INTRODUCTION

The learner was introduced to the guidelines of USP Chapter <797> in a previous Continuing Education lesson, “USP<797> Compliance in Nuclear Medicine – Parts 1 and 2.” This Continuing Education Unit will further explore the vital contribution of aseptic technique during the preparation of sterile radiopharmaceuticals according to the standards established in USP Chapter <797>.

PROGRAM OBJECTIVES

Upon completion of this program, the learner will be able to accomplish the tasks listed here:

- List three critical sites which may serve as entry portals for microbes into compounded sterile preparations.
- Compare and contrast two characteristics of laminar airflow workbench (LAFW) with a biological safety cabinet (BSC).
- Describe two conditions to be met for an immediate-use compound sterile preparation.
- Identify the requirements for a CSP to be classified as a “Low Risk” preparation.
BACKGROUND

The stated objective of USP Chapter <797> is to “describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients... (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in compounded sterile preparations (CSPs).”

Specific consideration must be given to the maintenance of sterility when compounding with sterile components and to the avoidance of introducing microbial contamination into a sterile preparation. This guideline applies to all parenteral medications for diagnosis and therapy; thus, radiopharmaceuticals are included.

Death and injury have resulted from contaminated parenteral pharmaceuticals that were compounded from both sterile and non-sterile components. Radiopharmaceuticals and small-volume parenteral preparations, like heparin flush solutions, have been involved in these incidents. Preparations of radiopharmaceuticals as CSPs in all practice settings, including nuclear medicine departments, are subject to the use of aseptic technique and the standards set by USP Chapter <797>.

ASEPTIC TECHNIQUE AND RADIATION SAFETY

The FDA defines compounding differently from USP Chapter <797>. The FDA 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” (21 USC 321 (k) and (m)). However, the FDA-approved labeling (product package insert) rarely describes environmental quality (e.g., ISO 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).

The Sterile Compounding Expert Committee (SCC) acknowledged that the FDA cites the manufacturer’s package labeling, which does not always account for such practices as proper environmental conditions and personnel garbing. This statement from the chapter reflects that opinion: “Manufactured sterile products that are either prepared strictly according to the instructions appearing in manufacturers’ approved labeling (product package inserts) or prepared differently than published in such labeling. [NOTE—Beyond-use exposure and storage dates or times (see General Notices and Requirements and Pharmaceutical Compounding—Nonsterile Preparations <795>) for sterile products that have been either opened or prepared for administration are not specified in all package inserts for all sterile products. Furthermore, when such durations are specified, they may refer to chemical stability and not necessarily to microbiological purity or safety.]

The SCC also recognized that special considerations are required when preparing radiopharmaceuticals as CSPs. Aseptic processing and environmental control are more complex for personnel preparing radiopharmaceuticals as CSPs due to the concern of radiation exposure, the use of special devices to reduce exposure and contain radioactive spills, and the use of equipment for radioactivity measurements. USP Chapter <797> presents modifications of standards for radiopharmaceutical preparations to take special handling and equipment into account. Certain definitions and activities are relaxed because of their hazardous nature, regulatory issues based on the use and storage of radioactive materials, and the general safety and protection of radioactive materials users. Nevertheless, there are basic aseptic techniques that must be followed when compounding diagnostic and therapeutic radiopharmaceuticals. The SCC addresses these standards found in Chapter <797>. This course will review various aspects of aseptic processing listed in the sections of the revised Chapter <797> shown here:
USP797 Aseptic Processing - Part 1

- Definitions
- Responsibility of Compounding Personnel
- Immediate-Use CSPs
- Personnel Training and Evaluation in Aseptic Manipulation Skills
- Radiopharmaceuticals as CSPs
- Verification of Compounding Accuracy and Sterility
- Personnel Training and Competency Evaluation of Garbing
- Aseptic Work Practices and Cleaning/Disinfection Procedures
- Suggested Standard Operating Procedures (SOPs)
- Elements of Quality Control
- Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs

DEFINITIONS

Several definitions are given that have relevance when the aseptic compounding of radiopharmaceuticals is considered under the standards of the chapter. The following definitions are required for a full understanding of microbial contamination control of personnel and the environment in aseptic processing. These are taken directly from the section:

Aseptic Processing - A mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers–closures or packaging material for medical devices) and the transfer of the product into the container and its closure under at least ISO Class 5 conditions.

Critical Area - An ISO Class 5 environment.

Critical Site - A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampoules, needle hubs) 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. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

Direct Compounding Area (DCA) - A critical area within the ISO Class 5 primary engineering control (PEC) where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Disinfectant - An agent that frees from infection, usually a chemical agent but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores. A disinfectant refers to substances applied to inanimate objects.

First Air - The air exiting the high-efficiency particulate air (HEPA) filter in a unidirectional air stream that is essentially particle free.
Media-Fill Test - A test used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile product without microbial contamination. During this test, a microbiological growth medium such as Soybean–Casein Digest Medium is substituted for the actual drug product to simulate admixture compounding. The issues to consider in the development of a media-fill test are media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.

Primary Engineering Control (PEC) - A device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs).

Segregated Compounding Area - A designated space, either a demarcated area or room, that is restricted to preparing low-risk level CSPs with 12-hour or less BUD. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of CSPs and shall be void of activities and materials that are extraneous to sterile compounding.

Microbial Contamination and Radiopharmaceuticals as CSPs

Microorganisms are of major concern when manipulating CSPs and compounding personnel are the most significant source of microorganism in the DCA. For example, infections from *Serratia marcescens* were found in heparin filled syringes that were involved in infections caused by the use of these small-volume flushes. This ubiquitous microorganism is commonly found in the respiratory and urinary tracts of adults. Microorganisms such as these could be carried by airborne saliva or dried saliva droplets on dust particles. *Streptococcus* and *staphylococcus* species may also be shed from the exposed skin of personnel.

Trissel et al, in a series of articles, reported contamination rates in several medium-fill simulations. One of the highest contamination rates occurred in the simulation of medium-risk level preparation compounding that yielded an overall contamination rate of 5.2%. Their follow-up research showed a reduction of the contamination rate to 0.34% when compounders used sterile gloves that were treated with repeated 70% isopropyl alcohol (IPA) disinfections.

Even though sterile gloves may be contaminated once they touch a surface that is contaminated, the reduced bioburden with the gloves’ initial use and the repeated application of 70% IPA had a significant effect on contamination. The group’s research convinced the SCC that the use of sterile gloves would have a significant impact on touch contamination of CSPs. USP Chapter <797> recommends the use of sterile gloves.

Touch contamination is most often the reason for the introduction of microorganisms into a parenteral product. Protection of the opening or surface between the sterile preparation and the environment becomes paramount. Critical sites that require protection when preparing a radiopharmaceutical kit or dispensing a dose from a vial for patient use include those listed here:

- Tip of the hypodermic needle.
- Syringe plunger.
- Septum of the vial.
Shielded syringes and shielded vials used when compounding and dispensing radiopharmaceuticals complicate aseptic processing because of:

- Decreased dexterity caused by shielding weight.
- Hampered vision caused by vial and syringe shields.
- Potential obstruction of “first air” when positioning activities behind leaded glass shielding in a vertical flow laminar airflow workbench.

Cleanliness of the environment and the maintenance of sterile injections are also a concern since mold spores are carried in the air. *Pseudomonas* species grow rapidly in water. Although molybdenum-99/technetium-99m generator systems are to be stored and eluted in ISO Class 8 environments, extreme care is required when eluting the fixed-needle systems. Appropriate measures to maintain the sterility of the needles include the manufacturer’s recommendations for covering the needles between elutions.

**RESPONSIBILITY OF COMPOUNDING PERSONNEL**

USP Chapter <797> states, among other requirements, that compounding personnel “maintain appropriate cleanliness conditions” to provide for aseptic processing. The specific objectives from that section can be related to the preparation and dispensing of radiopharmaceuticals as CSPs when considering aseptic compounding. The section notes that: “Qualified licensed healthcare professionals” (e.g., nuclear pharmacists and nuclear medicine physicians) “who supervise compounding and dispensing of CSPs shall ensure that the objectives listed here are achieved:

1. Compounding personnel are adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties:
   a. perform antiseptic hand cleansing and disinfection of non-sterile compounding surfaces;
   b. select and appropriately don protective garb;
   c. maintain or achieve sterility of CSPs in ISO Class 5 PEC devices and protect personnel and compounding environments from contamination by radioactive drugs,
   d. identify, weigh, and measure ingredients; and
   e. manipulate sterile products aseptically, sterilize high-risk level CSPs, and label and quality inspect CSPs.
2. Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended use.
3. While being used, the compounding environment maintains the sterility or the pre-sterilization purity, whichever is appropriate, of the CSP.
4. Deficiencies in compounding, labeling, packaging, and quality testing and inspection can be rapidly identified and corrected.”
Such factors as compounding environment, compounding personnel and their training, quality assessment and documentation, are all aspects of USP Chapter <797>. An understanding of how the chapter addresses risk is central to the development of aseptic compounding activities in nuclear medicine. There are three CSP microbial contamination risk levels given in the chapter. These risk levels are assigned according to potential for contamination during compounding. The chapter also states that “licensed healthcare professionals [nuclear medicine physicians and nuclear pharmacists] who supervise compounding are responsible for determining the procedural and environmental quality practices and attributes that are necessary for the risk level they assign to specific CSPs.” Most compounding activities in nuclear medicine can be categorized as low-risk level preparations, since they are designated as such by the radiopharmaceuticals as CSPs section: “For the purposes of this chapter, radiopharmaceuticals compounded from sterile components in closed sterile containers and with a volume of 100 mL or less for a single-dose injection or not more than 30 mL taken from a multiple-dose container (see Injections <1>) shall be designated as, and conform to, the standards for Low-Risk Level CSPs.”

The revision of USP Chapter <797> established an immediate-use category for CSPs. This category is intended for situations where there is a need for immediate patient administration and emergencies. This immediate use exemption allows nuclear medicine technologists to prepare radiopharmaceuticals for emergency procedures without regard to environmental controls or personnel garb.

Any immediate-use CSPs are exempted from the Low-Risk Level requirements of Chapter <797> when the criteria listed here are met:

1. The process involves simple transfer of not more than three commercially manufactured packages of radiopharmaceutical products from the manufacturers’ original containers with not more than two entries into any one container.
2. The continuous compounding process does not exceed 1 hour.
3. Aseptic technique is followed in the preparation of the CSP.
4. The administration of the CSP is begun within 1 hour following the start of the preparation.
5. The CSP must be labeled with patient identification information and the initials of the preparer unless it is immediately and completely administered as witnessed by the preparer.
6. If the radiopharmaceutical as a CSP is not administered within 1 hour following the start of its preparation, it must be “promptly, properly and safely discarded”.

ENVIRONMENTAL CONTROLS TO ENSURE AIR QUALITY

The quality of the air in the compounding area is based on the number of particles per cubic meter of air in the designated environment (see Table 1). In any of the risk classifications, the chapter specifies that: “The quality of the environmental air increases with movement from the outer boundary to the direct compounding area (DCA). Placement of devices in antearaeas and buffer areas is dictated by their effect on the designated environmental quality of atmospheres and surfaces, which shall be verified by monitoring. It is the responsibility of each compounding facility to ensure that each source of ISO Class 5 environment for exposure of critical sites and sterilization by filtration is properly located, operated, maintained, monitored, and verified. The PEC must provide the least number of particles reducing the potential for microbial contamination.”
Table 1. Air Quality Standards

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Particles/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3,520</td>
</tr>
<tr>
<td>7</td>
<td>352,000</td>
</tr>
<tr>
<td>8</td>
<td>3,520,000</td>
</tr>
</tbody>
</table>

The ISO Class 5 PEC most often used to prepare radiopharmaceuticals as CSPs is a vertical flow laminar air flow workbench (see Figure 1). This environment can be a biological safety cabinet. The unidirectional flow of the HEPA filtered air originates in the top of the cabinet and flows down on the surface of the workbench. The top-down direction of air flow protects the operator from contaminations that may be projected out of the workbench if the unidirectional airflow was horizontal. The top-down direction makes maintaining the critical sites of shielded syringes and vials difficult. A leaded glass shield is also required to reduce radiation exposure to the operator. Low shedding absorbent padding should be placed on the floor of the cabinet to contain and reduce the spread of potential radioactive spills. The process of compounding radiopharmaceuticals is further complicated by the placement of a dose calibrator and syringe pigs into the ISO Class 5 environment. The technologist or pharmacist must possess great dexterity to use time, shielding and distance to maintain radiation exposures ALARA and to keep critical sites in the first air of the DCA.
Once risk levels are determined for the nuclear medicine department, environmental controls are used to provide the quality of air needed in the compounding environment. The revised chapter provides conceptual representations to consider for placement of PECs in nuclear medicine departments and nuclear pharmacies.

If all the radiopharmaceuticals prepared in the department can be designated as “low-risk with a 12 hour or less beyond use date”, an ISO Class 5 PEC can be placed in a segregated compounding area (see Figure 2).

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Figure 1: Class II Type A2 Biological Safety Cabinet. The blower draws room air up to the plenum which distributes the air evenly over the HEPA filter which laminates and filters the air.
If the analyses of the compounding activities in the department reveal any higher risk level activities, the facility design becomes more complex. If the analysis shows that other non-radioactive pharmaceuticals are prepared in the same clean area, the compounding activities may require three ISO levels. An ante area and a buffer area should be added to accommodate the higher risk levels (See Figure 3).
Due to the exceptions made for ALARA and required shielding in the buffer areas in a nuclear medicine hot lab that is not actively involved in the preparation of non-radioactive CSPs, the environmental air quality requirements can be relaxed to an ISO Class 8 classification (see Figure 4). The controlled environments are intended to minimize airborne contamination from contacting critical sites and should provide a working environment for personnel to perform required tasks in relative comfort.

The preparation of radiopharmaceuticals as CSPs requires placement of shielding, absorbent materials, and a dose calibrator within the ISO Class 5 PEC. This can cause concern because of an increased difficulty in maintaining the low number of particles in the compounding area. In all cases, radiopharmaceuticals are to be manipulated in a fashion that exposes critical sites to the first air of the DCA.
CONCLUSION

If a reason to develop a standard of practice for compounding sterile parenteral products was needed, minimizing the risk of touch contamination could be cited as the major concern. To address this, the revisions in USP Chapter <797> have set specific standards of practice for the compounding of sterile preparations using aseptic techniques. These standards apply to nuclear medicine and nuclear pharmacy by acceptance of this chapter into regulations and statutes at state and federal levels. The revised standards address specific aspects of training in aseptic technique. These include initial and periodic assessment of knowledge and skills of nuclear medicine technologists and pharmacists. The standards also require the documentation of activities for personnel to maintain competency. Therefore, the development of and adherence to standard operating procedures are an integral part of this process. Departments must adopt the requirements of the chapter or use technologies, techniques, materials and procedures that “have been proven to be equivalent or superior with statistical significance to” those described in the revised chapter. In either circumstance, extra time and effort will be mandatory in the required training for and documentation of these activities. Furthermore, nuclear medicine technologists and nuclear pharmacists must develop an attitude to prevent microorganism contamination of radiopharmaceuticals.
QUIZ

QUESTION #1

Compounded sterile preparations may cause harm to patients due to the following examples except:

- the incorrect calculation of pharmaceutical ingredients.
- the inadvertent introduction of bacteria into the final preparation.
- ingredients meeting minimum quality standards as established by the USP.
- the presence of endotoxins.

QUESTION #2

The Food and Drug Administration bases their standards of compounding on:

- the same standards as the USP.
- the manufacturer’s product package insert.
- low-risk compounding guidelines.
- highly controlled environmental conditions.

QUESTION #3

A “critical area” is defined as:

- a vial septum.
- the exposed tip of a syringe.
- the extended plunger of a syringe.
- an ISO Class 5 environment.

QUESTION #4

Laminar airflow:

- travels in one direction.
- swirls around the direct compounding area in a circular pattern.
- is directly obtained from outside air.
- is not critical to the compounding process.
QUESTION #5

Microorganisms in compounded sterile preparations are most frequently caused by:

- storage times that exceed beyond-use exposure.
- touch contamination.
- ingredients of inappropriate quality.
- insufficient use of 70% isopropyl alcohol.

QUESTION #6

Mold spores are of greatest concern when the spores are:

- exposed to water.
- airborne.
- in small volume parenterals.
- refrigerated.

QUESTION #7

Radioactive preparations may be classified as immediate-use except:

- Tc-99m macroaggregated albumin.
- Tc-99m pentetate.
- Tc-99m mebrofenin.
- Tc-99m labeled leukocytes.

QUESTION #8

An advantage of the immediate-use directive allows the nuclear medicine technologist to compound radiopharmaceuticals without regard to:

- wearing gloves.
- time of injection.
- environmental controls.
- aseptic technique.
QUESTION #9

The most commonly used primary engineering control (PEC) for compounding radiopharmaceuticals within an ISO Class 8 environment is a:

- BSC.
- LAFW.
- CACI.
- CAI.

QUESTION #10

An ISO Class 7 environmental control contains:

- 3,520 particles/m³.
- 35,200 particles/m³.
- 352,000 particles/m³.
- 3,520,000 particles/m³.

GLOSSARY:

Aseptic Manipulations – Handling sterile materials in a manner to maintain their sterility.

Aseptic Processing – Processing of CSPs or transfer of sterile products into vials and syringes under at least ISO Class 5 conditions.

Critical Area – An ISO Class 5 environment.

CSP or Compounded Sterile Preparations – These are preparations that must be sterile when administered to a patient. They differ from manufactured sterile products because they are manipulated for constitution or transferred to an administration device.

DCA or Direct Compounding Area – This is the critical area within the ISO Class 5 primary engineering control. It is where the critical sites are exposed to cleanest air such as the first air in a laminar airflow workbench.

First Air – The air exiting the HEPA filter in a unidirectional air stream. First air is essentially particle free.

HEPA or High Efficiency Particulate Air – This is a classification of a high efficiency filter used to remove particles from air in order to improve the quality of an environment.

IPA or Isopropyl Alcohol – Isopropyl alcohol is a common alcohol used to disinfect surfaces.
ISO or International Organization for Standardization – A standard setting body that uses experts and specialists from other standard setting bodies from various countries to prepare internationally recognized standards for various industries.

Media-Fill Test – A test used to qualify aseptic technique of compounding personnel or processes to ensure that the processes used are able to produce sterile product without microbial contamination.

PEC or Primary Engineering Control – This is a system that maintains the air quality of an environment as defined within the context of this program. Biological Safety Cabinet, (BSC) Compounding Aseptic Isolators (CAI) and laminar airflow workbenches (LAFW) are examples of PECs.

QA or Quality Assurance – This is a method to provide evidence of quality in a preparation or process.

SOP or Standard Operation Procedure – This includes the guides, procedures, or methods to perform a given operation consistently.

AUTHOR

Sam C. Augustine, RPh, PharmD, FAPhA
Associate Professor, Pharmacy Practice
School of Pharmacy and Health Professions
Creighton University
Omaha, NE

DISCLAIMER

Although Dr. Augustine is a member of the USP Sterile Compounding Expert Committee, this CE Unit is presented in his individual capacity and not as a member of the Committee or as a USP representative. The views and opinions presented are entirely his own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.
REFERENCES:


