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Business, Consumer Services and Housing Agency
Department of Consumer Affairs
Gavin Newsom, Governor

COMPOUNDING COMMITTEE
MEETING MINUTES

DATE: June 4, 2019

LOCATION: Department of Consumer Affairs
First Floor Hearing Room
1625 N. Market Blvd.
Sacramento, CA 95834

COMMITTEE MEMBERS PRESENT: Maria Serpa, Licensee Member, Chairperson
Victor Law, Licensee Member
Allen Schaad, Licensee Member

COMMITTEE MEMBERS NOT PRESENT: Shirley Kim, Public Member
Stan Weisser, Licensee Member, Vice Chairperson

STAFF MEMBERS PRESENT: Anne Sodergren, Interim Executive Officer
Julia Ansel, Chief of Enforcement
Christine Acosta, Supervising Inspector
Debbie Damoth, Administration Manager
Laura Freedman, DCA Staff Counsel
Kelsey Pruden, DCA Staff Counsel

1. **Call to Order and Establishment of Quorum and General Announcements**

   Chairperson Serpa called the meeting to order at 10:04 am. Board members present at the meeting were: Allen Schaad, Maria Serpa, and Victor Law. A quorum was established.

2. **Public Comment on Items not on the Agenda/Agenda Items for Future Meetings**

   There were no comments from the committee or the public.

3. **Presentation on the Proposed USP Chapter 825 – Radiopharmaceutical – Preparation, Compounding, Dispensing, and Repackaging**

   The committee heard a presentation on the current proposed revisions to USP General Chapter 825 regarding radio pharmaceutical preparation, compounding, dispensing, and repackaging by Paul B. Mahan, RPh., BCNP, Senior Regulatory Affairs Specialist with PETNET Solutions/Siemens Corporation. A copy of the presentation is attached to the minutes.

Mr. Mahan provided the committee that he is a member of the Regulatory Affairs department at PETNET Solutions/Siemens Corporation and a member of the USP <825> Expert Panel. Mr. Mahan stated he is not representing the USP Organization during the presentation.

- USP Chapter <825> - Mr. Mahan provided an overview of the history of USP <825> as well as the official effective date of official effective date of Dec. 1, 2019. He explained USP <825> is not enforceable at the state level unless all USP standards have been incorporated by reference into regulations. USP Chapters under 1000 are enforceable by the 1938 Food, Drug and Cosmetic Act. USP Chapters over 1000 are informational Chapters.
- Representation within <825> - Mr. Mahan explained the representation of the committee as a diverse group including engagements with FDA agents and USP <797> Committee.
- Types of Nuclear Pharmacies – Mr. Mahan explained the two types of nuclear pharmacies as non-PET or SPET (single-photon emission computed tomography) and PET (positron emission tomography). In SPET, all activities conducted are included in the practice of pharmacy (e.g., diagnostic imaging, therapeutic and blood component agents). In PET, most of the activities conducted as an FDA-registered manufacturer where multi-dose vials of radiopharmaceuticals are made. For PET, pharmacy processes are limited to dispensing and repackaging after the product release.
- Table of Contents and Glossary – Mr. Mahan provided the USP <825> table of contents and industry terms.
- Introduction – Mr. Mahan informed the committee that USP <825> intends 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). He stated the standards apply to all radiopharmaceutical processing activities. Mr. Mahan provided for the activities the chapter does not apply.
- Nonsterile and Sterile Radiopharmaceuticals – Mr. Mahan explained the application of USP <825> to nonsterile and sterile radiopharmaceuticals.
- Radiation Safety Concerns – Mr. Mahan provided intent of worker safety and keeping exposure levels for workers involved as low as reasonably achievable (ALARA) practices as well as balancing aseptic handling practices with radiation safety concerns.
- Radiation Contamination Control – Mr. Mahan explained how USP <825> addresses radiation contamination control and the important concern for protection.
- Personnel Qualifications, Training and Hygiene – Mr. Mahan informed the committee personnel must be trained to work with radiopharmaceuticals according to policies and standard operating procedures.
- Aseptic Qualifications – Mr. Mahan reviewed for the committee gloved fingertip and thumb sampling and media-fill testing requirements.
- Re-Evaluation, Retraining and Requalification – Mr. Mahan provided the timing of re-evaluation and requalification. If personnel have not been working performing radiopharmaceutical processing in more than 6 months, the personnel must be requalified in all core competencies before resuming duties. Additionally, personnel who perform sterile compounding using nonsterile drug substance or components must be requalified in all core competencies every 6 months.
- Ancillary Personnel – Mr. Mahan explained only personnel who handle sterile preparations are required to complete training on media-fill testing. Visitors must adhere to garbing SOPs but not competencies.

- Facility Design and Environmental Controls – Mr. Mahan reviewed the temperature and humidity requirements as well as explained the temperature requirements apply to both processing and storage. Mr. Mahan also reviewed types of secondary engineering control and processing environment requirements specific to radiopharmaceuticals.
- Remote Aseptic Processing Involving a Hot-Cell – Mr. Mahan explained to the committee the unique requirements for the hot-cell device used with radiopharmaceuticals.
- Environmental Controls – Mr. Mahan provided an overview of environmental controls specific for radiopharmaceuticals.
- Microbiological Air and Surface Monitoring – Mr. Mahan reviewed requirements for air and surface monitoring procedures.
- General Monitoring Requirements – Mr. Mahan provided to the committee in addition to specific samplings described in the section, sampling is also required in certain circumstances (e.g., new or modification of facilities/equipment, in response to identified problems/trends, changes that could impact controlled area environments, etc.)
- Monitoring Air Quality for Viable Airborne Particulates: Viable Air Sampling: Timing and Locations – Mr. Mahan explained the frequency of required volumetric active air sampling in all classified areas.
- Monitoring Air Quality for Viable Airborne Particulates – Mr. Mahan explained requirements and required actions for measurements of viable air monitoring programs exceeding action levels. Investigations and corrective action required for measurements exceeding actions are consistent with USP <797>. A change was made requiring if levels exceed the action levels, an attempt must be made to identify any microorganism recovered to the genus level with the assistance of a qualified individual such as a microbiologist or industrial hygienist. This change is more consistent with California sterile compounding regulations.
- Monitoring Surfaces for Viable Particles: Surface Sampling: Timing and Locations – Mr. Mahan described the surface sampling is required at least monthly which is six times more stringent than previous requirements even though current USP <797> states periodically.
- Monitoring Surfaces for Viable Particles – Mr. Mahan noted the only change was for an ISO Class 8 levels dropped from greater than 100 to greater than 50.
- Cleaning and Disinfecting – Mr. Mahan reviewed the cleaning, disinfecting and sporicidal for various sites.
- Assigning BUD: Preparation Conditions – Mr. Mahan provided the different manipulations required for PECs, SECs, and BUD (h). Mr. Mahan noted they spend the most time on this section and brought in experts.
- Documentation – Mr. Mahan noted applicable hard-copy or electronic records including policies and SOPs must be maintained for all activities involved in repackaging, preparing, preparing with minor deviation, compounding, and dispensing radiopharmaceuticals. He reviewed the required documentation records.
- Master Formulation Record (MFR) – Mr. Mahan advised an MFR is required only for a preparation with minor deviations or compounding as described in USP Chapter <825>.
- Preparation Following Manufacturer Instructions: Nonsterile Preparations – Mr. Mahan reviewed the requirements for nonsterile preparations. He stated the area should be suitably clean and uncluttered to ensure the overall integrity and quality of the prepared radiopharmaceutical with a documented process. Mr. Mahan noted it is important between preparation cycles to make sure there is no contamination of other products.
- Preparation Following Manufacturer Instructions: Sterile Preparations – Mr. Mahan provided to follow instructions form the manufacturer while accounting for radiation safety, environmental controls, and aseptic handling to maintain sterility.

- Preparation with Minor Deviations – Mr. Mahan provided examples of minor deviations.
- Preparation of Radiolabeled Blood Components – Mr. Mahan noted the 6 hours after blood sample is obtained from the patient or blood bank. Mr. Mahan provided if the blood samples are taken, there is a high risk that the blood has an infection. Proper precautions must be followed to ensure the safety of the patients and workers.
- Compounding Nonsterile Radiopharmaceuticals – Mr. Mahan reviewed the requirements for the committee.
- Sterile Compounding – Mr. Mahan reviewed the requirements for sterile compounding and indicated the designated person is held accountable for all activities.
- Sterile Compounding Using a Nonsterile Drug Substance or Components – Mr. Mahan reviewed the requirements as well as when testing described in Chapter <85> must be performed .
- Dispensing and Radioassay – Mr. Mahan noted except for an unopened manufactured container, the final dose or ordered amount must be radioassayed.
- Labeling – Mr. Mahan noted the minimum labeling requirements are noted. If a blood product or therapeutic product, the patient name must be added.
- Repackaging – Mr. Mahan reviewed the definition of repackaging.
- Quality Assurance and Quality Control – Mr. Mahan differentiated the differences in definitions for quality assurance and quality control.
- Notification About and Recall of Out-of-Specification Dispensed Radiopharmaceuticals – Mr. Mahan reviewed the steps to take should such an event occur to immediately notify the prescriber and determine if a recall is necessary.
- Complaint Handling – Mr. Mahan provided a system must be in place to receive complaints customers who will be using the radiopharmaceuticals including facilities and patients.

Committee member Schaad inquired about the occasion of therapeutic use of nonsterile radiopharmaceuticals. Mr. Mahan provided there is occasion.

Board President Law inquired about the types of complaints received. Mr. Mahan provided the most common complaint for PETNET is that doses are late based on the contractual agreement. Board President Law thanked Mr. Mahan for the site tour provided to board members and staff the previous day.

Supervising Inspector Acosta asked if kit splitting was considered repackaging. Mr. Mahan responded it is considered compounding.

Chairperson Serpa thanked Mr. Mahan for the tours provided to board members and staff the previous day.

Chairperson Serpa inquired what is the role of the board for regulating the use of radiopharmaceuticals in licensed pharmacies where non-pharmacy personnel are doing activities in the licensed care environment but are not staff by pharmacy personnel. Mr. Mahan provided that is a difficult area as physicians are using it in the practice of medicine. Chairperson Serpa indicated this may be the purview of the board to inspect radiopharmaceuticals outside of the licensed pharmacy. Massachusetts has statutory authority. DCA Counsel Freedman added the board is working with the Medical Board. Interim Executive Officer Sodergren added that both entities have defined jurisdiction. At the staff level, the board will be looking at the Massachusetts model should the committee desire. Chairperson Serpa added even if it is not under the purview or scope of the board, it is still under the purview of

pharmacy leadership and other regulators (e.g., Joint Commission, CDPH) to hold the pharmacy accountable for all compounding including radiopharmaceuticals.

A member of the public inquired if the board will be forwarding the blood labeling process to the agency that accredits laboratories for CLIA certification. Chairperson Serpa provided it has not been discussed at the committee level as there are multiple regulators in the area.

4. Approval of the April 16, 2019, Meeting Minutes

Chairperson Serpa requested delay of the April 16, 2019, meeting minutes until the committee had time to review the minutes.

5. Future Committee Meeting Dates

Chairperson Serpa announced the committee's next meeting is scheduled for July 11, 2019, in Sacramento. Chairperson Serpa noted that the board's website has been updated to reflect the future meeting date.

6. Adjournment

Chairperson Serpa adjourned the meeting at 11:30 am.

Disclosures and Background for Presenter

- Regulatory Affairs department of PETNET Solutions/Siemens Corporation
- Member of the USP <825> Expert Panel, but not representing the USP Organization with this presentation

USP CHAPTER <825>

RADIOPHARMACEUTICALS – PREPARATION, COMPOUNDING, DISPENSING AND REPACKAGING

Paul B Mahan, RPh., BCNP

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USP Chapter <825>

- July 27, 2018 proposed <825> posted on USP website for public comment
- Published in Pharmacopeial Forum 44(5) September 2018.
- November 30, 2018 public comment period closed
- June 1, 2019 release date
- June 2019 Published in USP 42-NF 38 Second Supplement
- Official (i.e. effective) date December 1, 2019

Representation within <825>

Institution Nuclear	Commercial Nuclear	Academia	Regulatory	Consultant	Hospital Pharmacy Chain
3 Members	5 Members	1 Member	3 Members	1 Member	1 Member

Types of Nuclear Pharmacies

- **Non-PET**
  - All processing activities (i.e. preparing, compounding, dispensing and repackaging) are generally under the practice of pharmacy
  - Scope of Products: diagnostic imaging, therapeutic and blood component agents.
- **Positron Emission Tomography (PET)**
  - Majority of the process of "creation" is carried out as a manufacturer (i.e. registered with the FDA under 21 CFR Part 212)
  - Pharmacy processes are limited to dispensing and repackaging after product release
  - Scope of Products: diagnostic imaging

<825> - Table of Contents

USP Chapter <825>

Glossary First!

USP Chapter <825>

- **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.

USP Chapter <825>

- **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.

USP Chapter <825>

- **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.

USP Chapter <825>

- **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.

USP Chapter <825>

- **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.

Other Unique Glossary Terms for <825>

- **As low as (is) reasonably achievable** (ALARA)
- **Blood components**
- **Designated person**
- **Hot-cell**
- **Inverse square law**
- **Kit**
- **Kit-splitting**
- **Radioactive materials** (RAM) **license**
- **Radioassay**
- **Radiochemical purity**
- **Radionuclidic purity**
- **Restricted area**
- **Segregated radiopharmaceutical processing area** (SRPA)
- **Shielding**
- **Specific activity**

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.

1. INTRODUCTION

- **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).**

1. INTRODUCTION

- These standards apply to all radiopharmaceutical processing activities, including those with radionuclides that emit a single photon, a positron, or a therapeutic particle. Furthermore, these standards apply to sterile intravascular radioactive devices (e.g., radioactive microspheres for intravascular brachytherapy).

1. INTRODUCTION

This chapter does not apply to the following activities:

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

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

1.1 NONSTERILE RADIOPHARMACEUTICALS

- **For conventionally manufactured products or compounded preparations obtained from 503B-registered outsourcing facilities, dispensing can proceed as described within <825> (*12. Dispensing*).**
- For prepared or compounded preparations, such preparations must comply with applicable identity, quality, and purity standards, as described in manufacturer labeling, *USP* monographs, or other appropriate sources (e.g., documented, peer-reviewed materials).
- They can then be dispensed as described in this chapter.

1.2 STERILE RADIOPHARMACEUTICALS

- **Conventionally marketed products can proceed with dispensing as described within <825> (*12. Dispensing)*.**
- For prepared or compounded preparations, such preparations must comply with applicable identity, quality, and purity standards.
- **For compounded preparations involving one or more nonsterile components, a sterilization procedure (e.g., filtration with bubble point testing) must be performed prior to dispensing.**
- For injectable compounded preparations involving one or more components that are not certified to be pyrogen-free, bacterial endotoxin testing, as defined in *Bacterial Endotoxins Test* ⟨85⟩, must be performed prior to dispensing.

2. RADIATION SAFETY CONSIDERATIONS

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

2. RADIATION SAFETY CONSIDERATIONS

Aseptic handling practices must be balanced with radiation safety considerations, based on the following:

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

2.4 RADIATION CONTAMINATION CONTROL

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

2.4 RADIATION CONTAMINATION CONTROL

- Radiopharmaceuticals require measurement with a suitable radiation measuring device (e.g., dose calibrator). These and other necessary equipment (e.g., monitors, bar code scanner, label printer) may be placed inside an ISO Class 5 PEC but should be placed in a manner that minimizes disruptions of airflow.
- As per RAM license requirements, individuals must wear body and, as required, extremity dosimeters (e.g., a ring worn on a finger) for long-term monitoring of personnel radiation exposure.
- The body dosimeter should be worn underneath the gown.
- Any extremity dosimeter must be worn underneath gloves and must not interfere with proper fit of gloves.

4. PERSONNEL QUALIFICATIONS, TRAINING AND HYGIENE

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

4.1 ASEPTIC QUALIFICATIONS

Gloved Fingertip And Thumb Sampling

- **Garbing competency required for personnel that enter and perform tasks in the ISO-5 PEC** (e.g. aseptic manipulations, cleaning)
- Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming unis (cfu) and subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu (total for both hands)

4.1 ASEPTIC QUALIFICATIONS

Media-Fill Testing

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

4.2 RE-EVALUATION, RETRAINING AND REQUALIFICATION

TIMING OF RE-EVALUATION AND REQUALIFICATION

- **Visual observation:** Personnel must be visually observed while performing hand hygiene, garbing SOPs, and aseptic technique procedures initially, and then **at least once every 12 months**.
- **Gloved fingertip and thumb sampling:** Personnel must perform fingertip and thumb sampling three times initially, and then **every 12 months** (in conjunction with media-fill testing).
- **Media-fill testing:** After initial qualification, conduct a media-fill test of all personnel engaged in sterile radiopharmaceutical processing **at least every 12 months** (in conjunction with gloved fingertip and thumb sampling).
- **Cleaning and disinfecting:** Retrain and requalify personnel in the cleaning and disinfecting of sterile processing areas **every 12 months or in conjunction with any change(s) in cleaning and disinfecting SOPs, whichever is sooner.**

4.2 RE-EVALUATION, RETRAINING AND REQUALIFICATION

- **After a pause in sterile radiopharmaceutical processing:** Personnel that have not performed radiopharmaceutical processing in more than 6 months must be **requalified in all core competencies before resuming duties**.
- **Sterile compounding using a nonsterile drug substance or components:** Personnel who perform sterile compounding using a nonsterile drug substance or components **must be requalified in all core competencies every 6 months**.

4.3 ANCILLARY PERSONNEL

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

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

- The classified areas and SRPA **must be continuously maintained at a temperature of 25° or cooler** and **should be continuously maintained at a relative humidity (RH) below 60%** to minimize the risk for microbial proliferation and provide comfortable conditions for personnel attired in the required garb.
- The temperature and humidity must be monitored in the classified areas each day that it is used, either manually or by a continuous recording device.
- The results of the temperature and humidity readings must be documented at least once daily **or** stored in the continuous recording device, and must be retrievable.
- The temperature and humidity readings must be reviewed as described in the facility's SOPs.

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

TYPES OF SECONDARY ENGINEERING CONTROLS AND DESIGN

- The PEC **must** be located in a secondary engineering control (SEC), which may be either an **ISO-classified buffer room with ante-room or an SRPA**, in a manner that minimizes conditions that could increase the risk of microbial contamination.
- A PEC may be located within an unclassified area, without an ante-room or buffer area. This type of design is called an SRPA. **Only sterile radiopharmaceutical preparation, preparation with minor deviations, dispensing, and repackaging may be performed in an SRPA.**

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

TYPES OF SECONDARY ENGINEERING CONTROLS AND DESIGN

- If the SRPA meets ISO Class 8 total airborne particle count specifications, it can also be used for storage and elution of non-direct infusion radionuclide generators (e.g., Tc-99m).

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

The Radiopharmaceutical Processing Environment

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

- **In situ air pattern analysis via smoke studies must be conducted at the critical area to demonstrate unidirectional airflow and sweeping action under dynamic conditions.**

5.6 Remote Aseptic Processing Involving a Hot-Cell

- A hot-cell device provides an inherent physical segregation for the ISO Class 5 aseptic processing area.
- If the hot-cell is located in an ISO-classified space, personnel must garb according to requirements within <825>.
- 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 within <825>.

5.7 Environmental Controls

- All RAM users must comply with the conditions specified in their approved RAM license application and regulations, and **RAM license conditions may supersede the following requirements for environmental controls described in this section.**
- There **may be both positive and negative air pressure within the facility**; positive pressure to minimize the potential of microbial contamination in sterile drug preparation areas, and negative pressure to minimize potential radioactive contamination from volatile or airborne radiopharmaceuticals.

5.7 Environmental Controls

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

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

- **Facilities must develop and implement written air and surface monitoring procedures for all sterile radiopharmaceutical classified areas.**
- Air and surface monitoring results and the corrective actions must be documented, and records must be readily retrievable as required by jurisdictional laws and regulations.

6.1 General Monitoring Requirements

- **In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:**

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

6.2 Monitoring Air Quality for Viable Airborne Particulates

VIABLE AIR SAMPLING: TIMING AND LOCATIONS

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

6.2 Monitoring Air Quality for Viable Airborne Particulates

- **If levels measured during the viable air monitoring program exceed the Action Levels: the cause must be investigated and corrective action must be taken.**
- **If levels measured during viable air sampling exceed the Action Levels: an attempt must be made to identify any microorganism recovered to the genus level with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).**

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

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

6.3 Monitoring Surfaces for Viable Particles

Surface Sampling: 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.

6.3 Monitoring Surfaces for Viable Particles

- If levels measured during surface sampling exceed the Action Levels: the cause must be investigated and corrective action must be taken.
- If levels measured during surface sampling exceed the Action Levels: an attempt must be made to identify any microorganism recovered to the genus level with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).

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

7. Cleaning and Disinfecting

Site	Cleaning	Disinfecting	Sporicidal
PEC / equipment in PEC	Prior to daily sterile processing	Following cleaning	Monthly
Surfaces of sink(s)	Daily	Daily	Monthly
Hot-Cell interior	Daily	Daily	Monthly
Hot-Cell PEC and equip. in PEC	Prior to daily sterile processing	Following cleaning	Monthly
Work surfaces outside PEC	Daily	Daily	Monthly
Ceilings	Monthly	Monthly	Monthly
Walls/doors & fixtures	Monthly	Monthly	Monthly

7. Cleaning and Disinfecting

Site	Cleaning	Disinfecting	Sporicidal
Floor(s)	Daily	Daily	Monthly
Storage shelving and bins	Monthly	Monthly	Monthly

8. Assigning BUD

Preparation Conditions

Manipulation	PEC	SEC	BUD (h)
Dispensing, repackaging, preparation with and without minor deviations	ISO-5	SRPA	12
Radionuclide generator storage/elution (e.g. Tc-99m)	-	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage/elution (e.g. Tc 99m)	-	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	

8. Assigning BUD

Preparation Conditions

Manipulation	PEC	SEC	BUD (h)
Dispensing, repackaging, preparation with and without minor deviations	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24

8. Assigning BUD

Preparation Conditions

Manipulation	PEC	SEC	BUD (h)
Dispensing, repackaging, preparation with and without minor deviations and compounding **using a nonsterile component and performing sterilization procedure (w/o sterility testing)**	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	24

9. Documentation

- Applicable records (hard-copy or electronic), including policies and SOPs, must be maintained for all activities involved in repackaging, preparing, preparing with minor deviations, compounding, and dispensing radiopharmaceuticals.

9. Documentation

Documentation records include, but are not limited to:

- Personnel training and testing, including visual assessments
- Testing and monitoring of environmental controls
- Equipment maintenance and cleaning/disinfecting
- End product radiochemical purity and other testing, as applicable, results of preparations, preparations with minor deviations, and compounded preparations
- Master Formulation Record (MFR) for preparation with minor deviation(s) and compounding
- Validation of stability testing to support the assigned BUD from SOPs established by the compounder or derived from accepted literature
- Investigations/corrective actions/tracking of events to closure.

9.1 Master Formulation Record

- **A MFR is required only for a preparation with minor deviations or compounding, as described in <825> (*11. Compounding*)**

9.2 Records for Preparation with Minor Deviation/Compounding

- **A record for preparation with minor deviation or compounding must be completed**

10.1 Preparation Following Manufacturer Instructions

Nonsterile Preparations

- For nonsterile preparations, follow manufacturer preparation instructions, taking into account appropriate radiation safety considerations and environmental controls, if applicable (e.g., negative air pressure area).
- **The area should be suitably cleaned and uncluttered to ensure the overall integrity and quality of the prepared radiopharmaceutical(s).**
- **There should be a documented process for activities (e.g., cleaning) between the preparation cycles of different nonsterile products, to decrease the likelihood of contamination from other prepared products.**

10.1 Preparation Following Manufacturer Instructions

Sterile Preparations

- For sterile preparations (including intravascular devices), follow manufacturer preparation instructions, taking into account appropriate radiation safety considerations, appropriate environmental controls, and aseptic handling practices to maintain sterility.

10.2 Preparation with Minor Deviations

- In some cases, radiopharmaceuticals are prepared with minor deviations from manufacturer instructions that are necessary to accommodate circumstances not contemplated in the FDA-approved labeling.

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

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

10.3 Preparation of Radiolabeled Blood Components

- Handling blood and radiolabeling of blood components require special attention to biological risks and must be handled with standard precautions using aseptic technique to prevent the introduction of new microorganisms into the preparation that will be administered.
- Due to the potential presence of microorganisms in the original blood sample, the preparation must be administered as soon as possible **but no later than 6 hours after blood sample is obtained from the patient or blood bank.**
- The presence of microorganisms in a blood sample may present a risk to the individual performing the preparation as well as cross-contamination to other blood samples or other non-blood related radiopharmaceuticals.

11.1 Compounding Nonsterile Radiopharmaceuticals

- Compounding nonsterile radiopharmaceuticals is the combining, mixing, diluting, pooling, reconstituting or otherwise altering a drug or bulk drug substance other than as provided by the manufacturer's package insert to create a nonsterile radiopharmaceutical.
- **Areas designated for nonsterile compounding must be cleaned and uncluttered and separated from areas designated for sterile radiopharmaceuticals.**
- Compounding should take into account RAM licensing requirements for appropriate radiation safety considerations and utilize appropriate environmental controls.
- The placement of equipment and materials must take into account a design that prevents cross-contamination.

11.2 Sterile Compounding

- **Some compounding activities involve only the addition of a conventionally manufactured drug product, approved by the appropriate regulatory agency, to a radiopharmaceutical.**
- Personnel responsible for compounding must consider all possible interactions between the components.
- In some cases, this may require systematic quality control testing over time to validate the appropriateness of a particular BUD.
- Another activity which is considered a compounding activity is the splitting of conventionally marketed kits.
- Kit-splitting (also referred to as “fractionation”) may be used to meet patient need.

11.3 Sterile Compounding Using a Nonsterile Drug Substance or Components

- Some sterile compounding activities involve the use of materials other than commercially marketed products, such as drug substances and/or radionuclides.
- **If one or more materials or components are not certified to be sterile and pyrogen-free, a sterilization procedure (e.g., filtration with bubble point testing) and testing described in ⟨85⟩ must be performed.**
- The designated person for compounding is responsible for ensuring that the final preparation complies with preestablished standards or acceptance criteria for identity, quality, and purity, and must consider all possible interactions between the components

12.1 Dispensing and Radioassay

- **Dispensing refers to the manipulations necessary to transfer the prescribed or ordered amount of radiopharmaceutical into the final container (e.g., syringe or vial).**
- Dispensing can take place from single-dose or multi-dose containers of prepared, prepared with minor deviations, compounded, or manufactured radiopharmaceuticals.
- Dispensing may involve needle changes, affixing a sterile cap, or dilution (e.g., adding 0.9% sodium chloride injection) in the final container.
- Except for an unopened manufacturer container, the final dose or ordered amount must be radioassayed (i.e., in a dose calibrator).

12.2 Labeling

- The labeling of radiopharmaceuticals can fall under the jurisdiction of numerous regulatory agencies
- Individual boards of pharmacy and other regulatory bodies may have very specific statutes and/or regulations concerning this process.
- **The requirements specified within <825> must be considered the minimum requirements for the labeling of the inner container (e.g., syringe, vial) and the outer shielding (e.g., syringe or vial shielding).**
- All personnel distributing and/or dispensing radiopharmaceuticals should verify that any labeling is in compliance with regulatory agencies.

13. Repackaging

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

14. Quality Assurance and Quality Control

- **Quality assurance (QA):** system of procedures, activities, and oversight that ensures that radiopharmaceutical processing consistently meets quality standards
- **Quality control (QC):** sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the radiopharmaceutical(s)
- **A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the handling of radiopharmaceuticals are conducted in accordance with this chapter and applicable federal, state, and local laws and regulations**.

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

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

- 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)
- Determine whether a recall is necessary

14.2 Complaint Handling

- Radiopharmaceutical facilities must develop and implement SOPs for handling complaints.
- Complaints may include concerns or reports on the quality and container labeling of, or possible adverse reactions to, a specific radiopharmaceutical.
- **A designated person must review all complaints to determine if it indicates a potential quality problem with the radiopharmaceutical. If it does, an investigation into the potential cause of the problem must be completed.**
- The investigation must consider whether the quality problem could extend to other radiopharmaceuticals.
- Corrective action, if necessary, must be implemented for all potentially affected radiopharmaceuticals.
- A readily retrievable record (written or electronic) of each complaint must be kept by the facility, regardless of the source of the complaint.

USP Chapter <825>

Radiopharmaceuticals – preparation, compounding, dispensing and repackaging

Thank You!!

Questions??