterile radiopharmaceuticals. The process of cleaning involves removing organic and inorganic residues from surfaces, usually with a manual or mechanical process and a cleaning agent. The process of disinfecting involves destruction of microorganisms, usually with a chemical or physical agent. Surfaces must be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA)-registered (or equivalent) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. After cleaning and disinfecting or the application of a one-step disinfectant cleaner in a PEC, apply sterile 70% IPA to remove any residue.

Cleaning and disinfecting surfaces should occur at the minimum frequencies specified in *Table 5* or if activities are not performed daily, cleaning and disinfecting must be completed before initiating activities. The act of reducing or removing radioactivity (radioactive decontamination) from an object or surface must be balanced with the risk of spreading radioactive contamination. At times the best approach may be to shield the area until the radiation exposure levels are lower. This balance must be specified in SOPs (e.g., trigger levels for safe cleaning). The PEC should be checked for radioactive contamination prior to cleaning and disinfecting to prevent spreading radioactive contamination in the PEC.

All cleaning and disinfecting activities must be performed by trained and appropriately garbed personnel using facility-approved agents and procedures that must be described in written SOPs. Cleaning must be performed in the direction of most

to least clean areas. The frequency, method(s), and location(s) of cleaning, disinfecting, and sporicidal agent use must be established in written SOPs, in accordance with the manufacturer's instructions when available, or based on sound microbiological cleaning techniques when unavailable, and must be followed by all cleaning personnel. The manufacturer's direction or published data for the minimum contact time must be followed for the cleaning, disinfecting, and sporicidal agents used. When sterile 70% IPA is used, it must be allowed to dry. All cleaning, disinfecting, and application of sporicidal agents must be documented according to facility SOPs.

Table 5. Minimum Frequency for Cleaning and Disinfecting Surfaces in Classified Areas and within the Perimeter of the SRPA

Site	Cleaning	Disinfecting[a]	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield and any exposed surface of equipment inside the PEC must be cleaned to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist). Radioactive contamination may be shielded with appropriate temporary material, providing the material is covered with low-lint absorbent pads or has equivalent low-shedding properties.	Following cleaning on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist). When used, remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.	Monthly
Surfaces of sink(s)	Daily	Daily	Monthly
Hot-cells (all interior surfaces, dependent on design, equipment, and shielding present)	Daily	Daily	Monthly
PEC and the equipment inside the PEC(s) located in a hot-cell	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield, and any exposed surface of equipment inside the PEC to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist). Radioactive contamination may be temporarily shielded with appropriate temporary material providing the material is covered with low-lint absorbent pads or has equivalent low-shedding properties.	Following cleaning on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent possible as specified by the equipment manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist) and should be specified by SOPs. Remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.	Monthly
Work surface(s) outside the PEC	Daily	Daily	Monthly
Ceiling(s)	Monthly	Monthly	Monthly
Wall(s), door(s), door frame(s), and other fixtures	Monthly	Monthly	Monthly
Floor(s)	Daily	Daily	Monthly
Storage shelving and storage bins	Monthly	Monthly	Monthly

[a] Many disinfectants registered with the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Cleaning and disinfecting must be balanced with the risk of spreading radiation contamination. The best approach may be to shield the area until the radiation exposure levels are lower.

7.1 Cleaning, Disinfecting, and Sporicidal Agents

Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and user safety. Considerations when selecting and using disinfectants include their anti-microbial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected (see *Disinfectants and Antiseptics* ⟨1072⟩). After the disinfectant is applied on the surface to be disinfected, the disinfectant must be allowed to dwell for the minimum contact time specified by the manufacturer, during which time the surface cannot be disturbed. Only the 70% IPA used in the ISO Class 5 PEC must be sterile. Sporicidal agents must be used at least monthly on all surfaces in classified areas and SRPAs. Some EPA-registered (or equivalent) one-step disinfectant cleaners may have sporicidal properties. See *Table 6* for a summary of the purpose of the cleaning, disinfecting, and sporicidal agents.

Table 6. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

Type of Agent	Purpose
Cleaning agent	An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfecting agent	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.

Table 6. Purpose of Cleaning, Disinfecting, and Sporicidal Agents *(continued)*

Type of Agent	Purpose
Sporicidal agent	A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

7.2 Cleaning Supplies

All cleaning supplies (e.g., wipers and mop heads), with the exception of tool handles and holders, must be low-lint and should be disposable. If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable materials (e.g., no wooden handles) and must be cleaned and disinfected before and after each use. Reusable cleaning tools must be dedicated for use in the classified areas or SRPAs and must not be removed from these areas except for disposal. They must be discarded after an appropriate amount of time, to be determined based on the condition of the tools. Cleaning supplies and solutions used in the classified areas and SRPAs should be monitored for radioactive contamination after use and prior to disposal, as per facility SOPs. Dispose of cleaning supplies used in the classified areas and SRPAs in a manner that minimizes the potential for dispersing particulates into the air (e.g., with minimal agitation, away from work surfaces).

7.3 Cleaning and Disinfecting the PEC

Clean and disinfect the PEC at the minimum frequencies specified in *Table 5*. If the PEC contains a removable work tray, all sides of the work tray and the area underneath the work tray must be cleaned and disinfected at least monthly.

1. Survey all surfaces of the PEC for radioactive contamination and follow facility SOPs to decontaminate, if necessary.
2. Remove, if necessary, any particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
3. Apply a cleaning agent followed by a disinfecting agent or apply an EPA-registered (or equivalent) one-step disinfectant cleaner and ensure that the contact time specified per manufacturer instructions is achieved.
4. Apply sterile 70% IPA
5. Allow the surface to dry completely before beginning activities.
6. The PEC must be wiped with a sporicidal agent at least monthly.

7.4 Disinfecting Supplies for Classified Areas and SRPAs

No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the classified area (e.g., clean side of ante-room) or within the perimeter of the SRPA. Before items are introduced into a classified area or SRPA, they must be wiped with a sporicidal agent, EPA-registered (or equivalent) one-step disinfectant cleaner, or sterile 70% IPA using low-lint wipers. After the sporicidal or sterile disinfectant is applied onto the surface, the agent must be allowed to dwell on the surface for the minimum contact time specified by the manufacturer (see *6.1 General Monitoring Requirements*). The agent used for disinfecting the packaging must be compatible with the packaging and must not render the product label unreadable.

Any item to be transferred into the PEC from the classified area or SRPA must be disinfected with a sterile disinfectant (e.g., sterile 70% IPA).

In the case of radiopharmaceuticals being processed by remote means in a hot-cell, the opening of sterile packages (e.g., syringes, luer lock caps) may not be possible by remote means within the ISO Class 5 area. In this case, the syringes may be opened and appropriately labeled outside of the ISO Class 5 environment and placed in disinfected shielding, immediately prior to the forthcoming dispensing cycle.

7.5 Disinfecting Critical Sites

Critical sites (e.g., vial stoppers) must be wiped with sterile 70% IPA. The critical site must be wiped ensuring that both chemical and mechanical actions are used to remove contaminants. The sterile 70% IPA must be allowed to dry before piercing critical sites.

7.6 Cleaning and Disinfecting Items from Patient Care Area

Radiation shielding and equipment used in the classified area/SRPA or PEC that is exposed to patient care areas during the process of administration must be cleaned and disinfected before returning to any classified area (e.g., buffer or ante-room) or SRPA in accordance with the Centers for Disease Control and Prevention guidelines[1] as noncritical equipment requiring low-risk disinfection. Syringes that have been used in a patient care area must not be brought back into the classified area (e.g., buffer or ante-room) or SRPA for re-assaying or disposal unless the syringe is sealed inside an impervious container (e.g., sealed plastic bag) that is disinfected prior to entry into the classified area or SRPA. Equipment that has been exposed to needles and syringes contaminated with blood-borne pathogens and RAMs are considered mixed waste (e.g., syringe shields and syringe carrying containers). This equipment must be cleaned and disinfected through actions regulated by the facilities' SOPs. Equipment that contained or was in contact with mixed waste must be cleaned and disinfected with an appropriate agent(s) for blood.

[1] Centers for Disease Control and Prevention. *Guideline for Disinfection and Sterilization in Healthcare Facilities*, 2008.

8. ASSIGNING BUD

BUDs are based on the risk of microbial contamination with the assumption that the radiopharmaceutical(s) should remain chemically and physically stable, and its container–closure system should maintain its integrity for the duration of the BUD (*Table 7*). The time starts at the moment of the first sterile vial puncture or exposure of a critical site (e.g., syringe tip, needle hub, or needle) to ambient air, whichever is first. The BUDs stated in *Table 7* are maximum values in the absence of sterility testing, and the assigned BUD may be shorter for a variety of reasons discussed below. The individual responsible for the manipulation assigns the BUD based on established testing data, either performed in-house or obtained from peer-reviewed literature.

Table 7. Preparation Conditions for Sterile Radiopharmaceuticals

Preparation Conditions			
Manipulation	**PEC**	**SEC**	**BUD (hours)**
Immediate use	—	—	1
Direct infusion system, one puncture only (e.g., PET patient infusion system, Rb-82 generator)	—	—	10
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	SRPA	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using sterile components	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	96
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using a nonsterile component and performing sterilization procedure (e.g., filtration with bubble point testing) but without performing *Sterility Tests* ⟨71⟩ testing	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	24
Radiolabeled blood components for immediate use [e.g., Tc 99m red blood cells (RBC)]	—	—	1
Radiolabeled blood components (e.g., radiolabeled leukocytes)	ISO Class 5 BSC	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	6 h after the blood sample is obtained

For compounded preparations (sterile and nonsterile), the BUD is also dependent on maintenance of appropriate quality and purity, including radiochemical purity, radionuclidic purity, and other applicable parameters as specified in individual monographs or as clinically appropriate.

For preparations with minor deviations involving conventionally manufactured kits (sterile and nonsterile), the kit may state or suggest a use-by time in the package insert. For certain radiopharmaceuticals transportation time, radionuclide availability, and other factors may necessitate extending manufacturer-stated/suggested use-by time to meet patient needs. Assigning a BUD longer than the manufacturer-stated/suggested use-by time interval must be supported by evidence of the maintenance of appropriate quality and purity, including radiochemical purity and radionuclidic purity as specified in individual monographs, and other applicable parameters as clinically appropriate.

Assignment of a BUD for a radiopharmaceutical(s) must consider several factors, as applicable. Issues of concern include, but are not limited to, the following:

- Sterility: Maintenance of sterility is a major concern for any sterile preparation or product. Good aseptic handling practices in an appropriate environmentally-controlled area are the most critical factors in ensuring sterility. See *Table 7* for maximum BUD. The assigned BUD should not exceed the sterility-related times listed in *Table 7*, unless a longer time is justified by *Sterility Tests* ⟨71⟩.
- Radiochemical purity: Maintenance of radiochemical purity is affected by a variety of factors including, but not limited to, storage temperature, quantity of radioactivity, radioactivity concentration, presence or absence of antioxidants or other stabilizing agents, and container type (e.g., glass vial vs. plastic syringe). The assigned BUD must be based on stability studies in which these variables are controlled and are representative of the conditions of actual use. For factors that allow

a range of values (e.g., storage temperature, quantity of radioactivity, radioactivity concentration), studies should be conducted at the extremes of the ranges.

- Radionuclidic purity: Because radionuclidic impurities may decay away more slowly than the primary radionuclide, the radionuclidic purity may decrease over time. For example, the ratio of Mo-99 (half-life of about 66 hours) to Tc-99m (half-life of about 6 hours) continuously increases over time. *USP* monographs for Tc-99m radiopharmaceuticals require that the radionuclidic impurity Mo-99 not exceed 0.15 µCi Mo-99 per mCi Tc-99m at the time of administration. Calculation of radionuclidic purity at future times is necessary to ensure compliance throughout the assigned BUD.
- Age of generator eluate: As a generator eluate decays, the desired daughter radionuclide decays to form other nuclides and potential radiolytic products, which may interfere with radiolabeling of kits. For example, Tc-99m undergoes decay to Tc-99. More importantly, increasing amounts of peroxides formed as radiation interacts with water molecules. Increased amounts of Tc-99 and peroxides can interfere with the radiolabeling of many kits. Extension of the BUD for Tc-99m pertechnetate intended for radiolabeling of kits must take into account the build-up of Tc-99 and peroxides over time.
- Number of particles: For radiolabeled particulates, the number of particles per unit radioactivity increases over time as the radionuclide decays. For example, the BUD for Tc-99m albumin aggregated [macroaggregated albumin (MAA)] must take into account the increasing ratio over time of the number of particles per unit radioactivity. For example, if an MAA kit is prepared such that the radioactive patient dose is 200,000 particles at the time of calibration, the same patient dose will contain 700,000 particles at 10.85 hours after calibration. Calculation of the number of MAA particles in the patient dose is necessary to ensure compliance with the prescribed particle range throughout the assigned BUD.
- Specific activity: For some receptor-based radiopharmaceuticals, the mass quantity may influence uptake (i.e., too much mass may result in saturation of receptor sites and reduce target uptake of the radiopharmaceutical). As radioactivity decays over time, specific activity decreases resulting in more mass per unit radioactivity. In such situations, the assigned BUD must ensure that the patient dose contains no more than the specified maximum mass.
- Container type: Because radiochemical stability or other quality attributes of a radiopharmaceutical may be affected by its container characteristics, the BUD for a radiopharmaceutical dose dispensed in a plastic syringe may be different than the BUD of that same radiopharmaceutical maintained in a glass vial. The assigned BUD must be determined in the proper storage container.
- Cell viability: The viability of radiolabeled blood cells (e.g., leukocytes) decreases over time, and may also be affected by other factors such as the suspending medium, temperature, and agitation. The assigned BUD should be as short as circumstances reasonably allow so as to maximize cell viability.
- In the case of manufactured radiopharmaceuticals that are distributed to nuclear pharmacies or other healthcare facilities for terminal distribution/dispensing, the assigned BUD of the dispensed dose cannot exceed the expiration date/time of the manufactured radiopharmaceutical(s).
- In the case of radiopharmaceuticals prepared from kits, the BUD of a dispensed dose cannot exceed the assigned BUD of the finished kit preparation.
- A radiopharmaceutical may not exceed the shortest BUD of any of its components.

The facility must have policies and SOPs appropriate to the assignment of BUD and maintain documentation of applicable study results and calculations. Studies of radiolabeling efficiency and radiochemical stability should employ quality control (QC) testing methods described in the manufacturer's package insert, *USP* monographs and general chapters, or other equivalent testing methods and be sufficiently rigorous to allow statistical confidence in the results.

The facility must have SOPs to collect and evaluate complaints associated with the use of radiopharmaceuticals having assigned BUDs. Policies and SOPs should also be in place to reevaluate the assigned BUD based on complaints, which may include repeating studies and/or performing additional studies on radiolabeling efficiency and/or radiochemical stability.

9. DOCUMENTATION

Applicable records (hard-copy or electronic), including policies and SOPs, must be maintained for all activities involved in repackaging, preparing, preparing with minor deviations, compounding, and dispensing radiopharmaceuticals. Such records include, but are not limited to:

- Personnel training and testing, including visual assessment of aseptic technique competency, validation, garbing, hand hygiene, equipment/environment cleaning and disinfecting, gloved fingertip and thumb sampling, and media fill evaluation initially and follow up testing at specified intervals.
- Testing and monitoring of environmental controls, including ISO classification, ACPH, pressure differentials, temperature, humidity and viable air/surface and total airborne particle test results
- Equipment maintenance and cleaning/disinfecting
- End product radiochemical purity and other testing, as applicable, results of preparations, preparations with minor deviations, and compounded preparations
- Master Formulation Record (MFR) for preparation with minor deviation(s) and compounding
- Validation of stability testing to support the assigned BUD from SOPs by the compounder or derived from accepted literature
- Investigations and corrective actions and tracking of events to closure.

9.1 Master Formulation Record

A MFR is required only for a preparation with minor deviations or compounding, as described in *11. Compounding*. A MFR is not required for a preparation following the manufacturer's instructions.

Data that must be included in the MFR are as follows:

- Name of the radiopharmaceutical
- Name, identity, strength, purity, quality, and quantity of ingredients with validated documentation (e.g., CoA)
- Detailed procedure (e.g., heating, components, incubation time)
- Range of radioactivity
- Range of volume
- Equipment to be used
- PEC and SEC to be used, if applicable
- Quality control tests to be performed for final release of the radiopharmaceutical (e.g., radiochemical purity, pH)
- Procedures for depyrogenation and sterility procedures and validations, as applicable, including limits
- Trained personnel
- Garbing procedure, if different than standard procedure
- Container(s)
- Reference source of the BUD assignment and storage conditions

9.2 Records for Preparation with Minor Deviations/Compounding

A record for preparation with minor deviation or compounding must include the following:

- Name of the radiopharmaceutical
- Physical form (e.g., capsule or solution)
- Name and quantity of ingredients including calibration time for radioactive ingredients (e.g., 100 mCi Tc 99m sodium pertechnetate @ 1300)
- Total volume
- Reference to the MFR
- Any deviation from the MFR, if applicable
- Name of vendor or manufacturer, lot numbers, and expiration dates of all ingredients and components
- Name of the person who prepared and name of the supervising personnel (e.g., ANP or AU physician)
- Date and time of preparation
- Assigned internal identification number (e.g., lot number)
- Unique reference [e.g., prescription, order number(s)]
- Assigned BUD and storage requirements
- Documentation of QC results

10. PREPARATION

The individual responsible for preparing the radiopharmaceutical(s) must ensure that the final preparation complies with quality and purity specifications throughout the assigned BUD. This includes, as appropriate for the preparation, radionuclidic purity, radiochemical purity, chemical purity, and physical and chemical properties.

10.1 Preparation Following Manufacturer Instructions

NONSTERILE PREPARATIONS

For nonsterile preparations, follow manufacturer preparation instructions (e.g., I-131 NaI capsules or solution), taking into account appropriate radiation safety considerations and environmental controls, if applicable (e.g., negative air pressure area, chemical fume hood, activated charcoal filters when handling a potentially volatile radionuclide). The area should be suitably cleaned and uncluttered to ensure the overall integrity and quality of the prepared radiopharmaceutical(s). There should be a documented process for activities (e.g., cleaning) between the preparation cycles of different nonsterile products, to decrease the likelihood of contamination from other prepared products.

STERILE PREPARATIONS

For sterile preparations (including intravascular devices), follow manufacturer preparation instructions, taking into account appropriate radiation safety considerations, appropriate environmental controls, and aseptic handling practices to maintain sterility. The minimum environmental standard for the preparation of sterile radiopharmaceuticals beyond immediate-use is within an ISO Classified area or device (see *Table 7*). Refer to *5. Facilities and Environmental Controls* and *Table 7* on the location of the PEC and the assignment of the BUD.

10.2 Preparation with Minor Deviations

In some cases, radiopharmaceuticals are prepared with minor deviations from manufacturer instructions that are necessary to accommodate circumstances not contemplated in the FDA-approved labeling. Note that *General Notices, 5.20.20.1 In Compounded Preparations* includes the statement: "Deviation from the specified processes or methods of compounding,

although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process." However, except for a few receptor-based radiopharmaceuticals where specific activity is an important parameter, there is a very broad range of acceptable values for specific activity and for proportions of ingredients. Deviations from manufacturer preparation instructions for radiopharmaceuticals must maintain the same ingredients but may differ in their proportions.

This requires appropriate in-house QC testing, designed to validate the radiochemical purity of the product for the entirety of the BUD or is supported by appropriate peer-reviewed publications for the minor deviation utilized.

Examples of minor deviations include, but are not limited to, the following:

- Altering the quantity of radioactivity or volume added to the vial
- Changes in step-by-step operations (e.g., dilute Tc-99m sodium pertechnetate after rather than before addition to the vial)
- Using alternative devices or equipment (e.g., a heating block rather than a hot water bath, using a different sized needle, different shielding materials)
- Using QC test methods other than those described in the product labeling (e.g., radiochemical purity)
- Filtering Tc-99m sulfur colloid

10.3 Preparation of Radiolabeled Blood Components

Handling blood and radiolabeling of blood components requires special attention to biological risks and must be handled with standard precautions using aseptic technique to prevent the introduction of new microorganisms into the preparation that will be administered. Due to the potential presence of microorganisms in the original blood sample, the preparation must be administered as soon as possible but no later than 6 hours after the blood sample is obtained from the patient or blood bank.

The presence of microorganisms in a blood sample may present a risk to the individual performing the preparation as well as cross-contamination to other blood samples or other non-blood related radiopharmaceuticals. Equipment and supplies should never be shared with other activities unless they are first thoroughly cleaned and disinfected. Special precautions when radiolabeling of blood components for non-immediate use include:

- There must be complete physical separation (either fixed or non-fixed wall) of areas where blood products are handled from areas where non-blood products are handled. An ISO Class 5 BSC located in an ISO Class 7 buffer area is required for blood-labeling processes. If more than one ISO Class 5 PEC is located within the ISO Class 7 buffer area, policies and SOPs must be in place to include certification that the SEC meets conditions of air quality at maximum occupancy under dynamic operating conditions.
- One radiolabeling procedure per PEC at a time. Blood products from more than one patient must never be manipulated at the same workstation at the same time. Each area should have dedicated supplies, equipment (including dose calibrator), and waste disposal to eliminate sharing of these items or overlap in pathways.
- Thorough cleaning and disinfection of the ISO Class 5 BSC and all reusable equipment within, prior to starting another blood component radiolabeling procedure.
- If a dedicated dose calibrator is not available, then a means of preventing the blood container(s) from contaminating the dose calibrator must be used or the dose calibrator dipper and liner must be cleaned and disinfected following the radioassay.
- Centrifuge should be located within the ISO Class 7 buffer area that is dedicated for blood component radiolabeling processes.
- Dedicated (per each radiolabeling procedure) consumable products (e.g., 0.9% sodium chloride injection, diluent, tubes, syringes, and other supplies) necessary for each individual patient radiolabeling procedure.
- All tubes and syringes in contact with the patient's blood components must be clearly labeled with the patient's name and at least one additional identifier (e.g., date of birth, medical record number, barcode).
- Dedicated syringe shields and vial shields.
- Remove and replace any garb that enters the ISO Class 5 BSC before handling anything else not related to performing this procedure.
- Removal of all disposable items from the ISO Class 5 BSC utilized in each radiolabeling procedure.
- Cleaning and disinfection of all reusable equipment and components (e.g., BSC, centrifuge, dose calibrator, syringe shields, vial shields, syringe transport shields and delivery cases) after each radiolabeling procedure prior to any further use. Policies and SOPs must address cleaning and disinfection processes including the use of an EPA-registered (or equivalent) one-step disinfectant cleaner with activity against blood-borne pathogens followed by sterile 70% IPA. Sterile 70% IPA alone is not sufficient.
- After the completion of blood radiolabeling procedures, follow all requirements in *4.5 Hand Hygiene and Garbing for Buffer Areas and segregated Radiopharmaceutical Processing Area*.

10.4 Preparation of Radiolabeled Red Blood Cells for Immediate Use

In vitro red blood cell labeling must be prepared while following the conditions below:

- A dedicated space for blood handling must be designated through the entirety of the blood radiolabeling process. This area must be free from clutter and not used for any other radiopharmaceutical preparation or handling until the completion of cleaning and disinfection.
- Perform only one radiolabeling procedure at a time or have documented processes that maintain the integrity of samples and environment.

- Dedicated equipment must be used for blood radiolabeling procedure (e.g., L-block, syringe shield, vial shield, forceps, needle recapper).
- If a dedicated dose calibrator is not available, then a means of preventing the blood container(s) from contaminating the dose calibrator or a cleaning and disinfecting procedure with an appropriate product must be used to decontaminate the dipper and liner of the dose calibrator following the radioassay
- A cleaning and disinfecting procedure with an appropriate agent(s) must be used to decontaminate the area and equipment prior to and after the radiolabeling is complete and all disposable components have been discarded
- Follow all requirements in *4.4 Hand Hygiene and Garbing for Immediate Use Preparations*.
- The start time of the preparation must begin with the initial container puncture or the exposure of a critical site (e.g., syringe tip, needle hub or needle) to ambient air, whichever is first.
- BUD of 1 hour (see *Table 7*).

11. COMPOUNDING

Each compounding activity must be based on a pre-established written procedure and must include maintenance of compounding records. The compounding record must provide traceability (see *9. Documentation*).

All sterile compounding, using aseptic technique, must be performed in an ISO 5 PEC. Refer to *5.7 Environmental Controls* and *Table 7* for further clarification on the location of the PEC and the applicability of the radiopharmaceutical BUD.

Compounding must not be performed for any radiopharmaceutical(s) that has been withdrawn from the market because of safety or lack of effectiveness, unless part of an institutional review board approved investigational study. Radiopharmaceuticals that are essentially copies of marketed FDA-approved radiopharmaceuticals must not be compounded unless there is a change that produces a clinical difference for an identified individual patient, as determined by a prescriber.

11.1 Compounding Nonsterile Radiopharmaceuticals

Compounding nonsterile radiopharmaceuticals is the combining, mixing, diluting, pooling, reconstituting or otherwise altering a drug or bulk drug substance other than as provided by the manufacturer's package insert to create a nonsterile radiopharmaceutical. Examples of compounding nonsterile radiopharmaceuticals include: changing the dosage form of a capsule to a solution, changing an intravenous dosage form to an oral dosage form, and radiolabeling a food for oral administration (e.g., Tc-99m sulfur colloid in eggs). Areas designated for nonsterile compounding must be cleaned and uncluttered and separated from areas designated for sterile radiopharmaceuticals. Compounding should take into account RAM licensing requirements for appropriate radiation safety considerations and utilize appropriate environmental controls, if applicable (e.g., chemical fume hood, activated charcoal filters when handling potentially volatile radionuclides). The placement of equipment and materials must take into account a design that prevents cross-contamination.

When feasible, disposable material should be used to reduce the chance of cross-contamination. Each compound must have a unique MFR (see *9.1 Master Formulation Record*). The preparation information is documented on a compounding record (see *9.2 Records for Preparation with Minor Deviations/Compounding*). The MFR details the selection of all components. The ingredients must be obtained from sources in this preferential order: FDA-approved product; FDA-registered facility; and lastly, if the ingredients for the compound are not available from either of these two sources, the MFR must detail the selection of a material that is suitable for the intended use. The MFR must establish the identity, strength, purity, and quality of the ingredients by validated means (e.g., CoA). Requirements for nonsterile oral meal components are limited to common food grade description and are not required to establish identity by validated means.

A BUD for the compounded radiopharmaceutical must be validated, taking into account the stability of the ingredients, any intermediate containers, the final container, and the storage conditions. A BUD cannot be extended past the labeled expiration date of any component in the compound. If the compounded radiopharmaceutical(s) includes components from other preparations or preparations with minor deviations, the BUD of the final compounded radiopharmaceutical must not exceed the shortest remaining BUD of any of those components.

11.2 Sterile Compounding

Some compounding activities involve only the addition of a conventionally manufactured drug product (e.g., *Ascorbic Acid Injection*, *Lidocaine Hydrochloride Injection*, *Sodium Bicarbonate Injection*) approved by the appropriate regulatory agency to a radiopharmaceutical.

Personnel responsible for compounding must consider all possible interactions between the components, such as altered chemical stability, radiochemical stability, solubility, or other parameters (e.g., osmolality) related to changes in pH, excipients, or other factors, in determining an appropriate BUD. In some cases, this may require systematic QC testing over time to validate the appropriateness of a particular BUD.

Another activity that is considered a compounding activity is the splitting of conventionally marketed kits. Kit-splitting (also referred to as "fractionation") may be used to meet patient need. For example, the contents of a kit vial can be reconstituted with 0.9% sodium chloride injection and aliquoted into other containers for storage and subsequent radiolabeling. The individual responsible must consider all possible interactions of kit components with these other containers (e.g., container walls, closures), as well as possible alterations in stability (e.g., physical stability, chemical stability) that may affect radiolabeling yields or performance parameters, when determining an appropriate BUD. Systematic QC testing is required to validate the appropriateness of a particular BUD.

11.3 Sterile Compounding Using a Nonsterile Drug Substance or Components

Some sterile compounding activities involve the use of materials other than commercially marketed products, such as drug substances and/or radionuclides. If one or more materials or components are not certified to be sterile and pyrogen-free, a sterilization procedure (e.g., filtration with bubble point testing) and testing described in ⟨85⟩ must be performed. The designated person for compounding is responsible for ensuring that the final preparation complies with pre-established standards or acceptance criteria for identity, quality, and purity, and must consider all possible interactions between the components, such as altered chemical stability, radiochemical stability, solubility, or other parameters (e.g., osmolality) related to changes in pH, excipients, or other factors, in determining an appropriate BUD. This may require testing to validate the appropriateness of a particular BUD.

If compounding involves a bulk drug substance, the radiopharmaceutical must comply with standards of an applicable *USP* or *NF* monograph, if one exists, or be a component of an approved drug product. For this chapter, a bulk drug substance includes a radionuclide, a ligand, or other substance, such as a precursor that becomes an active ingredient in the final radiopharmaceutical. Each bulk drug substance should be manufactured by drug establishments registered with FDA and be accompanied by a valid CoA or equivalent testing procedures.

If compounding involves excipients or other inactive ingredients, the excipients or other inactive ingredients must comply with standards of an applicable *USP* or *NF* monograph, if one exists. It is also acceptable that any excipients or other inactive ingredients be approved products, manufactured by a drug establishment registered with the FDA.

12. DISPENSING

12.1 Dispensing and Radioassay

Dispensing refers to the manipulations necessary to transfer the prescribed or ordered amount of radiopharmaceutical into the final container (e.g., syringe or vial). Dispensing can take place from single-dose or multiple-dose containers of prepared, prepared with minor deviations, compounded, or manufactured radiopharmaceuticals, and may involve needle changes, affixing a sterile cap, or dilution (e.g., adding 0.9% sodium chloride injection) in the final container. For nonsterile radiopharmaceuticals, an example is obtaining 1 capsule from a container holding 1 or more capsules. For sterile radiopharmaceuticals, an example is withdrawing a volume of solution from a single-use or multiple-dose container into a syringe. Labeling of the final patient-ready dose or ordered amount of a radiopharmaceutical is also a component of the dispensing process.

Except for an unopened manufacturer container, the final dose or ordered amount must be radioassayed (i.e., in a dose calibrator). The measured activity should be mathematically corrected for radioactive decay to the time of scheduled administration (calibration time) (refer to *14. Quality Assurance and Quality Control*). The activity at calibration time must always be within federal, state, and local variance limits.

12.2 Labeling

The labeling of radiopharmaceuticals can fall under the jurisdiction of numerous regulatory agencies. Individual boards of pharmacy and other regulatory bodies may have very specific statutes and/or regulations concerning this process. The requirements specified in this chapter must be considered the minimum requirements for the labeling of the inner container (e.g., syringe, vial) and the outer shielding (e.g., syringe or vial shielding). Therefore, all personnel distributing and/or dispensing radiopharmaceuticals should verify that any labeling is in compliance with regulatory agencies.

The inner container must be labeled with the following:

- Standard radiation symbol
- The words "Caution—Radioactive Material"
- For all therapeutic and blood-products, the patient name/identifier
- Radionuclide and chemical form (generic name)
- Radioactivity at the date and time of calibration

The outer shielding must be labeled with the following:

- Standard radiation symbol
- The words "Caution—Radioactive Material"
- For all therapeutic and blood-products, the patient name/identifier
- Radionuclide and chemical form (generic name)
- Radioactivity at the date and time of calibration
- Volume or number of units dispensed (e.g., 2 capsules), as applicable
- Product expiration or BUD (see *Table 7*), as applicable, and any special storage and handling instructions for non-immediate use (e.g., refrigeration, resuspension)
- Route of administration

12.3 Direct Infusion Systems

The information in this section is limited to the sterility and aseptic technique for direct infusion systems. The described infusion systems are FDA-cleared medical devices or FDA-approved direct infusion generators without an ISO-5 environment. The manner in which all necessary solutions (e.g., radiopharmaceutical and eluant/diluent) are used in conjunction with the

system was a consideration in the overall approval process for the system. Therefore, all operators of the direct infusion systems must follow the "Instructions for Use" in the device labeling.

- Direct infusion generators (e.g., rubidium chloride Rb 82 injection) may employ a container of eluant (e.g., bag of 0.9% sodium chloride injection) to allow administration of the eluate directly to patient(s).
- Direct infusion devices (e.g., portable PET patient-infusion system) provide a method for dispensing and administration from a multiple-dose container of the radiopharmaceutical (e.g., fludeoxyglucose F 18 injection) and the diluent (e.g., 0.9% sodium chloride injection) directly to patients to reduce the radiation exposure to personnel.

In each of these situations, the radiopharmaceutical container must be attached to or be needle-punctured by the respective direct infusion system. Given that such direct infusion systems are intended for multiple patients over the course of several hours, there could be a sterility concern if not operated properly. Therefore, the following parameters must be considered by the operator of the system:

- Setup attachment or needle-puncture should be performed in a defined environment
- Aseptic handling in ambient air with a maximum BUD of 10 hours is allowed for these direct infusion systems (see *Table 7*)
- The 0.9% sodium chloride bag attached to the device may only be punctured once and may be used for no more than 10 hours. The bag must be labeled with the date and time of puncture and the BUD
- Any nonsterile parts of the device that may encounter the septum of the radiopharmaceutical vial must be disinfected with sterile 70% IPA prior to puncturing the vial with the needle
- The septum of any vial and the ports of any diluent bag must be wiped with sterile 70% IPA prior to puncturing
- When puncturing the vial in ambient air, it must only be punctured once
- If there are problems with the infusion device, no sterile container(s) associated with the system can be repunctured or transferred to a PEC for further manipulations and the container, with contents, must be discarded

12.4 Transporting Generators Between Facilities

The following standards must be followed if transporting generators between facilities:

- The generator needle and/or ports must be capped in ISO Class 8 air or better with sterile protectors
- The generator must be packaged and transported in a manner to maintain the integrity and sterility of the generator system

13. REPACKAGING

Repackaging refers to the act of removing conventionally manufactured radiopharmaceutical(s) from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers of the same finished drug product into one container, as long as the container does not include other ingredients. Repackaging may be performed for nonsterile radiopharmaceuticals (e.g., I-131 sodium iodide oral capsules) and for sterile radiopharmaceuticals (e.g., thallous chloride Tl 201 injection).

Except for unopened manufacturer dosage units (e.g., capsules, Xe-133 vials), the repackaged radiopharmaceutical must be radioassayed (i.e., in a dose calibrator). The inner container should be labeled with the following:

- Standard radiation symbol
- The words "Caution—Radioactive Material"
- The radionuclide and chemical form (generic name)
- Radioactivity with units at time of calibration and the calibration time

The outer shielding should be labeled with the following:

- Standard radiation symbol
- The words "Caution—Radioactive Material"
- The radionuclide and chemical form (generic name)
- Radioactivity with units at time of calibration and the calibration time
- Volume, or number of units (e.g., capsules), as applicable
- Product expiration or BUD (see *Table 7*), as applicable
- Special storage and handling instructions

14. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance (QA) is a system of procedures, activities, and oversight that ensures that radiopharmaceutical processing consistently meets quality standards (see *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩). Quality control (QC) is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the radiopharmaceutical(s).

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the handling of radiopharmaceuticals are conducted in accordance with this chapter and applicable federal, state, and local laws and regulations. A designated person must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures,

2. Prevention and detection of errors and other quality problems,
3. Evaluation of complaints and adverse events, and
4. Appropriate investigations and corrective actions.

The SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. The overall QA and QC program must be reviewed at least once every 12 months by the designated person. The results of the review must be documented and appropriate corrective action taken, if needed.

14.1 Notification About and Recall of Out-of-Specification Dispensed Radiopharmaceuticals

If a radiopharmaceutical is dispensed or administered before the results of release testing are known, the facility must have SOPs in place to:

1. Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes), and
2. Determine whether a recall is necessary.

The SOP for recall of out-of-specification dispensed radiopharmaceuticals must contain procedures to:

- Determine the severity of the problem and the urgency for the implementation and completion of the recall
- Determine the distribution of any affected radiopharmaceutical, including the date and quantity
- Identify patients who have received the radiopharmaceutical
- Outline the disposition and reconciliation of the recalled radiopharmaceutical

The facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by laws and regulations of the applicable regulatory jurisdiction (e.g., state board of pharmacy, state health department).

14.2 Complaint Handling

Radiopharmaceutical facilities must develop and implement SOPs for handling complaints. Complaints may include concerns or reports on the quality and container labeling of, or possible adverse reactions to, a specific radiopharmaceutical.

A designated person must review all complaints to determine if they indicate potential quality problems with the radiopharmaceutical. If a complaint does, an investigation into the potential cause of the problem must be completed. The investigation must consider whether the quality problem could extend to other radiopharmaceuticals. Corrective action, if necessary, must be implemented for all potentially affected radiopharmaceuticals. Consider whether to initiate a recall of potentially affected radiopharmaceuticals and whether to cease sterile compounding until all underlying problems have been identified and corrected.

A readily retrievable record (written or electronic) of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., e-mail, telephone, mail). The record must contain the name of the complainant, the date the complaint was received, the nature of the complaint, the response to the complaint, and, if known, the name and strength of the radiopharmaceutical and the assigned internal identification number (e.g., prescription, order, or lot number).

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record keeping requirements in *9. Documentation*. A radiopharmaceutical that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with applicable jurisdictional laws and regulations.

14.3 Adverse Event Reporting

Adverse events potentially associated with the quality of radiopharmaceuticals must be reported in accordance with the facility's SOPs and all applicable jurisdictional laws and regulations. In addition, adverse events potentially associated with the quality of the radiopharmaceutical preparation should be reported to the applicable jurisdictional regulatory body (e.g., state boards of pharmacy, state health departments, FDA's MedWatch program for human drugs).

GLOSSARY

Administration: The direct and immediate application of a radiopharmaceutical to a patient by injecting, infusing, ingesting, or otherwise providing a radiopharmaceutical in its final form.

Airlock: A space with interlocked doors, constructed to maintain air pressure control when items move between two adjoining areas.

Ante-room: An ISO Class 8 or cleaner area with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ante-room is the transition area between the unclassified area in a facility and the classified buffer area.

Aseptic processing or preparation: A process by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility.

Aseptic technique: Methods utilized during the processing of radiopharmaceuticals to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbe count at a nearly irreducible number.

As low as (is) reasonably achievable (ALARA): The effort to maintain exposures to ionizing radiation as far below the dose limits as practical. These efforts should be consistent with the purpose for which the licensed activity is undertaken, in relation to utilization of licensed materials in the public interest. Limiting exposure time, using adequate shielding, and

maintaining the most distance possible from all radioactive sources (i.e., time, distance, shielding) are the basic principles for successfully following ALARA guidelines.

Authorized nuclear pharmacist (ANP): A pharmacist recognized by the U.S. Nuclear Regulatory Commission or an Agreement State agency as having met training and experience requirements for the practice of nuclear pharmacy.

Authorized user (AU): A physician recognized by the U.S. Nuclear Regulatory Commission or an Agreement State agency as meeting training and experience requirements for specified medical uses of radioactive material.

Beyond-use date (BUD): The assigned date and time beyond which the radiopharmaceutical must not be administered.

Biological safety cabinet (BSC) Class II: A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust.

Blood components: Any constituent of blood that is separated by physical or mechanical means (e.g., red cells, white cells, platelets)

Buffer area: An ISO Class 8 or cleaner area with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer area may only be accessed through the ante-room.

Chemical purity: The fraction of the total chemical species present in the radiopharmaceutical as the specified chemical component(s). A chemical impurity is the presence of an unwanted non-radioactive chemical.

Classified area: An area that maintains an air quality classification based on the ISO guidelines (i.e., ante-room, buffer area). See *ISO class*.

Cleaning agent: A material for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Compounding: The combining, mixing, pooling, or otherwise altering (excluding preparation with minor deviations) of a conventionally manufactured radiopharmaceutical or synthesizing/formulating a radiopharmaceutical from bulk drug substances and radionuclides. See *Preparation with minor deviations*.

Container–closure system: The packaging components that contain or come in contact with the radiopharmaceutical and maintain the integrity of the radiopharmaceutical contained within. Examples include (but are not limited to) vials, tubes and syringes.

Critical site: A location that includes any component or fluid pathway surface (e.g., vial septa, injection ports) or openings (e.g., needle hubs) that, when exposed is at risk for contamination by direct contact with air (e.g., ambient area or HEPA-filtered), moisture (e.g., oral and mucosal secretions), or touch.

Designated person: One or more individuals assigned to be responsible and accountable for the performance and operation of the radiopharmaceutical processing facility and for personnel who prepare, compound, dispense, and repackage radiopharmaceuticals.

Direct infusion system: An FDA-cleared medical device used to dispense and/or administer radiopharmaceuticals to multiple patients. The standards of this chapter pertain to devices with ambient air that lack and ISO Class 5 environment.

Direct processing area (DPA): An area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy microbiological contamination (e.g., fungi, viruses, and bacteria) when used in the appropriate concentrations and for the appropriate contact times. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores and fungal spores.

Dispensing: The manipulation or labeling of a radiopharmaceutical to render it in its final form for administration, typically obtained from a single-dose or multiple-dose container (e.g., withdrawing a volume of finished product or preparation from a vial into a syringe). Dispensing is performed under the supervision of a physician or pharmacist and for radiopharmaceuticals includes dilution with an appropriate diluent or adjusting the activity in an individual dosage.

Dose pooling: The combining of doses from two or more syringes to meet one patient's need, also see "repackaging".

Dose splitting: The splitting of a patient-ready unit dose for use with more than one patient.

Dynamic operating conditions: Conditions in the SRPA or classified area in which operating personnel are present and performing actual or simulated activities. The PEC should contain equipment and materials regularly used for radiopharmaceutical processing (e.g., low-lint absorbent pads, dose calibrator, syringe shields).

Expiration date: For conventionally manufactured radiopharmaceuticals, the specified date (and time) beyond which the product must not be administered. The expiration date is determined by the manufacturer.

First air: The air exiting the HEPA filter in a unidirectional air stream.

Garb: Gloves, gowns, shoe covers, head (covers ears and all hair) and facial hair covers, masks, and other items designed to reduce particle shedding from personnel and minimize the risk of microbiological contamination to radiopharmaceuticals.

High efficiency particulate air (HEPA) filtration: Using a tested and certified air filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter from the air passing through it.

Hot-cell: A device used for the shielding and containment of radioactive materials. The shielding material(s) (e.g., lead) is generally incorporated into the structure of the unit itself. Radiopharmaceutical personnel carry out the majority of the tasks within the hot-cell from the exterior of the unit. This is accomplished by the use of remote manipulation systems (e.g., manipulator arms, automated dispensing system) of various designs. Numerous air quality configurations of the hot-cell may exist, including integrated HEPA filtration systems to render all or a specified portion (DPA) of the device capable of certifying to a controlled ISO Class 5 environment. In other situations, the hot-cell offers only radiation protection and a laminar flow PEC, capable of achieving an ISO Class 5 environment, is placed within the enclosure to allow for safe aseptic manipulations. A hot-cell may also be referred to by other designations (e.g., shielded isolator with laminar flow, PET dispensing station, manipulator hot-cell, shielded isolators for dispensing, radiopharmaceutical dispensing isolator).

Hot lab: Unclassified radiopharmaceutical processing area located within a hospital or clinical site that is only appropriate for immediate use radiopharmaceuticals if there is not an ISO 5 PEC within SRPA located within the area.

Immediate use: A preparation (including preparations with minor deviations) and/or dispensing of a sterile radiopharmaceutical that is limited for a single patient. Only sterile conventionally manufactured drug products (e.g., NDA, ANDA) or drugs produced under an approved IND or RDRC protocol may be used. Administration must begin within 1 hour

of the first container puncture or exposure of any critical site involved (e.g., syringe tip, needle hub or needle) to ambient air, whichever is first.

Individual dose (unit dose): A radiopharmaceutical in its final form ready for administration (e.g., capsule, sterile solution in a syringe) consisting of the amount (dose) prescribed, ordered, or other intended for an individual patient or research subject.

Inverse square law: The specified physical quantity or intensity of a radiation emission is inversely proportional to the square of the distance from the source of the emission.

ISO class: A quality classification from the International Organization for Standardization based on quantity and size of particles per volume of air.

Kit: Conventionally manufactured package containing all ingredients required to prepare a radiopharmaceutical with the exception of the radionuclide.

Kit-splitting (fractionation): The act of dividing the contents of a kit vial and transferring aliquots into other containers for storage and subsequent radiolabeling.

Ligand: An ion or molecule that incorporates a metal atom to form a coordination complex.

Line of demarcation: A visible line on the floor that separates the clean and less clean sides of the ante-room.

Low-lint wiper: A wiper exhibiting few, if any, fibers or other particulates, visible without magnification, which are separate from, or easily removed from, the wiper material in a dry condition.

Master Formulation Record (MFR): A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished preparations as well as the processing instructions, including the in-process controls.

Media-fill test: A simulation used to qualify processes and personnel engaged in sterile radiopharmaceutical processing to ensure that the processes and personnel are able to prepare radiopharmaceuticals without microbiological contamination.

Molar mass: The measured mass that is attained from a molar amount of a given substance (e.g., element, compound). It is generally expressed with units such as g/mol and kg/mol.

Multiple-dose container: A container of a radiopharmaceutical for administration that is designed to contain more than one patient dose of the radiopharmaceutical.

Negative-pressure area: An area that is maintained at lower pressure than the adjacent spaces, and therefore the net airflow is into the area. This area is appropriate for volatile or gaseous radionuclides and radiopharmaceuticals (e.g., I-131 NaI, N-13 ammonia) and intended to lend a measure of protection for the radiation workers and the general public.

One-step disinfectant cleaner: A product with an EPA-registered claim (or equivalent) that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

Pass-through: An enclosure with sealed doors on both sides to ensure that both doors are not opened at the same time. The pass-through is positioned between two spaces creating an airlock for the purpose of minimizing particulate transfer while moving materials from one space to another.

Perimeter: A visible demarcation on the floor that defines the boundaries of the SRPA.

Positive-pressure area: An area that is maintained at higher pressure than the adjacent spaces, and therefore the net airflow is out of the area.

Preparation: The act of combining a conventionally manufactured kit with a conventionally manufactured radionuclide following manufacturer's recommended instructions. Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.

Preparation with minor deviations: The act of preparing a conventionally manufactured kit with a conventionally manufactured radionuclide with volume, and/or radioactivity, and/or step-by-step deviations from the manufacturers recommended labeling while ensuring that the final preparation maintains appropriate radiochemical and radionuclidic purity for the entirety of the BUD. Examples of minor deviations include, but are not limited to, altering the amount of activity or volume added to the vial, changes in step-by-step operations (e.g., dilute Tc-99m solution after, rather than before, addition to the vial, use of a venting needle or filter), using alternative devices or equipment (e.g., a heating block rather than a hot water bath), and using alternative radiochemical purity testing methods.

Primary engineering control (PEC): A device or zone that provides an ISO Class 5 air quality environment for sterile processing.

Pyrogen: A substance that induces a febrile reaction in a patient.

Quality assurance (QA): The system of procedures, activities, and oversight that ensures that radiopharmaceutical processing consistently meets quality standards.

Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the radiopharmaceutical.

Radioactive materials (RAM) license: A document(s) issued by the US NRC or an Agreement State agency that authorizes various activities involving the use of radioactive materials. These uses can include possession, research and development, distribution, medical use, and other purposes not included in this list. Only those activities specifically authorized are allowed.

Radioassay: Measurement of the quantity of radioactivity present in a container using a suitable and calibrated instrument, such as a well-type ionization chamber (i.e., dose calibrator).

Radiochemical purity: The ratio, expressed as a percentage, of the radioactivity of the intended active radiopharmaceutical ingredient to the total radioactivity of all radioactive ingredients and impurities present in the radiopharmaceutical preparation (see *Radioactivity* ⟨821⟩).

Radionuclidic purity: The ratio, expressed as a percentage, of the radioactivity of the intended radionuclide to the total radioactivity of all radionuclides in the radiopharmaceutical preparation (see ⟨821⟩).

Radiopharmaceutical (radiopharmaceutical preparation/radioactive drug): (See ⟨821⟩.) A finished dosage form that contains a radioactive substance in association with one or more other ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy. A radiopharmaceutical includes any non-radioactive reagent kit or radionuclide generator that is intended to be used in the preparation of any such substance. The terms "radiopharmaceutical" and "radioactive drug" are commonly used interchangeably.

Repackaging: The act of removing a conventionally manufactured radiopharmaceutical from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients. Radiopharmaceutical manipulation in any other way, including reconstitution, dilution, mixing, or combination with another ingredient, is not considered repackaging.

Restricted area: Any area to which access is controlled for the protection of individuals from exposures to radiation and radioactive materials.

Secondary engineering control (SEC): The area where the PEC is placed (e.g., a classified area or an SRPA). It incorporates specific design and operational parameters required to minimize the risk of microbial contamination.

Segregated radiopharmaceutical processing area (SRPA): A designated, unclassified space, area, or room with a defined (by facility procedures) perimeter that contains a PEC. An SRPA is only suitable for radiopharmaceutical preparation (with and without minor deviations), dispensing, and repackaging. If the SRPA is used to elute radionuclide generators it must have ISO Class 8 particle count non-viable particle count air quality.

Shielding: Barriers of appropriate radiation attenuating material, used for radiopharmaceuticals, to protect the personnel. These barriers can be general in nature (e.g., L-block, hot-cell), as to afford protection from a radiation field, or specific to a container used to hold a particular radiopharmaceutical (e.g., syringe shield, vial shields, "pigs").

Single-dose container: A container of a radiopharmaceutical for administration that is designed for use with a single patient as a single administration.

Specific activity: The radioactivity of a radionuclide per unit mass of the compound involved with the radionuclide (see *Radioactivity—Theory and Practice* ⟨1821⟩). The units of specific activity involve those for the activity (e.g., mCi, MBq, Ci, GBq) and those for the unit of mass (e.g., µg, mmol); expressed on an activity per mass basis (e.g., mCi/µg, MBq/µg, Ci/mmol, GBq/mmol).

Sporicidal agent: A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Start of preparation: Time at which a vial septum is punctured or a component container is opened (e.g., removal of cap on a pre-filled syringe), whichever comes first.

Sterility: The absence of viable microorganisms.

Strength: The radioactivity concentration of the radiopharmaceutical at the calibration time (see ⟨821⟩). Strength is expressed as the quantity of radioactivity on a volume basis (e.g., mCi/mL or MBq/mL).

Unclassified space: A space not required to meet any ISO air cleanliness classification.

Unrestricted area: An area in which a person should not be exposed to radiation levels in excess of 2 millirems in any 1 h from external sources.

Use-by time: For radiopharmaceuticals prepared from kits, the time period after preparation during which the radiopharmaceutical should be used or administered, as suggested or stated in the manufacturer's prescribing information.

APPENDIX

Abbreviations

ACPH	Air changes per hour
ALARA	As low as reasonably achievable
ANDA	Abbreviated new drug application
ANP	Authorized nuclear pharmacist
AU	Authorized user
BLA	Biologics license application
BSC	Biological safety cabinet
BUD	Beyond-use date
CETA	Controlled Environment Testing Association
cfu	Colony-forming unit
CoA	Certificate of analysis
DPA	Direct processing area
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
IND	Investigational new drug
IPA	Isopropyl alcohol
ISO	International Organization for Standardization

Abbreviations *(continued)*

LAFW	Laminar airflow workbench
MAA	Macroaggregated albumin
MEA	Malt extract agar
MFR	Master Formulation Record
NDA	New drug application
NRC	Nuclear Regulatory Commission
PEC	Primary engineering control
PET	Positron emission tomography
RAM	Radioactive material
RDRC	Radioactive drug research committee
RH	Relative humidity
SDA	Sabouraud dextrose agar
SEC	Secondary engineering control
SOP	Standard operating procedure
SRPA	Segregated radiopharmaceutical processing area
TSA	Trypticase soy agar▲ (Postponed on 1-Dec-2019)