BRIEFING

⟨825⟩ Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging. Radiopharmaceuticals (radioactive drugs) represent a distinct class of drugs where processing activities include the use of radionuclide generators, preparation and dispensing from commercially manufactured radiopharmaceutical kits, the dispensing and repackaging of commercially manufactured radiopharmaceutical finished products into a patient-ready container, compounding sterile and nonsterile radiopharmaceuticals, and the labeling of blood components with radionuclides. These activities occur in an environment where individualized patient needs and the safe handling of radioactive materials demand a high level of professional expertise and clearly defined standards that support these activities. While the original title in the prospectus was restricted to only the compounding of radiopharmaceuticals, the proposed title is the outcome of the consideration of all processing activities.

Many aspects of sterile radiopharmaceutical practices are similar to sterile compounding of conventional drugs (e.g., aseptic practices, environmental facilities). However, radiopharmaceutical processing also involves (as applicable) many unique aspects, including worker and public radiation protection measures (e.g., time, distance, shielding, negative pressure gradients), presence and use of special ancillary supplies (e.g., radiation shields, absorbent pads for radioactive contamination control), and special equipment (e.g., radioactivity measuring devices, radiation monitors, remote manipulation systems). Radiation safety considerations often necessitate a deviation from the standard sterile practices described in *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩ and the nonsterile practices detailed in *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.

The intent of this chapter is to describe practices to provide a reasonable assurance of maintaining patient safety associated with the administration of sterile and nonsterile radiopharmaceuticals, while also ensuring the safety of the individuals performing these radiopharmaceutical processing activities.

The current proposed chapter in *PF* 44(5) [Sep.–Oct. 2018] is posted online at https://www.usp.org/compounding/825-download with line numbers. Please submit comments using the form available at https://usp.az1.qualtrics.com/jfe/form/SV_2i3rw7KKrcLaZ3D. The Expert Committee seeks stakeholder feedback on the proposed chapter.

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Add the following:

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

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) also have control over certain activities related to radiopharmaceuticals. Hence, 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 radiopharmaceuticals, 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:

- Radiopharmaceuticals manufactured in FDA-registered manufacturing establishments according to §510 of the Food, Drug, and Cosmetic Act
- Radiopharmaceuticals compounded in FDA-registered outsourcing establishments according to §503B of the Food, Drug, and Cosmetic Act
- Aspects of positron emission tomography (PET) drug preparation, as defined in *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses* ⟨823⟩
- Administration to patients

It is important to note that 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, 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. Hence, 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 a reasonable assurance of maintaining, 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 marketed products, dispensing can proceed as described in *11. 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. 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, and ophthalmics. For commercially marketed products, see *11. 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 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.

It is appropriate to emphasize that the most important factor for maintaining sterility is the avoidance of touch contamination. Disinfection of the vial septum with sterile 70% isopropyl alcohol (IPA) must be performed prior to needle puncture. If the vial shield top is then closed or the vial septum otherwise covered with a piece of radiation shielding, the septum must be redisinfected 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 a right-angle forceps to hold a sterile 70% IPA wipe and direct it down onto the vial septum. It is also acknowledged that such vial shields will disrupt first air contacting the vial septum during certain handling conditions. Hence, redisinfection of the septum with sterile 70% IPA should be performed frequently whenever multiple punctures are occurring (e.g., removing several individual doses from a multiple-dose vial).

2. RADIATION SAFETY CONSIDERATIONS

The handling of radiopharmaceuticals necessitates special radiation regulatory authority required precautions for radiation safety [i.e., as low as (is) 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, experience, and professional judgment related to the type, abundance, and energy of the radioactive emissions
- The quantity of radioactivity, volume, handling steps, and timing thereof
- Other factors, which can vary on a case-by-case basis

2.1 Time

Radiation exposure to personnel is dependent on the amount of radiation handled and the time handling the radiopharmaceuticals; minimizing handling time will minimize radiation exposure. Hence, handlers of 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 will markedly decrease radiation exposure to personnel. Hence, handlers of radiopharmaceuticals may utilize techniques to increase distance between worker and radiopharmaceutical, such as using remote handling tools to manipulate RAMs.

2.3 Shielding

Radiation exposure to personnel decreases as a function 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 are 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, vial contents are maintained at neutral or negative pressure, because positive pressure in a vial 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 in a PEC can be used as a measure for contamination control. When exposure to blood and other potentially infectious material is reasonably anticipated, needleless systems 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.

As per 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. PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE

Personnel must be trained to work with radiopharmaceuticals per the policies and procedures authorized by an ANP or AU physician. These employees (e.g., nuclear medicine technologists or nuclear pharmacy technicians) must follow these policies and procedures of the ANP or AU physician and work under their supervision.

Individuals that may have a higher risk of contaminating the radiopharmaceutical and the environment with microorganisms (e.g., personnel with 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 because of the risk of microbial contamination to the radiopharmaceutical and the environment.

3.1 Aseptic Qualifications

Personnel must prove competency, as applicable to their job functions, prior to performing radiopharmaceuticals aseptic tasks that are beyond immediate use. These qualifications must be completed and documented initially, and then successfully repeated every 6 months thereafter under the observation of a trained individual and include the following:

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

For sterile compounding with nonsterile ingredients, these qualifications must be completed successfully and documented every 6 months.

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). Personnel that perform such functions must be required to prove their competency in this process, including gloved fingertip sampling.

- Gloved fingertip sampling must be performed initially with hand-hygiene and garbing three times with zero colony-forming unit (cfu)
- Gloving fingertip sampling must also be performed post-media fill testing, with NMT 3 cfu total for both hands
- The gloved fingertip 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)
- Do not disinfect gloves immediately before touching the sampling device, as this could cause a false-negative result
- Using a separate sampling device for each hand, collect a gloved fingertip and thumb sample from both hands by rolling finger pads and thumb pad over the agar surface
- The plates must be incubated in a temperature-controlled incubator for 30°–35° for 48–72 h, and then at 20°–25° for 5–7 additional days

MEDIA-FILL TESTING

Media-fill challenges are 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 radiopharmaceutical worker and it 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 procedures.
- 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 start with nonsterile powder media.
- The certificate of analysis (CoA) must be filed with 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 one or more container–closure unit(s) on or before 14 days. Investigate media-fill failures to determine possible causes.

3.2 Re-evaluation, 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 re-evaluations in the deficient area(s) before they can resume processing of sterile preparations. The designated person must investigate the cause of failure and determine appropriate retraining requirements. All failures, retraining, and re-evaluations must be documented.

REQUALIFICATION PROGRAM

Personnel must successfully complete requalification every 6 months in the core competencies listed in *3.1 Aseptic Qualifications*. Successful completion must be demonstrated through written testing and hands-on demonstration of skills.

TIMING OF REEVALUATION AND REQUALIFICATION

Visual observation: Personnel must be visually observed while performing hand hygiene and garbing procedures initially, and then at least once every 6 months.

Gloved fingertip and thumb sampling: Personnel must perform fingertip and thumb sampling three times initially, and then every 6 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 6 months (in conjunction with gloved fingertip and thumb sampling).

Cleaning and disinfecting: Retrain and requalify personnel in cleaning and sterile processing areas in conjunction with any change(s) in cleaning and disinfecting procedures.

After a pause in sterile radiopharmaceutical processing: Personnel who have not performed radiopharmaceutical processing in more than 6 months must be requalified in all core competencies before resuming duties.

3.3 Ancillary Personnel

Personnel that are authorized to be within the sterile processing area who 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 or regulators) must comply with garbing and gloving standard operating procedures (SOPs) but do not need to prove competency.

3.4 Hand Hygiene and Garbing for Immediate Use Preparations

In situations where sterile radiopharmaceuticals cannot be provided to a single patient in a timely manner and the potential benefits to the patient outweigh the potential risks, radiopharmaceuticals may be prepared and dispensed as immediate use. Precautions related to personal hygiene to be followed must include:

- Hand hygiene: Wash hands and arms up the elbows with soap and water for at least 30 s. If no sink is present, use a suitable alcohol-based hand rub with persistent antimicrobial activity 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.]

3.5 Hand Hygiene and Garbing for Buffer Rooms and Segregated Radiopharmaceutical Processing Area

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

- Before entering the segregated radiopharmaceutical processing area (SRPA) or buffer room, personnel must remove: outer garments (e.g., bandanas, coats, hats, jackets, scarves, sweaters, vests); all cosmetics; and visible jewelry or piercings that can interfere with the effectiveness of the garb (e.g., rings with protruding elements that may cause tears in gloves). Artificial nails, polish, or extenders are prohibited. Natural nails must be kept neat and trimmed. Remove ear buds and headphones or other similar devices. Radiation dosimetry devices are allowed, as required by the RAM license.
- Immediately before entering the SRPA or buffer room, 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 garb, as described below.
- Personnel must don the following garb (e.g., shoe covers, head/hair covers, face mask) in an order that eliminates the greatest risk of contamination (e.g., dirtiest to cleanest), as defined in facility procedures.
- If not already performed, personnel must then wash hands and arms up the elbows with soap and water for at least 30 s and then apply a suitable alcohol-based hand rub with persistent antimicrobial activity,

and then dry hands using low-lint towels. Electronic hand dryers are not permitted.

- Personnel who performed hand hygiene prior to garbing, as described previously, must perform antiseptic hand cleansing using a suitable alcohol-based hand rub with persistent antimicrobial activity.
- Personnel must then don a low-lint gown with sleeves that fit snugly around the wrists and enclosed at the neck (e.g., solid front with back covered and secured, or fastened or zippered up to the neck in front). Disposable gowns are preferred. If reusable gowns are used, they must be laundered daily.
- Personnel must then aseptically don sterile, powder-free gloves. Gloves must completely and snuggly cover the ends of the gown cuffs so that skin on the wrists and upper hands are completely enveloped.
- Because gloves may not remain sterile due to touching or handling potentially nonsterile materials, personnel must perform periodic disinfection of gloves with sterile 70% IPA 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 with persistent antimicrobial activity, and don new gloves.
- Direct personnel touch contamination is the most common source of microorganisms, so personnel must avoid touch contamination of container septa, needle, syringe and needle hubs, and other critical sites.

When personnel exit the buffer room or SRPA, the exterior gown, shoe covers, head/hair covers, face masks, and gloves must be properly disposed of and new ones donned for each re-entry into the buffer room or SRPA.

4. FACILITIES AND ENGINEERING CONTROLS

4.1 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 rooms must be continuously maintained at a temperature of 25° or cooler and should be continuously maintained at a relative humidity 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 rooms each day that it is used,

either manually or by a continuous recording device, and the results must be readily retrievable, reviewed by the designated person, and documented. Temperature and humidity in the classified rooms must be controlled through an efficient HVAC system. Free-standing humidifiers/dehumidifiers and air conditioners must not be used within the classified room 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 must ensure 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 areas are located, operated, maintained, monitored, and certified to have appropriate air quality.

TYPES OF SECONDARY ENGINEERING CONTROLS AND DESIGN

The PEC must be located in a secondary engineering control (SEC), which may be either a buffer room with ante-room or an SRPA (see *Appendix 2: Example Designs for Radiopharmaceutical Handling* for examples of facility designs).

The ISO-classified ante-room must be separated from the surrounding unclassified rooms of the facility with fixed walls and doors, and controls must be in place to minimize the flow of lower-quality air into the more controlled areas. Air supplied to the classified rooms must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms. Returns must be low on the wall or appropriate to remove airborne particles from specific sources, such as refrigerators. Appropriate studies, such as a smoke study of the PEC, must be repeated whenever a change to the placement of the PEC within the room is made. The classified rooms 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 dirty side. The ante-room is entered through the dirty side, and the clean side is the area closest to the buffer room. Required garb must be worn on the clean side of the line of demarcation (see *3. Personnel Qualifications, Training, and Hygiene*).

A PEC may be located in an area within an unclassified room, without an ante-room or buffer room. 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. 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. An SRPA must not be located adjacent to environmental control challenges (e.g., restrooms, warehouses, or food preparation areas). 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.

The PEC must be located in the buffer room of the classified room or the 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).

It is also critical to control materials (e.g., supplies and equipment) as they move from classified rooms of lower quality to those of higher quality (e.g., ISO Class 8 ante-room to ISO Class 7 buffer room to ISO Class 5 PEC) to prevent the influx of contaminants. Airlocks and interlocking doors can be used to facilitate better control of air balance between areas of differing ISO classification (e.g., between the buffer room and ante-room), or between a classified room and an unclassified room (e.g., between the ante-room and an unclassified room such as a hallway) See *4.7 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, and doors must be interlocking.

Due to the interdependence of the various rooms or areas that make up a sterile radiopharmaceutical processing facility, it is essential to carefully define and control the dynamic interactions permitted between areas and rooms. 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 rooms.

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 during 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 critical areas (ISO Class 5; see *Table 1*) at a velocity sufficient to sweep particles away from aseptic processing areas and maintain unidirectional airflow during operations. Proper design and control prevents turbulence and stagnant air in the critical area. In situ air pattern analysis via smoke studies must be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the site under dynamic 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 PEC provides unidirectional HEPA-filtered airflow that is designed to minimize microbial contamination of a sterile processing environment. The unidirectional airflow within the PEC helps protect the direct processing area (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.

Class II biological safety cabinet (BSC): A Class II BSC is a cabinet with an open front and inward airflow and 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 room 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 room and 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 rooms, adequate HEPA-filtered airflow to the buffer room(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 room, the room pressure, and the effects of temperature. The summary of ACPH requirements is listed in *Table 1*.

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

- 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 rooms from the HVAC through HEPA filters that are located in the ceiling.

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering factors listed above
- 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 1. 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

4.2 Creating Areas to Achieve Easily Cleanable Conditions

CLASSIFIED ROOMS

The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified room must 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. 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, the panels must be caulked or otherwise sealed and secured around each panel to seal them to the support frame. Ceiling panels must be washable and soil resistant, designed for use in a clean room environment.

Walls must be constructed of, or may be covered with, 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 be smooth, sealed (e.g., continuous, welded seams), and impervious. Floors must include coving to the sidewall. Classified rooms 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) in 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.

4.3 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 room, the sink used for hand hygiene may be placed either inside or outside of the ante-room. The buffer room must not contain sink(s), eyewash(es), shower(s), or floor drains. The ante-room must not contain floor drain(s). If installed, sprinkler systems in classified rooms should be recessed and covered, and must be easily cleanable. In a facility with an SRPA design, the sink must be accessible but located at least 1 m from the PEC. The sink must not be located inside the perimeter of the SRPA.

4.4 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary are permitted in the classified room 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. Certain items are not permitted on the clean side of the ante-rooms and in buffer rooms, including, but not limited to, corrugated cardboard, external shipping containers, and nonessential paper (e.g., paper towels and tissues).

Carts used to transport components or equipment into classified rooms must be constructed from nonporous materials with cleanable casters and wheels to promote mobility and ensure ease of disinfection. All items must be disinfected by personnel wearing gloves before they are brought into the clean side of ante-room(s), placed into pass-through(s), or brought into an SRPA. In a classified room, 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.

4.5 Classified Rooms

Activities and tasks carried out within the buffer room must be limited to only those necessary when working within a controlled environment. Food, drinks, and materials exposed in patient care and treatment areas must not enter ante-rooms or buffer rooms. When processing activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a 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.

4.6 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 *3.5 Hand Hygiene and Garbing for Buffer Rooms 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 *3.5 Hand Hygiene and Garbing for Buffer Rooms 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. However, hand and arm incursions into the interior of the hot-cell might be necessary for personnel to stage the materials and supplies necessary for aseptic manipulations. In these instances, 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 does not allow the influx of non-controlled air into the PEC. Personnel can be donned 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 *3.5 Hand Hygiene and Garbing for Buffer Rooms 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 can be donned 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 *3.5 Hand Hygiene and Garbing for Buffer Rooms and Segregated Radiopharmaceutical Processing Area* for all incursions into the PEC.

Since other hot-cell configurations and technologies may exist, verification (either by airflow smoke pattern tests or other manufacturer specified methods) must assure, 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 *3.5 Hand Hygiene and Garbing for Buffer Rooms and Segregated Radiopharmaceutical Processing Area* for all incursions into the hot-cell.

4.7 Environmental Controls

All RAM users must comply with the conditions specified in their approved RAM license application and regulations. Pass-through enclosures for transferring radiopharmaceuticals from controlled handling areas (e.g., buffer room) 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 system or mechanism in place that assures that both doors cannot be open at the same time. There may be both positive and negative air pressure within the facility; positive air flow to minimize the potential of microbial contamination in sterile drug preparation areas, and negative air flow to minimize potential radioactive contamination from volatile or airborne radiopharmaceuticals. Positive pressure environments must have a minimum differential positive pressure of a 0.02-inch water column between each ISO-classified room (e.g., between the buffer room and ante-room). The pressure differential between the ante-room and the unclassified room must be NLT a positive 0.02-inch water column. Refer to the RAM license for

negative pressure obligations. For preparation of sterile radiopharmaceuticals, consideration of both concerns could be addressed as follows:

1. Buffer room, if present, must be positive pressure compared to the ante-room
2. Ante-room, if present, must be positive pressure compared to the restricted area
3. Restricted area 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.

Various environmental controls for various preparation scenarios [see *Table 5* for maximum beyond-use dates (BUDs) for differing environments] are described in the following sections. *Table 2* details the limits for particle counts for each specific ISO classification.

Table 2. ISO Classification of Particulate Matter in Room Air[a]

ISO Class	Particle Count[b] / m^3
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

[a] Adapted from ISO 14644-1, Cleanrooms 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.

ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS

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

AMBIENT ATMOSPHERE FOR IMMEDIATE USE PREPERARATIONS

The following requirements should be met in ambient atmosphere environments:

- Non-patient care space, functionally separate (not another room) from the patient care area, such as a radiopharmaceutical handling space, or hot lab, in a hospital, clinic, or mobile coach
- A designated space for medication preparation that is clean and free from clutter
- Low traffic (i.e., few people going in and out or moving around the area)

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

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

1. Area surrounding the PEC may be ambient (non-classified) atmosphere
2. Area must be clean, uncluttered, and dedicated to the processing of radiopharmaceuticals
3. Appropriate for preparation, preparation with minor deviations, repackaging, and dispensing of radiopharmaceuticals
4. A room that meets ISO Class 8 particle-count specifications may be used to store and elute radionuclide generators

A BUFFER ROOM WITH AN ISO CLASS 8 ENVIRONMENT WITH VERTICAL 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 ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

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

This environment is appropriate for all activities listed in *A Buffer Room with an ISO Class 8 Environment with Vertical 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 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:

- Airflow testing: To determine acceptability of the air velocity, the air exchange rate, and room pressure cascade to ensure that air consistently flows from clean to dirty areas, and that the appropriate quality of air is maintained under dynamic operating conditions.
- HEPA filter integrity testing: HEPA filters must be leak tested at the factory and then leak tested again after installation and as part of recertification.
- Total particle counts testing: Conducted under dynamic operating conditions using current, state-of-the-art electronic equipment.
- Smoke visualization studies: Performed for each PEC under 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 substituted. 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 non- or lesser controlled air. Manufacturer verification instructions, along with professional expertise in controlled environment testing, may be used to create a plan for the necessary assurance testing techniques.

DAILY MONITORING OF ENVIRONMENT

The temperature, humidity, and pressure gradient must be monitored in the classified room each day that preparations are made, either manually or by a continuous recording device. The following guidelines must 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 should be documented and, if applicable, appropriate corrective actions taken
- Temperature monitoring devices must be verified for accuracy annually or as required by the manufacturer
- Monitoring of pressure differentials must be performed

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

5. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective air and surface monitoring program provides information on the environmental quality of the classified rooms where sterile radiopharmaceuticals are processed. In addition, an effective air and surface monitoring 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 rooms. 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, whichever is longer.

5.1 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.

Air and surface monitoring must be performed initially for classified rooms in a facility to establish a baseline level of environmental quality. After initial sampling, the classified rooms 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 airborne and surface contaminants. The data from airborne and surface sampling are then used to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfection agents specified in the facility procedures. 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.

In addition, results from air and surface sampling 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 essential to maintain the necessary environmental quality for sterile radiopharmaceutical activities. 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 monitoring must be conducted during dynamic operating conditions to confirm that the required environmental quality in classified

rooms 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. In this case, simulated tasks that are reflective of the routine aseptic activities are permissible. 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 or 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)

The microbiological air and surface monitoring program must include viable impact volumetric airborne particulate sampling and surface sampling.

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 rooms. 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 or the environment.

The air and surface monitoring program must include a diagram of the sampling locations, procedures 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 rooms, 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. In addition, sampling methods, locations, frequencies, and timing must be clearly described in the established SOPs of the facility.

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 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.

5.2 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 rooms.

VIABLE AIR SAMPLING: TIMING AND LOCATIONS

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

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

1. Follow the manufacturer's instructions for operation of the active air sampling device, including placement of media.
2. Using the sampling device, test at least 1 m^3 or 1000 L of air from each location sampled.
3. At the end of the sampling, retrieve the media and cover.
4. Invert the media and incubate at 30°–35° for 48–72 h. 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), sample location, and sample date.
5. Then incubate the inverted media at 20°–25° for 5–7 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), sample location, and sample date.

Alternatively, two pieces of media may be collected for each sample location and incubated concurrently in separate incubators at 30°–35° for NLT 5 days and at 20°–25° for NLT 5 days. 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), 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]. Certificates of analysis 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. The microbiological incubator must be placed in a location outside of any classified room. 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 examine counts in relation to previous data to identify adverse results or trends. If two pieces of media were collected at a single location, all recovered growth on each is documented and action levels are applied individually to each sampling (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*, the genus of any microorganism recovered must be identified (see *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩) with the assistance of a microbiologist.

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.

5.3 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 via inadvertent touch contact by personnel is a potential source of contamination of the radiopharmaceutical. 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 it must be sampled. Staging or work surfaces in classified rooms near the PEC frequently touched surfaces in classified rooms and pass-through enclosure(s) for all classified rooms are to be evaluated to determine the locations that pose the greatest risk to the SRPA.

When conducted, 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 devices 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.

For the procedures for surface sampling on flat surfaces, use the following:

1. Remove the cover from the contact sampling device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The contact sampling device should leave a residue of

growth medium on the sample site. After sampling, use a low-lint sterile wiper to thoroughly clean the sampled area with sterile 70% IPA.

2. Cover each contact sampling device.
3. If using plates, invert the plates and incubate the contact sampling devices at 30°–35° for 48–72 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
4. Incubate the inverted plates at 20°–25° for 5–7 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), sample location, and sample date.
5. Alternatively, two devices may be collected for each sample location and incubated concurrently in separate incubators at 30°–35° for NLT 5 days and at 20°–25° for NLT 5 days.
6. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface), location, and date.

For the procedures for surface sampling on irregular surfaces, use the following:

1. Sterile swabs wetted with sterile water or a sterile neutralizing buffer should be used.
2. If using the neutralizing buffer, the residue must be removed from the surface after sampling using sterile 70% IPA. Swabs sampled with sterile water must be processed with a neutralizing buffer or plated in a neutralizing medium.
3. After swabbing the area, place the swab in appropriate diluent or sterile packaging until it can be processed. The swab must be processed using a diluent and an extraction step to aid in the removal of any microorganisms from the swab.
4. Plate all or a portion of the diluent in TSA (or TSA with neutralizers). If the diluent is diluted, the dilution factor must be applied to the raw count to determine the actual total microbial count.
5. Incubate the plates at 30°–35° for 48–72 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
6. Incubate the plates at 20°–25° for 5–7 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/sample on the environmental

sampling form based on sample type (i.e., surface), sample location, and sample date/time.

7. Alternatively, two devices may be collected for each area and incubated concurrently in separate incubators at 30°–35° for NLT 5 days and at 20°–25° for NLT 5 days.
8. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface), location, and date.

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 is documented and action levels are applied to each device 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. 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 surface sampling exceed the levels in *Table 4*, the genus of any microorganism recovered must be identified (see ⟨1113⟩) with the assistance of a microbiologist.

Table 4. Action Levels for Surface Sampling

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

6. 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 materials 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 agent. Surfaces must be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA)-registered one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. Some EPA-registered one-step disinfectant cleaners may have sporicidal properties.

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. Radioactive decontamination is the act of reducing or removing radioactivity from an object or surface and 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 clean to dirty areas. The frequency, method(s), and location(s) of cleaning and disinfection 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. All cleaning and disinfecting activities must be documented.

Table 5. Minimum Frequency for Cleaning and Disinfecting Surfaces in Classified Rooms 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 to the extent possible as specified by the equipment manufacturer or the assessment of a	Prior to performing sterile processing of radiopharmaceuticals 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 trained microbiologist or	Monthly

Site	Cleaning	Disinfecting[a]	Applying Sporicidal
	trained 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.	industrial hygienist and should be specified by SOPs. 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.	
Surfaces of sink(s)	Daily	Daily	Monthly
Hot-cells (all interior surfaces)	Daily	Daily	Monthly
PEC and the equipment within a PEC 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 trained 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.	Prior to performing sterile processing of radiopharmaceuticals 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 trained microbiologist or industrial hygienist and should be specified by SOPs. 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
Work	Daily	Daily	Monthly

Site	Cleaning	Disinfecting[a]	Applying Sporicidal
surface(s) outside the PEC			
Floor(s)	Daily	Daily	Monthly
Wall(s), door(s), door frame(s), and other fixtures	Monthly	Monthly	Monthly
Ceiling(s)	Monthly	Monthly	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.

6.1 Cleaning, Disinfecting, and Sporicidal Agents

Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues or fumes. 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 and wiped 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. Sporicidal agents, shown to be effective against *Bacillus* species, must be used at least monthly to disinfect all surfaces in classified rooms and SRPAs. The disinfecting agents (e.g., sterile 70% IPA) used in the ISO Class 5 PEC must be sterile. See *Table 6* for a summary of the purpose of the cleaning disinfectant 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. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores.
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.

6.2 Cleaning Supplies

All cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-lint. Wipes, sponges, and mop heads 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 before and after each use. Reusable cleaning tools must be dedicated for use in the classified rooms 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. Dispose of cleaning supplies used in the classified rooms and SRPAs in a manner that minimizes the potential for dispersing particulates into the air (e.g., with minimal agitation, away from work surfaces).

6.3 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. 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
2. Apply a cleaning agent (e.g., EPA-registered, one-step disinfectant cleaner)
3. Disinfect with a sterile disinfectant (e.g., sterile 70% IPA)
4. Allow the surface to dry completely before beginning activities
5. The PEC must be wiped with a sporicidal agent at least monthly

6.4 Disinfecting Supplies for Classified Rooms and SRPAs

No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the classified room or SRPA. Before items are introduced into a classified room or SRPA, they must be disinfected with a sporicidal agent or sterile disinfectant (e.g., sterile 70% IPA). After the sporicidal or sterile disinfectant is applied, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer (see *5.1 General Monitoring Requirements*), during which time the item cannot be disturbed. The agent used for disinfecting the packaging must be compatible with the packaging and must not alter the product label.

Any item to be transferred into the PEC from the classified room or SRPA must be disinfected with a sterile disinfectant (e.g., sterile 70% IPA). The sterile disinfectant must be allowed to dry before using the item.

In the case of PET radiopharmaceuticals being processed by remote means in a hot-cell, the opening of sterile syringe packages 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.

6.5 Disinfecting Critical Sites within the PEC

Critical sites (e.g., vial stoppers) must be disinfected by wiping them with sterile 70% IPA in the PEC. 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 stoppers.

6.6 Cleaning and Disinfecting Items from Patient Care Area

Radiation shielding equipment used in the classified room/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 room (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 room (e.g., buffer or ante-room) or SRPA for re-assaying or disposal. 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 in procedures regulated by the facilities' RAMs license and application. Equipment that contained mixed waste must be cleaned and disinfected with an appropriate agent(s) for blood.

7. ASSIGNING BUD

BUDs are based on the risk of microbial contamination with the assumption that the radiopharmaceutical 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 vial puncture. 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 (h)**
Immediate use	—	—	1
Direct infusion system, one needle 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 non-viable particle count	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	ISO Class 8 or better buffer room 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 room ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding	ISO Class 5	ISO Class 7 or better buffer room with ISO Class 8 or better ante-	96

Preparation Conditions			
Manipulation	**PEC**	**SEC**	**BUD (h)**
		room	
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 7 or better buffer room 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 7 or better buffer room with ISO Class 8 or better ante-room	6

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 kits (sterile and nonsterile), the kit manufacturer may state or suggest a use-by time in their package inserts. For certain radiopharmaceuticals transportation time, radionuclide availability, and other factors may necessitate extending manufacturer-suggested use-by time to meet patient needs. Assigning a BUD longer than the manufacturer-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 must necessarily 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 does not exceed the sterility-related times listed in *Table 7*, unless a longer time is justified by *Sterility Tests* ⟨71⟩.

- Radiochemical purity: Radiochemical stability is affected by a variety of factors including, but not limited to, storage temperature, amount 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, amount of radioactivity, radioactivity concentration), studies should be conducted at the extremes of the ranges.
- Radionuclidic purity: Because radionuclide 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 h) to Tc-99m (half-life of about 6 h) continuously increases over time. *USP* monographs for Tc-99m radiopharmaceuticals require that the radionuclidic impurity Mo-99 not exceed 0.15 mCi Mo-99 per mCi Tc-99m at the time of administration. Hence, calculation of radionuclidic purity at future times is necessary to ensure compliance throughout the assigned BUD.
- Age of generator: As a generator eluate decays, the desired daughter radionuclide atoms themselves decay to form other nuclides and potential radiolytic products, which may interfere with radiolabeling of kits. For example, as Tc-99m ages, Tc-99m atoms decay to become Tc-99 atoms. More importantly, there should also be increasing amounts of peroxides formed as radiation interacts with water molecules. Increased amounts of Tc-99 and peroxides present in aged Tc 99m can interfere with the radiolabeling of many kits. Hence, extension of the use-by time 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 radioactivity patient dose. For example, if an MAA kit is prepared such that the radioactivity patient dose is 200,000 particles at the time of calibration, the same radioactivity patient dose will contain 700,000 particles at 10.85 h after calibration. Hence, calculation of the number of MAA particles in the radioactivity patient dose is necessary to ensure compliance with the prescribed particle range throughout the assigned BUD.
- Specific activity (molar mass): For some receptor-based radiopharmaceuticals, the mass amount may influence uptake (i.e.,

too much mass may result in saturation of receptor sites with excess radiopharmaceutical going elsewhere). As radioactivity decays over time, specific activity decreases resulting in more mass per unit radioactivity. Hence, in such situations, the assigned BUD must ensure that the patient dose contains NMT the specified maximum mass.

- Container type: Because radiochemical stability or other quality attributes of a radiopharmaceutical may be affected by its container type, 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.
- In the case of manufactured radiopharmaceuticals (both PET and non-PET) 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.
- In the case of radiopharmaceuticals prepared from kits, the BUD of a dispensed dose cannot exceed the assigned BUD of the finished preparation.
- In the case of compounded radiopharmaceutical, the radiopharmaceutical may not exceed the shortest BUD of any of its components.

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

8. DOCUMENTATION

Applicable policies and procedures should be established and maintained for activities involved in preparing, compounding, dispensing, and repackaging radiopharmaceuticals.

Records (hard-copy or electronic) 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 competency, validation, gloved fingertip testing, and media fill evaluation initially and follow up testing at specified intervals.
- Testing of environmental controls, including ISO classification, ACPH, pressure differentials, and viable test results
- Maintenance and cleaning
- End product radiochemical purity and other testing, as applicable, results of preparations, preparations with minor deviations, and compounded preparations
- Master Formulation Record (MFR) (i.e., preparation with minor deviation and compounding)
- Validation of stability testing to support the assigned BUD from procedures established by the compounder or derived from accepted literature
- Records of compounded radiopharmaceuticals
- Investigations and remedial actions and tracking of events to closure.

8.1 Master Formulation Record

MFR are required only for:

- Preparation with minor deviations
- Compounding as described in *10. Compounding*

MFR are not required for preparation following the manufacturer's instructions.

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

- Name of the radiopharmaceutical
- Ingredients and their specifications
- 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 done for final release of the radiopharmaceutical (e.g., radiochemical purity, pH)
- Depyrogenation and sterility procedures and validations, as applicable, including limits
- Personnel
- Garbing procedure, if different than standard procedure
- Container(s)

- BUD assignment and storage conditions

8.2 Records for Preparation with Minor Deviation/Compounding

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

- Name of radiopharmaceutical
- Physical description of the final radiopharmaceutical (e.g., capsule or solution)
- Name and quantity of ingredients including calibration time for radioactive ingredients (e.g., 100 mCi Tc 99m sodium pertechnetate @ 13:00)
- 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) who verified the final drug product
- Date and time of preparation
- Assigned internal identification number (e.g., lot number)
- Prescription or order number(s)
- Assigned BUD and storage requirements
- PEC used
- Documentation of quality control results
- Reference source of the BUD assignment and storage requirements

9. PREPARATION

The individual responsible for preparing the radiopharmaceutical 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.

9.1 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. Utilize appropriate environmental controls, if applicable (e.g., chemical fume hood, activated charcoal filters when handling potentially volatile radionuclides). The area utilized for the

preparation of all nonsterile radiopharmaceuticals should be suitably cleaned and uncluttered to assure the overall integrity and quality of the prepared product. There should be a documented process between the preparation cycles of different nonsterile products, to decrease the likelihood of contamination from other prepared products.

STERILE PREPARATIONS

For sterile preparations, follow manufacturer preparation instructions, taking into account appropriate radiation safety considerations. Utilize 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 Class 5 PEC. Refer to *4. Facilities and Environmental Controls* and *Table 7* on the location of the PEC and the applicability toward the radiopharmaceutical BUD.

9.2 Preparation with Minor Deviations

In some cases, radiopharmaceuticals are prepared with minor deviations 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." 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. Hence, deviations from manufacturer preparation instructions for radiopharmaceuticals must maintain the same ingredients but may differ in their proportions.

This requires appropriate in-house quality control testing, designed to validate the quality and 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 amount 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 test methods other than those described in the product labelling (e.g., radiochemical purity)
- Filtering Tc-99m sulfur colloid

9.3 Preparation of Radiolabeled Blood Components

Handling and radiolabeling of blood components requires special attention to biological risks and must be handled with universal precautions using aseptic technique, to avoid introducing new microorganisms into the preparation that will be administered. Because of microorganisms potentially present in the original blood sample, the preparation must be administered as soon as possible but no later than 6 hours after the labeling process is complete.

The potential presence of microorganisms in a non-immediate use 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 radiopharmaceutical products. Hence, equipment and supplies should never be shared with other activities unless they can first be thoroughly cleaned and disinfected. Special precautions when labeling of blood components for non-immediate use include:

- Use of an ISO Class 5 BSC located in an ISO Class 7 buffer room dedicated for blood-labeling processes. There must be complete physical separation of areas where blood products are being handled from areas where non-blood products are being handled. If more than one ISO Class 5 PEC is located within the ISO Class 7 buffer room, policies and procedures must be in place to include certification that the SEC meets conditions of air quality at maximum occupancy under dynamic operating conditions.
- Personnel should work in one PEC and with only one labeling 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 from contaminating the dose calibrator or a cleaning and disinfection procedure with an appropriate product must be used to decontaminate the dipper and liner of the dose calibrator following the radioassay.
- Centrifuge should be located within the ISO Class 7 buffer room that is dedicated for blood labeling processes.
- Dedicated (per each labeling process) consumable products (e.g., 0.9% sodium chloride injection, diluent, tubes, syringes, and other supplies) necessary to radiolabel each individual patient sample.

- Blood products must be completely separated from one another to prevent cross-contamination. 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 environment 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 process.
- Cleaning and disinfection of all reusable equipment and components (e.g., BSC, centrifuge, dose calibrator, syringe shields, vial shields, pigs, ammo cases) after each procedure prior to any further use. Policies and procedures must address cleaning and disinfection processes including the use of an EPA-registered one-step disinfectant with activity against bloodborne pathogens followed by sterile 70% IPA. Sterile 70% IPA alone is not sufficient.
- After the completion of blood labeling procedures, hand hygiene must be performed.

9.4 Immediate Use of Red Blood Cell Labeling

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

- A dedicated space for blood handling must be designated. This area must be free from clutter and not used for any other radiopharmaceutical preparation or handling
- Only one labeling procedure at a time or have documented processes that maintain the integrity of samples and environment
- Dedicated equipment must be used for blood handling (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 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
- Hand hygiene must be performed (see *4. Facilities and Engineering Controls*) before and after procedure
- The area must be disinfected with sterile 70% IPA prior to beginning the radiolabeling procedure
- Follow all requirements under *3.4 Hand Hygiene and Garbing for Immediate Use Preparations*

- A cleaning and disinfecting procedure with an appropriate product must be used to decontaminate the area and equipment after the radiolabeling is complete and all disposable components have been discarded
- The start time of the preparation must begin with the initial container puncture

10. COMPOUNDING

Each compounding activity must be based on a pre-established written procedure and include maintenance of compounding records. The compounding record must provide traceability (see *8. Documentation*).

For all sterile compounding processes described in this section, aseptic handling in an appropriate environment must be performed when compounding a sterile radiopharmaceutical within an ISO Class 5 PEC. Refer to *4.7 Environmental Controls* and *Table 7* for further clarification on the location of the PEC and the applicability of the radiopharmaceutical BUD.

10.1 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 in 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., eggs). Areas intended for nonsterile compounding must be separated from areas intended 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 area utilized for compounding nonsterile radiopharmaceuticals must be maintained in a clean and uncluttered condition. The placement of equipment and materials must take into account a design that prevents cross-contamination from noncompounding areas.

When feasible, disposable material should be used to reduce the chance of cross-contamination. Each compound must have a unique MFR (see *8.1 Master Formulation Record*). The preparation information is documented on a compounding record. 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).

A BUD for the compound 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 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.

10.2 Compounding Using Conventionally Marketed Drug Products

Some compounding activities involve only the addition of a commercially marketed drug product to a radiopharmaceutical (e.g., *Ascorbic Acid Injection*, *Lidocaine Hydrochloride Injection*, *Sodium Bicarbonate Injection*).

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 quality control testing over time to validate the appropriateness of a particular BUD.

Another activity considered a compounding activity is splitting of commercially marketed kits. Kit-splitting (also referred to as "fractionation") should be restricted to times of shortage to stretch existing inventory to meet patient need. For example, the contents of a kit vial can be constituted 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. In some cases, systematic quality control testing is required to validate the appropriateness of a particular BUD.

10.3 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 prior to dispensing. The individual responsible for compounding is responsible for ensuring that the final preparation complies with pre-established standards or acceptability criteria for identity, quality, and purity. The individual

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 quality control testing over time 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, or be a component of an approved drug product. For this chapter, a bulk drug substance includes a radioisotope, 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.

Compounding must not be performed for any radiopharmaceutical that has been withdrawn from the market because of safety or lack of effectiveness, unless part of an institutional review board approved investigational study.

11. DISPENSING

11.1 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-use or multi-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., 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 multi-dose vial into a syringe. Labeling of the final patient-specific dose or ordered amount of a radiopharmaceutical is also a component of the dispensing process.

Except for an unopened manufacturer container, the final patient 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 *13. Quality Assurance and Quality Control*). However, the activity at calibration time must always be within federal, state, and local variance limits.

11.2 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 final 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 the expectations of their respective regulatory oversight agency.

Due to the additional vigilance that should be applied toward therapeutic and blood-product radiopharmaceuticals, the patient name or, in the case of a research subject, a unique identifier should be present on all inner radiopharmaceutical containers and outer shielding.

As part of dispensing, 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 with units at time of calibration and the calibration time

As part of dispensing, 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
- Calibration date and time for the dose
- Activity dispensed with units at calibration date and time
- Radionuclide and chemical form (generic name)
- Volume dispensed (as applicable)
- Number of dosage units dispensed (e.g., 2 capsules, as applicable)
- BUD (see *Table 7*) and special storage and handling instructions for non-immediate use (e.g., refrigeration, resuspension)

11.3 Direct Infusion Systems

The information in this chapter is strictly limited to the sterility and aseptic practices to use for direct infusion systems. The described infusion systems are approved medical devices by the FDA. The manner in which all necessary solutions (e.g., radiopharmaceutical and diluent) are used in conjunction with the system was a consideration in the overall approval process for the

system. Therefore, all operators for the described or future approved direct infusion systems must follow the "Instructions for Use" in the device labeling.

- Direct infusion generators (e.g., rubidium 82 Cl) 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 multi-dose container of the radiopharmaceutical (e.g., fludeoxyglucose F18 injection) and the diluent (e.g., 0.9% sodium chloride injection) directly in 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 h is allowed for these direct infusion systems (see *Table 7*)
    - The saline bag attached to the device may only be punctured once and may be used for NMT 10 h. The bag must be labeled with the date and time of puncture and the BUD
    - Any 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 disinfected with a sterile 70% IPA wipe 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 associated with the system can be repunctured or transferred to a PEC for further manipulations and the container, with contents, must be discarded

11.4 Transporting Generators Between Facilities

The following guidelines must be followed when 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 sterility of the generator system and prevent damage

12. REPACKAGING

Repackaging refers to the act of removing an FDA-approved 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 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 nonsterile 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

13. 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. 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. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation 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 must be taken, if needed.

13.1 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 procedures 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 of distribution
- Identify patients who have received the radiopharmaceutical
- Outline the disposition and reconciliation of the recalled radiopharmaceutical

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

13.2 Complaint Handling

Radiopharmaceutical facilities must develop and implement SOPs for handling complaints. Complaints may include concerns or reports on the

quality and labeling of, or possible adverse reactions to, a specific radiopharmaceutical.

A designated person must review all complaints to determine whether the complaint indicates a potential quality problem with the radiopharmaceutical. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends 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 written or electronic record 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, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: 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 *8. 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.

13.3 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, or FDA Form 1932a for animal drugs).

GLOSSARY

Administration: The direct and immediate application of a radiopharmaceutical to a patient by injecting, infusing, 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 (generally with different air cleanliness standards). The intent of an airlock is to

prevent ingress of particulate matter and microbial contamination from a lesser-controlled area.

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

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. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration, autoclave).

Aseptic technique: A type of technique used 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 an irreducible minimum.

As low as (is) reasonably achievable (ALARA)**:** The effort to maintain exposures to ionizing radiation as far below the dose limits as practical, 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., distance & shielding) are the basic principles for successfully following ALARA guidelines.

Beyond-use date (BUD)**:** For compounded, prepared, repackaged, or dispensed radiopharmaceuticals, the date and time beyond which it cannot be administered. Determination of the BUD is based on the stability of quality attributes, such as sterility, radiochemical purity, radionuclidic purity, and other applicable parameters.

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

Buffer room: An ISO Class 8 or cleaner room with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer room 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). Hence, a chemical impurity is the presence of an unwanted nonradioactive chemical.

Class II biological safety cabinet (BSC)**:** A cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare radiopharmaceuticals must be capable of providing an ISO Class 5 environment.

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

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

Compounding: The making of an unapproved radiopharmaceutical, pursuant to a valid prescription, for administration to a patient in situations where an FDA-approved, commercially manufactured drug product is not available or appropriate. Examples of compounding include, but are not limited to, mixing of two or more FDA-approved drug products (except diluents), not consistent with preparation (see *9. Preparation*); alteration of the FDA-approved dosage form (e.g., making a solution or suspension from a solid oral dosage form); "extemporaneous" preparation using an FDA-approved drug substance and/or raw materials.

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

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

Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores.

Dispensing: The making and labeling of a patient-specific dose obtained from a single-use or multi-dose container (e.g., withdrawing a volume of finished product or preparation from a vial into a syringe). As part of dispensing, the patient-specific dose may be diluted, as appropriate, to a larger volume with an appropriate diluent. A sub-set of dispensing is "repackaging" which is the act of removing an FDA-approved radiopharmaceutical from the container in which it was distributed by the manufacturer and placing it into a different container without further manipulation of the product. It is the responsibility of the individual

responsible for the dispensing to ensure appropriate identity, strength, and purity throughout the assigned BUD.

Dynamic operating condition: Conditions in the SRPA or classified room 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 manufactured drug products (including, but not limited to, finished radiopharmaceuticals, generators, and kits), the specified date (and time) beyond which the product cannot be administered. The expiration date is determined by the manufacturer and cannot be extended by individual practitioners. A BUD must be assigned to compounded and prepared radiopharmaceuticals, taking into account conditions outlined in *6. Assigning BUD* and *Table 7* and established in accordance with a facility's SOPs.

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

Garb: Items such as gloves, gowns, shoe covers, head and facial hair covers, masks, and other items designed to reduce particle shedding from personnel and minimize the risk of bacterial contamination to radiopharmaceuticals.

High efficiency particulate air (HEPA) **filtration:** Being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.

Hot-cell: A device used for the shielding and the 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) 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 (direct compounding area) 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 hood, 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, etc.). However, the overall functionality and purpose of these devices remains the same.

Hot lab: Nonclassified radiopharmaceutical processing area without a PEC located within a hospital or clinical site that is only appropriate for immediate use radiopharmaceuticals.

Immediate use: A preparation of a sterile radiopharmaceutical for a single patient using only sterile FDA-approved starting ingredients when administration will begin within 1 hour of beginning the preparation (e.g., within 1 hour of initial entry or puncture of any container) and is only required to follow the immediate use standards in this chapter (see *3.4 Hand Hygiene and Garbing for Immediate Use Preparations* and *9.4 Immediate Use of Red Blood Cell Labeling*).

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: An air quality classification from the International Organization for Standardization.

Kit: Commercially 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 binds to a metal atom to form a coordination complex.

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

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

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 bacterial contamination.

Multiple-dose container: A container of a sterile radiopharmaceutical for parenteral administration (e.g., injection or infusion) that is designed to contain more than one dose of the radiopharmaceutical.

Negative-pressure room: A room that is maintained at lower pressure than the adjacent spaces, and therefore the net airflow is into the room. This room is appropriate for volatile radiopharmaceuticals (e.g., I-131 NaI).

One-step disinfectant: A product with an EPA-registered claim 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 that are interlocked. 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.

Patient-specific 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 a specific patient.

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

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

Preparing: The act of combining a kit with a radionuclide solution and other kit components following manufacturer instructions.

Preparing with minor deviations: The act of combining a kit with a radionuclide solution and other kit components generally following manufacturer instructions but with minor deviations. 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), using alternative devices or equipment (e.g., a heating block rather than a hot water bath), and using alternative radiochemical purity testing methods. The individual preparing the radiopharmaceutical must ensure that the final preparation maintains appropriate quality and purity, including radiochemical purity and radionuclidic purity, as specified in individual monographs, manufacturer labeling, or other applicable parameters as clinically appropriate.

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.

Radioactive materials (RAM) license: A document(s) issued by the US NRC or an Agreement State 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. The prospective licensee submits an application stating the type of license(s) desired, what radionuclides and quantities are requested, the purpose for requesting a license, training and experience for one or more AUs, for a

radiation safety officer, and for general radiation personnel. The application also includes a copy of the applicant's Radiation Protection Program detailing how the applicant will ensure the safety of the employees, the public, and the environment while engaging in authorized activities. Licensees are subject to periodic inspection by the licensing agency.

Radioassay: Measurement of the amount of radioactivity present in a container using a suitable instrument, such as a well-type ionization chamber (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 nonradioactive 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 an FDA-approved 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. If a radiopharmaceutical is manipulated in any other way, including if it is reconstituted, diluted, mixed, or combined with another ingredient, that act is not considered repackaging. It is the responsibility of the individual responsible for the repackaging to ensure appropriate identity, strength, and purity throughout the assigned BUD.

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 room or an SRPA). It incorporates specific design and operational parameters required to minimize the risk of bacterial or fungal contamination.

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

Shielding: Barriers of appropriate radiation attenuating material, used in the radiopharmaceutical practice setting, 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, dispensing "pigs").

Single-dose containers: A container of a sterile radiopharmaceutical for parenteral administration (e.g., injection or infusion) that is designed for use with a single patient as a single injection/infusion.

Specific activity: The radioactivity of a radionuclide per unit mass of the element or compound (see *Radioactivity—Theory and Practice* ⟨1821⟩). The unit of specific activity is radioactivity per mass expressed on a gram or mole 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 the needle initially penetrates the container.

Sterility: The absence of viable microorganisms.

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

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

Unrestricted use: An area in which a person could not be exposed to radiation levels in excess of 2 mrems 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 by the kit manufacturer.

APPENDICES

Appendix 1: Abbreviations

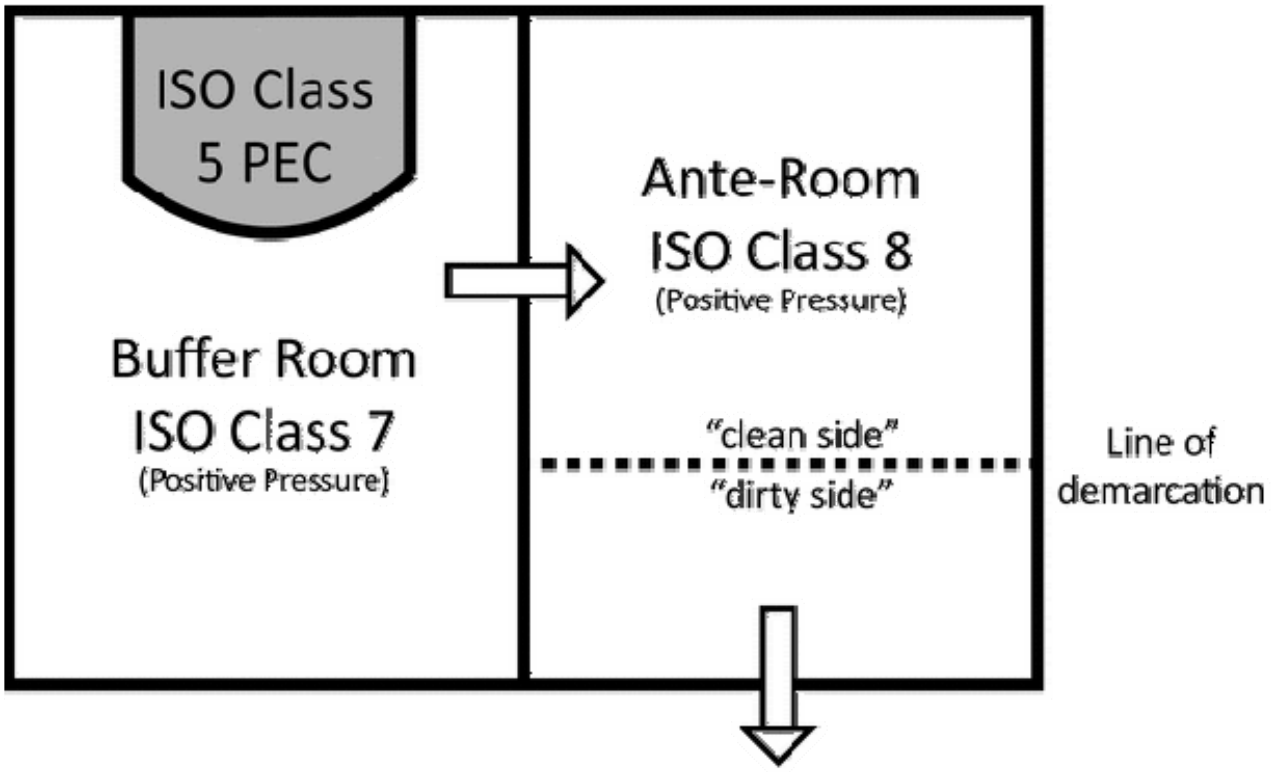
2173

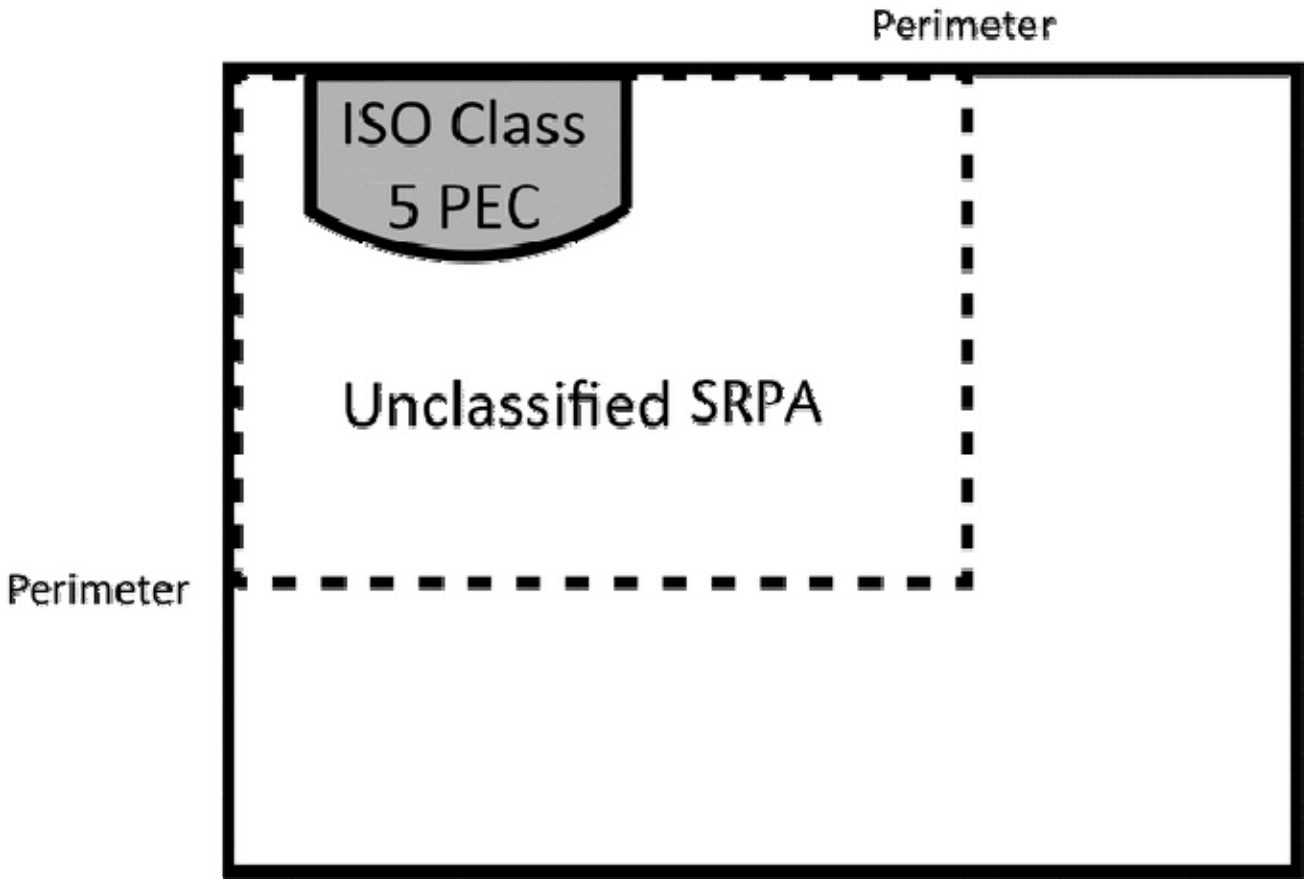
ACPH	Air changes per hour
ALARA	As low as (is) reasonably achievable
ANP	Authorized nuclear pharmacist
AU	Authorized user
BSC	Biological safety cabinet
BUD	Beyond-use date
CETA	Controlled Environment Testing Association
cfu	Colony-forming unit
CoA	Certificate of analysis
DPA	Direct processing area
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
IPA	Isopropyl alcohol
ISO	International Organization for Standardization
LAFW	Laminar airflow workbench
MFR	Master Formulation Record
MAA	Macroaggregated albumin
NRC	Nuclear Regulatory Commission
PEC	Primary engineering control
PET	Positron emission tomography
RAM	Radioactive material
SEC	Secondary engineering control
SOP	Standard operating procedure
SRPA	Segregated radiopharmaceutical processing area
TSA	Trypticase soy agar

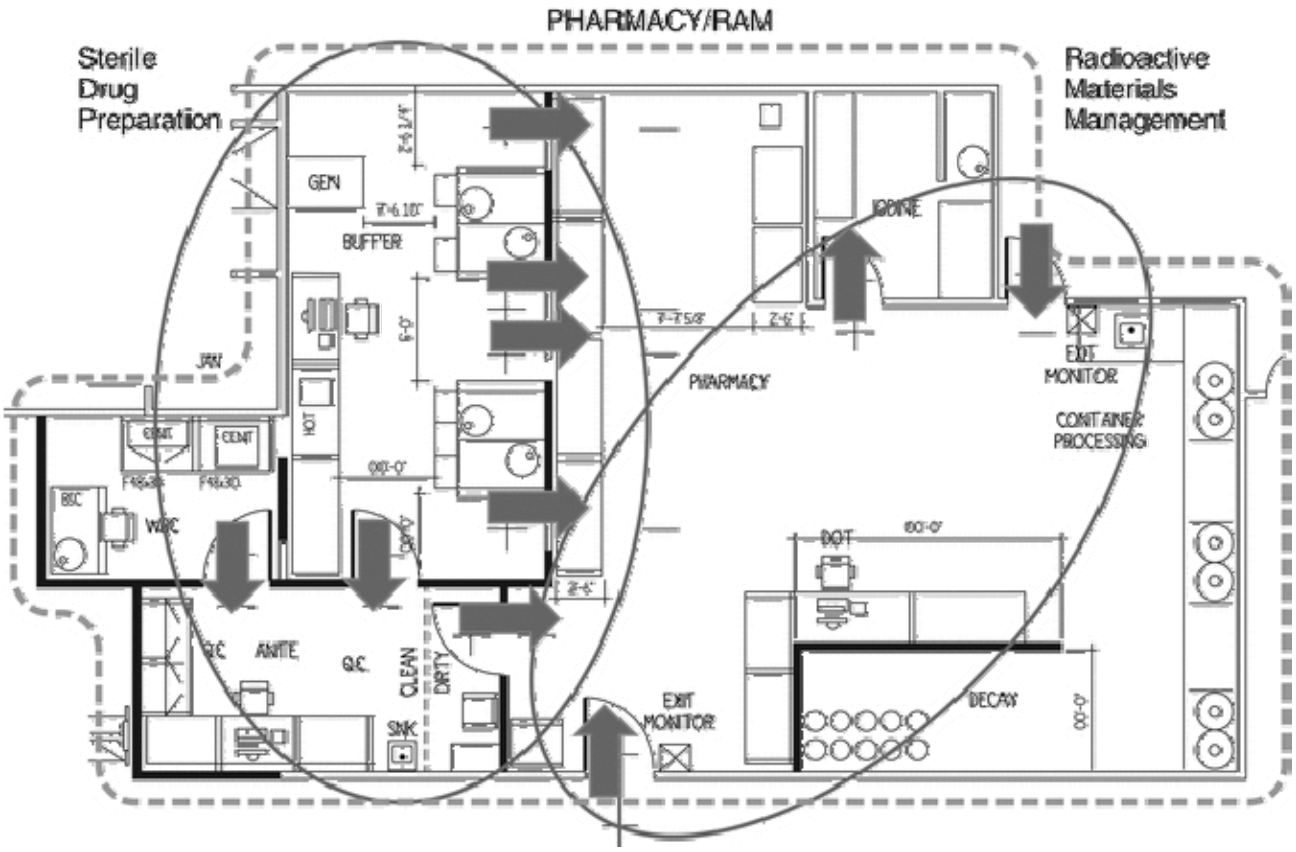
2174 **Appendix 2: Example Designs for Radiopharmaceutical Handling**

2175

Type of Facility Design	Example Design

Type of Facility Design	Example Design
Classified room[a]	

Type of Facility Design	Example Design
SRPA	

Type of Facility Design	Example Design
Sterile and nonsterile radiopharmaceutical processing areas[a]	

[a] The arrows indicate the direction of airflow.

2176 ■2S(*USP42*)

2177 [1] Centers for Disease Control and Prevention. *Guideline for Disinfection and*
2178 *Sterilization in Healthcare Facilities*, 2008.