Mayo Clinic Approaches to Meet United States Pharmacopeia <797> Requirements for Facility Design and Environmental Controls of Nuclear Pharmacy

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According to the United States Pharmacopeia (USP) General Chapter <797> (USP <797>), "Pharmaceutical Compounding—Sterile Preparations," the compounding facility must be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites. The goal of the project was to evaluate the appropriateness and effectiveness of our approaches in meeting <797> requirements. **Methods:** USP <797> standards, radiation safety concerns, and work-flow patterns were the focal points in our assessment of 4 laboratories: 2 nuclear pharmacy laboratories that engage in preparing sterile (low-, medium-, and high-risk levels), nonsterile, or possible hazardous radioactive drugs and 2 other laboratories in which only low–risk-level preparations are involved. **Results:** Each laboratory was constructed with a physically separated International Organization for Standardization Class 7 anteroom and clean room to allow us to maintain an appropriate air quality, a consistent operation, and a desirable flexibility. An isolated area within the laboratory was designated for preparing nonsterile products. Higher air change per hour was used in the areas with higher traffic or smaller space. Lead-lined biological safety cabinets (BSCs) were segregated and used depending on the risk category of the preparations. In 1 laboratory, the exhaust flow for the BSC was too great, and a lead-lined compounding aseptic containment isolator (CACI) was installed. Air in the BSC and CACI was 100% exhausted to the atmosphere. ^{99}Mo/^{99m}Tc generators were placed in the negative-pressure clean room to ensure a more efficient operation and cleaner air environment. Clean-room equipment (i.e., keyboards, printers, and telephones) was installed, and refrigerators or freezers and the central-processing unit of each computer were placed outside clean room. **Conclusion:** Our wide-range preparations of sterile, nonsterile, or potential hazardous radiopharmaceuticals, coupled with the limited space of each laboratory and existing antiquated mechanical systems, presented a challenge. Nevertheless, we successfully remodeled each nuclear pharmacy laboratory to meet USP <797> requirements for facility design and environmental controls.

Key Words: USP General Chapter <797>; nuclear pharmacy; radiopharmaceutical; facility design; environmental controls

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United States Pharmacopeia (USP) General Chapter <797>, "Pharmaceutical Compounding—Sterile Preparations" (USP <797>), became official on June 1, 2008 (*1*). USP <797> provides the minimum standard for sterile compounding practices and is designed mainly to prevent any harm to patients caused by nonsterility, endotoxins, variability of drug quality, chemical or physical contaminants, and suboptimal quality of ingredients. The impact of USP <797> on the health care field is far-reaching—it applies to all persons who prepare compounded sterile preparations (CSPs), all places in which CSPs are prepared, and all compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, with the exception of the production of PET radiopharmaceuticals, which are subject to the standards and requirements described in USP General Chapter <823>, "Radiopharmaceuticals for Positron Emission Tomograph—Compounding" (*2*). "Upon the release of a PET radiopharmaceutical as a finished drug product from a production facility," however, USP <797> indicates that "the further handling, manipulation, or use of the product will be considered compounding, and the content of this section and chapter is applicable" (*1*).

Per USP <797>, the compounding facility must be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites. Our nuclear pharmacy laboratories, operated under the practice of medicine, have operated in a semiclean-room setup since 1989. Each laboratory has had a continuous space, with various designated areas (e.g., radiopharmaceu-

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tical compounding or dispensing area, quality control [QC] area, and radioactive waste storage area) that were not physically separated (e.g., walled areas). A majority of the compounding and dispensing of radiopharmaceuticals has been performed in glove boxes, which are not primary engineering control (PEC) devices (i.e., they do not provide an International Organization for Standardization [ISO] Class 5 air environment). Lead-lined biological safety cabinets (BSCs) have been used primarily for radiolabeling leukocytes, red blood cells, or other radiopharmaceuticals studied under the Investigational New Drug Application process. BSCs were also used for dispensing certain critical radiopharmaceuticals (e.g., an ^{111}In-pentetate injection for cisternography). The air of each nuclear pharmacy laboratory has been filtered using prefilters with a minimum efficiency reporting value (MERV) of 8 (a 30%−35% efficiency of removing 3- to 10-μm particles) and final filters with a MERV of 14 (90%−95% efficiency). In critical areas of a hospital, a MERV 14 filter is typically the filter of choice to prevent transfer of bacteria and infectious disease.

With the new practice and quality standards for CSPs as stipulated in USP <797>, however, especially in the areas of facility design and environmental controls, we needed to reevaluate the layouts and infrastructures of our 4 nuclear pharmacy laboratories to ensure that they meet the requirements of USP <797>. Hence, the goal of this project was to evaluate the appropriateness and effectiveness of our approaches in meeting USP <797> requirements for facility design and environmental controls.

MATERIALS AND METHODS

Our 4 nuclear pharmacy laboratories (Labs 1–4) are located in 3 buildings of the 2 main medical complexes of the Mayo Clinic–Rochester, Minnesota (the downtown campus and St. Mary's Hospital, approximately 1.6 km [1 mile] apart). Each nuclear pharmacy laboratory is situated in an isolated room, adjacent to either the general nuclear medicine or the nuclear cardiology area that it serves, which allows us to provide efficient radiopharmaceutical care to our patients. For the majority of last-minute add-on studies, radiopharmaceuticals can be promptly prepared and dispensed. Likewise, the preparation or dispensing of radiopharmaceuticals used for on-call study can be adequately handled by the same technologist who performs the imaging or therapeutic procedure.

Lab 1 (located at our downtown campus) is our main hub for preparing various radioactive and nonradioactive and sterile and nonsterile drug products for the diagnostic or therapeutic needs of the inpatients and outpatients of our downtown medical facilities, 3 other nuclear pharmacy laboratories (with bulk radiopharmaceuticals), and our mobile services. Labs 2 and 3 (located at the downtown campus and at St. Mary's Hospital, respectively) compound only myocardial imaging drugs to be used at our inpatient and outpatient nuclear cardiology facilities at both medical campuses. Lab 4 provides radiopharmaceuticals for general nuclear medicine and is located at the same medical complex (St. Mary's Hospital) as Lab 3, which provides radiopharmaceuticals for nuclear cardiology. Although the clinical or research practice of nuclear cardiology is operated by both the Division of Nuclear Medicine and the Division of Cardiovascular Diseases, the nuclear cardiology imaging room and Labs 2 and 3 are placed within the cardiovascular diseases facility so that we may offer our cardiology patients more readily accessible and comprehensive medical and radiopharmaceutical care.

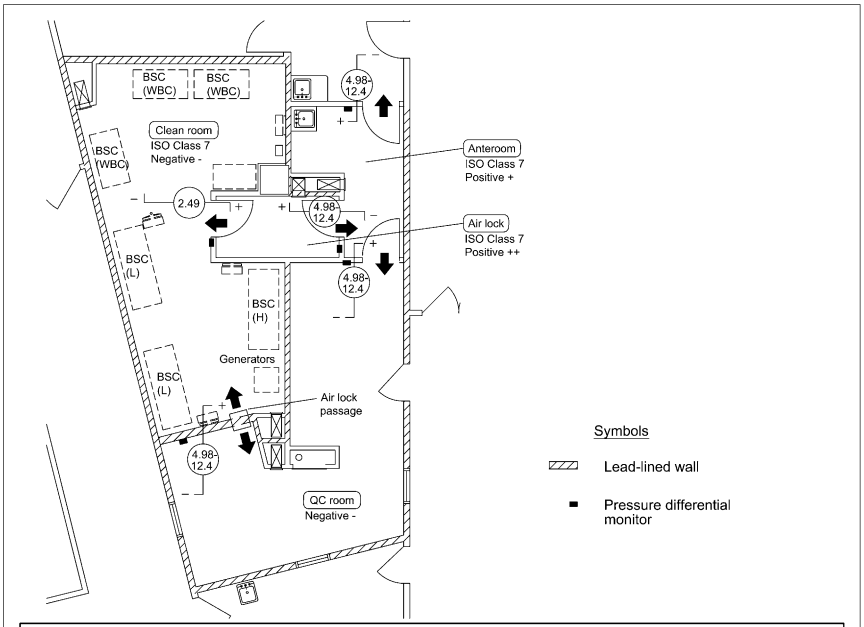
The risk levels of radiopharmaceuticals supplied by our 4 nuclear pharmacy laboratories are as follows: Lab 1 prepares various radiopharmaceuticals classified in all 3 risk levels (i.e., low-, medium-, and high-risk levels) and nonsterile radiopharmaceuticals. Lab 1 also handles sterile radioactive drugs that are potentially classified as hazardous drugs. Labs 2 and 3 are involved with only low–risk-level CSPs (i.e., ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and ^{201}Tl-chloride injections). Even though the majority of sterile radiopharmaceuticals prepared in Lab 4 are low-risk CSPs, this laboratory is currently designated as a medium-risk compounding area because of its involvement in the preparation of radiolabeled leukocytes. In addition, Lab 4 meets the facility design and environmental controls as specified in USP <797> for handling hazardous sterile drugs (*1*). Lab 4 is also an area in which we prepare various nonsterile radiopharmaceuticals (e.g., radioactive meals for gastric-emptying studies).

According to USP <797>, a clean room is a compounding environment that is supplied with high-efficiency particulate air (HEPA) or HEPA-filtered air that meets ISO Class 7, and "the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class" (*1*). Microorganisms in the environment of the clean room "are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class" (*1*). The USP <797> definition for a buffer area is "an area where the primary engineering control (PEC) is physically located" and that "provides at least ISO Class 7 air quality." Because the definition and description of the term *clean room* as stated in USP <797> relates more to the practice in our nuclear pharmacy laboratories (i.e., established testing program for environmental viable airborne particles), we have adopted the term *clean room* rather than *buffer area* or *buffer room* for use in this article.

A team consisting of a nuclear pharmacist, nuclear medicine technologists, a radiation safety officer, an architect, a mechanical designer, and an infection specialist conducted an in-depth analysis of the work-flow patterns of our practice, of the requirements of USP <797> for facility design and environmental controls, and of radiation safety during the design phase of our remodeling project. Special steps to enhance radiation safety were taken into consideration during the design phase of our remodeling project.

RESULTS

Each of our 4 nuclear pharmacy laboratories is constructed with a physical barrier (i.e., an interlocking door system) between the clean room and the anteroom (Figs. 1–4). An ISO Class 5 BSC or a compounding aseptic containment isolator (CACI) is placed in an ISO Class 7 negative-pressure clean room that is next to an ISO Class 7 positive-pressure anteroom (Figs. 1–4). A minimum-differential positive pressure of 4.98–12.4 Pa (0.02–0.05 in water column) was established between the positive-pressure anteroom and adjacent room or rooms, with negative pressure (the differential pressure between the anteroom and clean room is no less than 2.49 Pa [0.01 in water column]) (Figs. 1–4). The



Air Balance Schedule						
Room	Make-up air (L/s)	Exhaust (L/s)	%	ACPH	Area (m²)	Pressure differential (Pa)
Clean room	+1415	-1840	-23	70	34.2	2.49 minimum
Air lock	+127	-99	+22.2	31.5	4.6	4.98-12.4
Anteroom	+260	-235	+9	46	7.6	4.98-12.4

FIGURE 1. Floor plan and air-balance schedule for Lab 1. Each circled number indicates differential pressure expressed as Pascals. BSC (H) = BSC for preparing high–risk-level or hazardous CSPs; BSC (L) = BSC for preparing low–risk-level CSPs; BSC (WBC) = BSC for preparing radiolabeled leukocytes.

BSC and CACI are 100% exhausted to the outside air through HEPA filtration.

Room air exchanges are typically expressed as air changes per hour (ACPH). ACPH of not less than 30 was maintained in each clean room and anteroom. Higher ACPH was used in the area with higher traffic or smaller space. The clean room of Lab 2 has the highest ACPH (85) (Fig. 2).

A special air-lock passage was placed between the clean room and anteroom of Lab 1 to allow transfer of unit doses between these 2 rooms (Fig. 1).

Lead-lined BSCs are used in all the laboratories (Figs. 1, 2, and 4), with the exception of Lab 3. Because the exhaust flow for the BSC was too great for the clean room of Lab 3, a lead-lined CACI was installed (Fig. 3).

An isolated area within Lab 4 was designated for preparing nonsterile products (e.g., radioactive meals for gastric-emptying studies) (Fig. 4). To minimize any possible cross-contamination of various risk-level CSPs, lead-lined BSCs were segregated and used in accordance with the level of risk of the preparations (Figs. 1 and 4).

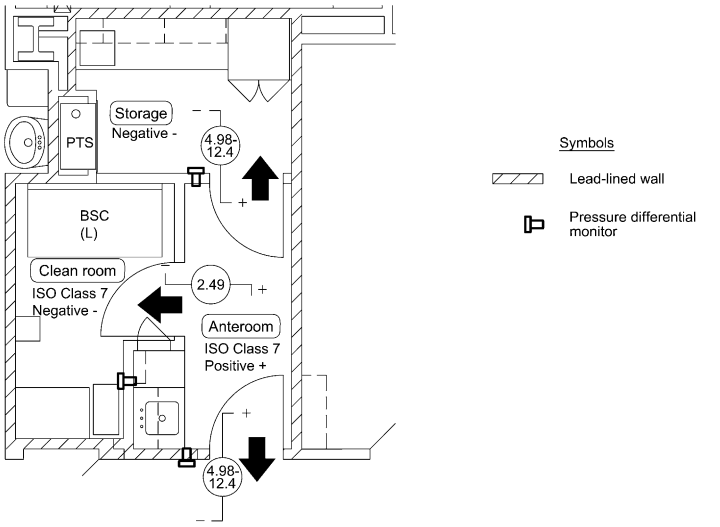
^{99}Mo/^{99m}Tc generators were placed and eluted in a clean room with an air quality of ISO Class 7 rather than the minimum ISO Class 8 air environment as required by USP <797>.

Telephones, intercoms, and keyboards specifically designed for placement in a clean room were installed to maintain the required environmental quality of air atmospheres and surfaces, and refrigerators and the central processing units of computers were placed outside the clean room.

DISCUSSION

Compounding and Dispensing

In general, the term *compounding* does not include the preparation of a drug that is commercially available, unless there is a significant difference between the compounded drug and the comparable commercially available drug. In addition, the Food and Drug Administration states that "compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling" (*1*). However, USP <797> indicates that "the FDA-approved labeling (product package insert) rarely describes environmental quality (e.g., ISO Class air designation, exposure durations to non-ISO classified air, personnel garbing and gloving, and other aseptic precautions by which sterile products are to be prepared for administration)" and "when such durations [expiration and storage dates or times] are specified [in the package insert], they may refer to chemical stability and not necessarily to microbiological purity or safety." As such, even sterile



Air Balance Schedule						
Room	Make-up air (L/s)	Exhaust (L/s)	%	ACPH	Area (m²)	Pressure differential (Pa)
Clean room	+350	-425	-17.7	85	5.4	2.49 minimum
Anteroom	+264	-207	+21.4	60	5.1	4.98-12.4
Storage	+47	-94	-50	22	4.8	4.98-12.4

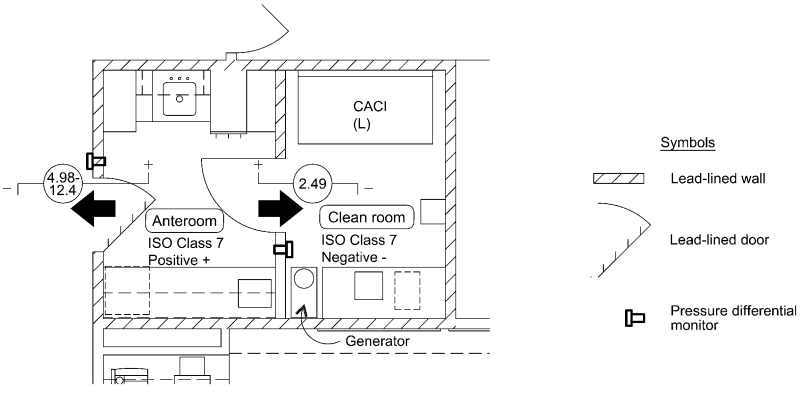
FIGURE 2. Floor plan and air balance schedule for Lab 2. Each circled number indicates differential pressure expressed as Pascals. BSC (L) = BSC for preparing low–risk-level CSPs; PTS = pneumatic tube system for delivery of PET radiopharmaceuticals from PET drug–production facility.

drugs (including sterile non-PET radiopharmaceuticals) that are prepared strictly according to the directions as stated in their package inserts would also be classified as CSPs under USP <797> (*1*).

USP <797> not only is applicable to the compounding of sterile non-PET radiopharmaceuticals but also indicates that "further handling, manipulation [such as dispensing], or use of the product will be considered compounding, and the content of this section [Radiopharmaceuticals as CSPs] and chapter [<797>] is applicable" (*1*).

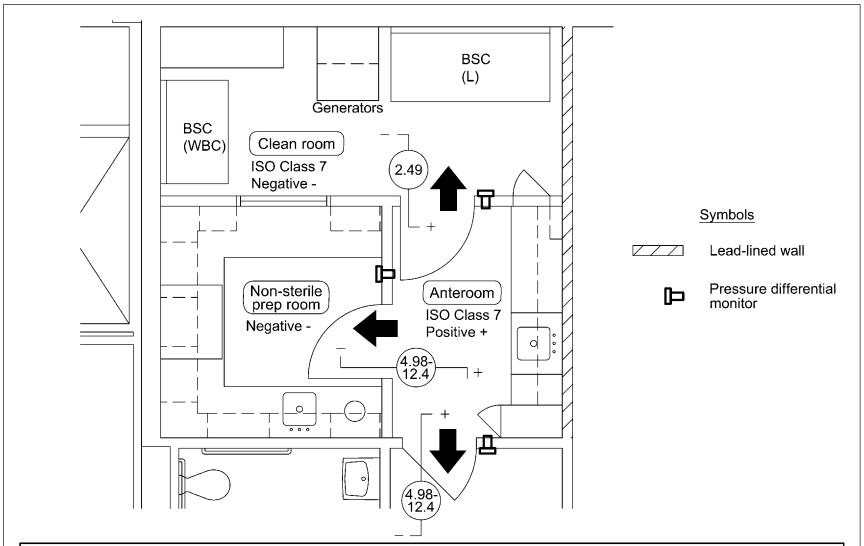
Negative or Positive Air Flow

According to the "Radiopharmaceuticals as CSPs" section of USP <797>, radiopharmaceuticals shall be compounded in a negative-airflow environment (*1*). The Nuclear Regulatory Commission (NRC) used to have a specific regulation (i.e., Title 10, Code of Federal Regulations, part 35.205) which indicated that noble gases must be used and stored in a room with negative pressure. When part 35—"Medical Use of Byproduct Material"—was changed in 2002, the NRC dropped the specific regulation



Air Balance Schedule						
Room	Make-up air (L/s)	Exhaust (L/s)	%	ACPH	Area (m²)	Pressure differential (Pa)
Clean room	+141	-165	-14.2	37	6.1	2.49 minimum
Anteroom	+165	-118	+28.5	31	5.3	4.98-12.4

FIGURE 3. Floor plan and air balance schedule for Lab 3. Each circled number indicates differential pressure expressed as Pascals. CACI (L) = CACI for preparing low–risk-level CSPs.



Air Balance Schedule

Room	Make-up air (L/s)	Exhaust (L/s)	%	ACPH	Area (m²)	Pressure differential (Pa)
Clean room	+463	-543	-15	72	10.4	2.49 minimum
Anteroom	+189	-118	+37.5	31	5.7	4.98-12.4
Non-sterile prep room	+94	-118	-20	20	7.8	4.98-12.4

FIGURE 4. Floor plan and air balance schedule for Lab 4. Each circled number indicates differential pressure expressed as Pascals. BSC (L) = BSC for preparing low–risk-level CSPs; BSC (WBC) = BSC for preparing radiolabeled leukocytes.

requiring negative-pressure rooms. However, removing the negative-pressure requirement from part 35 does not mean that one does not have to comply with the ALARA (as low as reasonably achievable) principle as stipulated in part 20—"Standards for Protection against Radiation." When the revised part 35 was enacted in 2002, the NRC stated in its "Summary of Public Comments and Responses to Comments" that "part 35 licensees must comply with the occupational and public dose limits of part 20" (*3*).

If there is a spill of a radioactive gas, aerosol, or even fine radioactive powders, a positive-airflow room would spread the radioactive material outside the room and could potentially contaminate outside areas or people. A negative pressure (or at least negative to the rooms around it) reduces the potential for the spread of radioactive materials. It is good radiation safety practice to maintain negative airflow in areas using such readily dispersible radioactive materials.

Demarcation Line or Physical Barrier

Although USP <797> allows a line of demarcation to define the segregated compounding area (SCA) for preparing low–risk-level radiopharmaceuticals with a beyond-use date (BUD) of 12 h or less, we installed a physical barrier (i.e., walls, doors, or a pass-through with interlocking door system) to separate the corridor, anteroom, and clean room in each of our 4 nuclear pharmacy laboratories (Figs. 1–4). We adopted the physical barrier rather than the demarcation-line approach in remodeling our 4 nuclear pharmacy laboratories because for an SCA that is not physically separated from the surrounding area and is defined simply by a line of demarcation, it is a common practice to use the principle of displacement airflow (*1*). The concept "utilizes a low pressure differential, high airflow [i.e., an air velocity of 0.23 m/s (40 ft/min) per minute or more] principle" to move "dirty" air from the SCA across the line of demarcation into a non-SCA. However, the concept of "displacement airflow" is only workable if the demarcated SCA has a positive-airflow pressure to the adjacent non-SCA. This is contrary to the negative-airflow requirements for a nuclear pharmacy facility.

Second, SCA can be used only to prepare sterile and nonhazardous radiopharmaceuticals that are classified as low–risk-level CSPs with a 12-h-or-less BUD (*1*), which may not work with certain radiopharmaceuticals that have a BUD longer than 12-h, such as ^{99m}Tc-mebrofenin (18 h) (*4*), ^{67}Ga-citrate (7 d), and ^{201}Tl-chloride (4 d). USP <797> states that "[t]he BUD after initially entering or opening (e.g., needle-punctured) multiple-dose containers [or vials (MDVs)] is 28 days (see *Antimicrobial Effectiveness_Testing* <51>) unless otherwise specified by the manufacturer" (*1,5*). Because the BUDs for the ^{99m}Tc-mebrofenin, ^{67}Ga-citrate, and ^{201}Tl-chloride are specifically assigned by the manufacturers, these BUDs should supersede the 28-d BUD usually assigned by USP to MDVs. Even though each of these 3 radiopharmaceuticals contains an antimicrobial preservative (*4,6,7*), USP <797> does not seem to make any exception for these sterile drug preparations. Therefore, the compounding and dispensing of MDVs are not exempted from the requirements as stipulated in USP <797>.

Third, per USP <797>, only low–risk-level nonhazardous CSPs with a 12-h-or-less BUD can be prepared or

dispensed in an SCA (*1*). Labs 1 and 4 also compound medium–risk-level CSPs (e.g., radiolabeled blood cells). Currently, Lab 1 is the only location designated for the compounding of high–risk-level sterile radiopharmaceuticals (e.g., investigational iobenguane sulfate ^{123}I injection) and the dispensing of possibly hazardous sterile radiopharmaceuticals (i.e., ^{89}Sr-chloride and ^{153}Sm-lexidronam). In 2006, the National Institute for Occupational Safety and Health (NIOSH) identified ^{89}Sr-chloride and ^{153}Sm-lexidronam as potentially hazardous to health care workers who handle them and suggested that these 2 radiopharmaceuticals be classified as hazardous drugs (*8*). According to the requirements stipulated in USP <797> for hazardous drugs as CSPs, the ISO Class 5 BSC or CACI for handling ^{89}Sr-chloride and ^{153}Sm-lexidronam must be placed in a negative-pressure (2.49 Pa [0.01 in water column]), ISO Class 7 area (e.g., a clean room) that is physically separated from the anteroom (*1*). Optimally, the BSC or CACI should be 100% exhausted to the outside air via HEPA filtration (*1*).

If a physical barrier is placed between the SCA and the non-SCA, the air quality of the adjacent positive-pressure non-SCA must be ISO Class 8 or cleaner. This is because air of the non-SCA will be drawn into the negative-pressure SCA, and thus any lesser quality of air from the non-SCA will affect negatively the minimum acceptable air quality of an ISO Class 8 in SCA (*1*). Therefore, the logistics and expense associated with the facility design, engineering controls, and routine maintenance of non-SCA to meet the ISO Class 8 or cleaner air environment must be taken into consideration when one is planning to set up an SCA operation for the compounding and dispensing of low–risk-level sterile radiopharmaceuticals with a 12-h-or-ess BUD.

ISO Class 8 or ISO Class 7

Per USP <797>, PECs must be placed within a restricted-access ISO Class 7 clean room (*1*). A PEC is normally referred to as a device that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include vertical laminar airflow workstations, BSCs, compounding aseptic isolators (CAIs), and CACIs. However, according to the "Radiopharmaceuticals as CSPs" section of <797>, these PECs can be situated in an ISO Class 8 air environment if the PECs are used to prepare a low risk level of sterile radiopharmaceuticals pursuant to a physician order for a specific patient; administration of the CSP should start within 12 h of preparation or as recommended in the package insert, whichever is less (*1*). In addition, the elution of a ^{99}Mo/^{99m}Tc generator system should take place in an area with at least an ISO Class 8 air quality (*1*).

If the clean room is used to prepare a medium or high risk level of sterile radiopharmaceuticals or hazardous CSPs, the air environment of the clean room must be ISO Class 7 and physically separated from an anteroom with the same ISO Class air quality. This is to preserve the air quality of the clean room, because it is a negative-pressure environment.

To maintain a better air quality, a uniform facility design and environmental control or maintenance, and a desirable flexibility (e.g., BUD longer than 12 h), we chose to maintain ISO Class 7 in all the controlled rooms (i.e., clean room, pass-through room, and anteroom) of our 4 nuclear pharmacy laboratories, including Labs 2 and 3, which do not compound medium– or high–risk-level sterile radiopharmaceuticals or hazardous CSPs (Figs. 1–4).

Total Exhaust or Recirculating

Class I BSCs provide personnel and environmental protection but no product protection, because unfiltered room air is drawn across the work surface. Class II BSCs have a hood that provides biologic protection to the personnel, environment, and product; Class II Types A2 and B1 recirculate 70% and 30%, respectively, of air back through the HEPA filter, whereas Class II Type B2 recirculates 0% of air (i.e., total exhaust).

For compounding hazardous drugs such as CSPs, USP <797> recommends that the BSC and CACI be 100% exhausted to the outside air through HEPA filtration (*1*). Although the NRC does not require the air in a BSC or isolator to be 100% exhausted to the atmosphere, it is prudent to select a BSC or CAI or CACI that does not recirculate air, to provide complete protection to the workers, environment, and product.

ACPH

Adequate HEPA-filtered airflow supplied to the anteroom and clean room is required so that the cleanliness classification of these rooms is maintained. The sufficient intake of air is controlled by the appropriate number of ACPHs. For an ISO Class 7 room supplied with HEPA-filtered air, USP <797> stipulates that the room should receive an ACPH of not less than 30 (*1*). All ISO Class 7 rooms in our 4 nuclear pharmacy laboratories meet this minimum ACPH threshold (Figs. 1–4).

The clean room of Lab 2 has a particularly high number of ACPHs (85) (Fig. 2), compared with the minimum of 30 required by USP <797>. The BSC placed in Lab 2 exhausts 425 L/s (900 ft^3/min) of air flow, and 349 L/s (740 ft^3/min) of airflow is supplied to the space to make up the air being exhausted (Fig. 2). The net-76 L/s (240 ft^3/min) maintains a negative-pressure environment in the clean room. The space has a small footprint of only 5.4 m^2 (58 ft^2) and a ceiling height of 2.7 m (9 ft). ACPH can be calculated with the following equation:

$$\text{ACPH} = (\text{fresh airflow through the room [L/s]} \times 3,600\,\text{s}) / \text{volume of space (L)}$$

The small volume of the clean room located at Lab 2 resulted in a higher number of ACPHs. On the contrary, a

larger room with the same airflow requirements would have a lower ACPH. If this were a clean room with an unducted Class II Type A2 or B1 BSC that did not have to be exhausted to atmosphere, one would have to supply the space with only about half the amount of airflow needed to obtain 30 ACPHs. USP <797> allows a minimum ACPH of 15 in the clean room if the area has a PEC that is an ISO Class 5 recirculating device to offer at least an additional 15 ACPHs so that the combined ACPH is not less than 30 (*1*). This clause did not pertain to our situation, however, because we used PECs that must be 100% exhausted to atmosphere. Thus, the supply air still had to be quite high to make up the air being exhausted. Also, the heat dissipated from the BSC (~600 BTU/h) and any other heat load in the space still had to be taken into account to determine whether the supply air was adequate for cooling purposes.

Another reason for designating a higher ACPH to Lab 2 was the high traffic in and out of the anteroom and the high frequency with which the windows were opened and closed (to pass out the dispensed unit dose) in the clean room each workday. It was estimated that the anteroom door and the pass-through window could open and close as many as 80 times per day. A higher ACPH in the clean room helped us keep the internally generated particles to a minimum.

The ACPH values designed for the clean rooms of Labs 1 and 4 are 70 and 72, respectively (Figs. 1 and 4). The area of these 2 rooms (i.e., 34.2 m^2 [368 ft^2] for the clean room of Lab 1 and 10.4 m^2 [112 ft^2] for the clean room of Lab 4) is significantly larger than that of the clean room of Lab 2 (Fig. 2). Nevertheless, the larger size of the room did not translate into a proportionally reduced ACPH value for each of the 2 clean rooms located at Labs 1 and 4. Higher exhaust airflow generated from 2 BSCs at Lab 4 (Fig. 4) and 6 BSCs at Lab 1 (Fig. 1) is the main reason for the required higher ACPH for both clean rooms. Additionally, there are routinely 3–5 nuclear pharmacy technologists working in the clean room of Lab 1. The number of personnel working in the room should be taken into consideration when determining ACPH. Because these 2 clean rooms also involve the compounding of medium– or high–risk-level sterile radiopharmaceuticals, and the possible handling of hazardous sterile radiopharmaceuticals, implementation of a higher ACPH in these 2 rooms would provide a cleaner and safer working environment.

CACI

We could not design Lab 3 using a 1.5- or 1.8-m (5-ft or 6-ft) BSC similar to those for Labs 2 and 4 because the exhaust requirements for the BSCs were too great. The proposed 1.8-m (6-ft) BSC needed 519 L/s (1,100 ft^3/min) of exhaust air exhausted to atmosphere. To accomplish this, we would have had to run a 30.5-cm (12-in)-diameter duct up through 3 building stories above to the roof. This would have required that approximately 472 L/s (1,000 ft^3/min) of makeup air be supplied to the space. The existing building infrastructure (i.e., supply-air–handling unit and supply-air ductwork) was undersized and unable to provide that much air.

By using a commercially available lead-lined CACI, we needed to exhaust only 57 L/s (120 ft^3/min) of air to atmosphere, in a much smaller 15.2-cm (6-in) duct. It was easy to find a path to route the 15.2-cm (6-in) duct through the floor above. We could also have used the existing exhaust that served the space before to provide enough air changes in the space to meet ISO Class 7 clean-room requirements. We were able to use a fan-powered box and the existing building infrastructure and supply air to make up the air being exhausted.

Placement of PECs

The locations of our BSCs and CACI were carefully selected to prevent any cross-contamination and to avoid airflow disruption.

Prevention of Cross-Contamination. Although the radiolabeling process of autologous leukocytes may fit well with condition 2 (i.e., "The compounding process includes complex aseptic manipulations other than the single-volume transfer.") as specified under the "Medium-Risk Level CSPs" section of USP <797> (*1*), it is uncertain whether patient blood can be perceived as a "sterile" ingredient or component. In any event, the process for radiolabeling blood cells (e.g., ^{111}In-oxyquinoline–labeled leukocytes or ^{99m}Tc-labeled red blood cells with the UltraTag RBC kit [Covidien, formerly Mallinckrodt Medical Inc.]), which involves the manipulation of patient blood, is generally viewed as entailing a "medium-risk level CSP" (*1*).

When compounding activities require the manipulation of a patient's blood-derived or other biologic material (e.g., radiolabeling leukocytes), the PECs used for the above-mentioned procedure are clearly separated from the other PECs located at the opposite end of the clean room (Figs. 1 and 4). Each BSC designated for the leukocyte-radiolabeling process is equipped with its own dose calibrators. Only 1 nuclear pharmacy technologist is assigned to work on 1 patient's blood in a specific BSC, and the technologist must adhere to the specific standard operating procedure to perform the radiolabeling process and identify the patient. The compounding area has to be properly arranged so that it will not contaminate the preparation of sterile drugs and the QC process conducted in the clean room and anteroom, respectively.

In Lab 1 (Fig. 1), the compounding of high–risk-level CSPs (e.g., investigational iobenguane sulfate ^{123}I injection) and dispensing of NIOSH-identified "hazardous" sterile radiopharmaceuticals, such as ^{89}Sr-chloride and ^{153}Sm-lexidronam, are handled in an isolated corner. The designated BSC is heavily shielded with a 6-mm (0.25-in) lead lining and a leaded-glass window with 6-mm lead equivalence; the BSC is also equipped with an activated charcoal filter.

Avoidance of Airflow Disturbance. Each PEC (especially the BSC) is strategically placed in each clean room out of

the personnel traffic flow; air streams from the heating, ventilation, and air conditioning; and room cross-drafts to avoid airflow disruption that could adversely affect the proper operation of PECs. The front of the hood of 2 of the BSCs (one in Lab 1 and the other in Lab 4) is directly facing the entrance door leading into the clean room (Figs. 1 and 4). The potentially strong air currents from opened doors could disrupt the unidirectional airflow in an open-faced BSC. Fortunately, each of these 2 BSCs (similar to the other BSCs designated for the compounding of non-radiolabeled blood components) was installed with 4 lead-lined sliding panels in the front of the hood. To prevent any outside airflow disturbance, the opening ports of the 2 panels can be easily blocked with the other 2 block panels when the BSC is not in use.

Placement of ^{99}Mo/^{99m}Tc Generator Systems

Because the ISO-rated rooms in our 4 nuclear pharmacy laboratories are all classified as ISO Class 7, the storage and elution conditions for ^{99}Mo/^{99m}Tc generators are a level cleaner than the minimum ISO Class 8 air environment as required by USP <797> (Figs. 1, 3, and 4); Lab 2 does not use a ^{99}Mo/^{99m}Tc generator because it obtains bulk radiopharmaceuticals directly from Lab 1.

The use of the anteroom as a storage location for the ^{99}Mo/^{99m}Tc generator (up to 3 super-hot generators, each one ~481 GBq [13 Ci] on the day of receipt) could lessen radiation exposure to the personnel who work in the clean room. However, we decided to place the generator in the clean room to handle the elution process in a more efficient and safer manner. The ability to elute the generator and transfer the eluted activity within the same room enhances the operation efficiency by avoiding the replacing of sterile gloves in and out of the clean room and the cross-traffic between clean room and anteroom. It would also minimize the likelihood of inadvertently dropping the highly radioactive elution vials when doors are opened. To ease the radiation exposure concern of our technologists who work relatively near the generator, we placed a thick auxiliary shield (Covidien) on each ^{99}Mo/^{99m}Tc generator, which has effectively and drastically reduced the radiation exposure to personnel.

Placement of Other Devices and Objects

According to USP <797>, "[p]lacement of devices (e.g., computers, printers) and objects (e.g., carts, cabinets) that are not essential to compounding in buffer areas is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which shall be verified by monitoring" (*1*). Thus, any of these items could be kept in the buffer area (or clean room) only if it is deemed essential to compounding or dispensing and tests of the environmental air demonstrate that the placement of such items does not diminish the environmental quality (i.e., acceptably low viable and nonviable particle levels are maintained).

Computers and Printers. To ensure that the required cleaning for the device (e.g., computer system) placed in the clean room is properly performed according to USP <797>, clean-room keyboards, printers, and flat-screen liquid crystal display computer monitors were selected. However, the central processing units of the computer were located in a separate non–ISO-rated room because cleaning the fan grill of the unit is difficult, and the grills tend to collect dust because of the air turbulence generated by these units.

Communication Systems. Telephones and intercoms designed for a clean-room environment were also installed to provide better control of contamination.

Refrigerators and Freezers. Refrigerators or freezers should be avoided in the clean room because the condenser coils and cooling fan behind the kick plate or toe grill of a refrigerator or freezer collect dust.

Air-Lock Pass-Through Area and Air-Lock Passage

Air-Lock Pass-Through. Lab 1 has an air-lock pass-through area that occupies 4.6 m^2 (50 ft^2) and provides additional physical separation between the clean room and anteroom (Fig. 1). As Lab 1 was the first of our 4 nuclear pharmacy laboratories to undergo USP <797> remodeling in early 2005, we mirrored the "air-lock pass-through" design from our existing current good manufacturing practice–compliant PET drug–production facility. The air-lock pass-through added another layer of air-quality assurance to the main hub of our radiopharmaceutical compounding facility.

Air-Lock Passage. A special air-lock passage was installed between the clean room and the QC room of Lab 1 (Fig. 1). This differential-pressure–controlled passage allows the QC samples or dispensed unit doses of radiopharmaceuticals to be passed out from the clean room without affecting the air quality of the clean room and avoiding the releasing of any volatile radioactive contamination into the other rooms.

CONCLUSION

Our nuclear pharmacy practice at the Mayo Clinic–Rochester involves the compounding of a variety of different risk-level radiopharmaceuticals (i.e., low–, medium–, and high–risk-level CSPs) and nonsterile radiopharmaceuticals and the dispensing of some potentially hazardous sterile radiopharmaceuticals. In addition to this, the limited space and existing antiquated mechanical or building infrastructure presented a challenging task to our team in seeking innovative ways to remodel our 4 nuclear pharmacy laboratories. Our approaches have successfully transformed each of our 4 nuclear pharmacy laboratories to meet the USP <797> requirements for facility design and environmental controls and to provide greater safety (especially assurance of sterility) for our patients.

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