USP <797> in Nuclear Pharmacy and Medicine

Personnel and Facility Requirements

Neil A. Petry, MS, RPh, BCNP, FAPhA
Clinical Assistant Professor in Radiology
Director, Radiopharmacy Services
Duke University Medical Center
petry005@mc.duke.edu

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“Our patients have never experienced any problems; therefore, we don’t need to change anything regarding how we prepare radiopharmaceuticals in nuclear pharmacy and nuclear medicine practice.”

- Anonymous Composite Statement
“Unfortunately, there are too many in health care who feel that if it hasn’t happened to them, the adverse experiences of others do not apply.”

– Michael Cohen, MS, FASHP
Institute for Safe Medication Practices
According to Ben . . .

“One of the greatest tragedies in life is the murder of a beautiful theory by a gang of brutal facts.”

- Benjamin Franklin, 1706 - 1790
USP Chapter <797> - Applicability to Personnel

- Standards in the chapter are intended to apply to all personnel who prepare CSPs
  - Pharmacists
  - Pharmacy technicians
  - Nurses
  - Physicians
  - All other healthcare personnel who prepare, store and transport CSPs
- Although not specifically stated, these standards do in fact apply to nuclear medicine technologists and other nuclear medicine personnel
Significance of Sterile Compounding Personnel

- Personnel are recognized as the principle source of contamination in cleanroom environments due to:
  - Inherent shedding of both viable and nonviable particles from their body surfaces and clothing
  - Movement around the environment while completing a variety of aseptic processing support tasks
  - Need to repeatedly touch sanitized (but not sterile) packages, PEC surfaces, other objects while working
  - Potential for touch contamination of critical sites
USP Chapter <797> - Responsible Personnel

- Identified categories include:
  - Compounding Personnel
  - Compounding Supervisors
  - Qualified Licensed Healthcare Professionals
    - Pharmacist – supervisor / compounder
    - Physician – supervisor
Compounding Personnel

- Must ensure CSPs are accurately identified, measured, diluted and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed.
- Performance responsibilities include:
  - Following written quality assurance procedures
  - Maintaining appropriate cleanliness conditions
  - Providing labeling and supplementary instructions for proper clinical administration of CSPs
Compounding Supervisors (1)

- Shall* ensure, through either direct measurement or appropriate information sources, that specific CSPs maintain their labeled strength within monograph limits for USP articles, or within 10% if not specified, until their BUD.
- Shall also ensure all CSPs are prepared in a manner that maintains sterility and minimizes the introduction of particulate matter.
- Create, maintain and follow written quality assurance (QA) procedures.

* Shall means required
Compounding Supervisors (2)

- Written QA procedures include the following in-process checks that are applied, as appropriate, to specific CSPs:
  - Accuracy and precision of measuring and weighing
  - Requirement for sterility
  - Methods of sterilization and purification
  - Safe limits and ranges for strength of ingredients
  - Bacterial endotoxins
  - Particulate matter and pH
  - Labeling accuracy and completeness
  - BUD assignment
  - Packaging and storage requirements

- The dispenser **shall**, when appropriate and practicable, obtain and evaluate results of testing of identity, strength, purity, and sterility **before** a CSP is dispensed
Qualified Licensed Healthcare Professionals . . .

- . . . who supervise the compounding and dispensing of CSPs shall* ensure that the quality objectives stated in USP Chapter <797> are achieved.
Primary Quality Objective

- Compounding personnel are adequately skilled, educated, instructed and trained to correctly perform their duties and document their activities:
  - Antiseptic hand cleansing and disinfection of nonsterile compounding surfaces
  - Selecting and appropriately donning protective garb
  - Maintain or achieve sterility of CSPs in ISO Class 5 PEC devices
  - Protect personnel and compounding environments from radioactive, cytotoxic and chemotoxic drug contamination
  - Identify, weigh, and measure ingredients
  - Manipulate sterile products aseptically, sterilize high-risk level CSPs, and label and quality inspect CSPs
Other Quality Objectives (1)

- Ingredients have correct identity, quality and purity
- Opened / partially used ingredients properly stored
- Minimize bacterial endotoxin generation in water-based CSPs
- Sterilization methods achieve sterility, maintain strength of active ingredients and the physical integrity of packaging
- Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended use
- Potential harm from added substances and differences in rate and extent of bioavailability of active ingredients are carefully evaluated before such CSPs are dispensed and administered
- Packaging selected for CSPs is appropriate to preserve the sterility and strength until the BUD
- Controlled environment maintains sterility or pre-sterilization purity
Other Quality Objectives (2)

- Appropriate labeling, visual inspection, quality checks prior to release
- BUDs assigned on basis of direct testing and extrapolation from reliable literature sources and other documentation
- Procedures for measuring, mixing, dilution, purification, sterilization, packaging, and labeling conform to the correct sequence and quality established for the specified CSP
- Deficiencies in compounding, labeling, packaging, and quality testing and inspection can be rapidly identified and corrected
- When time and personnel availability so permit, compounding manipulations and procedures are separated from post-compounding quality inspection and review before CSPs are dispensed
Responsibility of Compounding Personnel
Chapter <797> - Points of Emphasis

- Maintaining high standards for the quality and control of processes, components, and environments and for the skill and knowledge of personnel preparing CSPs
- Employing rigor and in-process quality control checks and/or post-compounding quality inspection and testing appropriate to potential hazard of the intended route of administration
- Recognizing potential danger of CSPs administered into the vascular and central nervous systems relative to:
  » Excessive bacterial endotoxin contamination
  » Large errors in strength of correct ingredients, and
  » Presence of incorrect ingredients
Training in Aseptic Manipulation Skills

- Personnel who prepare CSPs shall be trained conscientiously and skillfully in regards to:
  - Theoretical principles & practical aseptic manipulations skills
  - Achieving and maintaining ISO Class 5 conditions
- Personnel shall be trained before they prepare CSPs
- Available personnel training resources should include:
  - Expert personnel
  - Audio-video instructional sources
  - Professional publications
Evaluation of Aseptic Manipulation Skills

- Personnel **shall** pass didactic, practical skill assessment and an initial media-fill test **before** compounding
  - Annual assessment for a low- and medium-risk level
  - Semi-annual assessment for high-risk level
- Personnel who fail written tests, or whose media-fill test vials result in gross microbial colonization, **shall** be immediately reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies
Media-Fill Challenge Testing

- Evaluates skill of personnel to aseptically prepare CSPs using a media-fill verification
- Closely simulates actual compounding procedures to be performed by personnel
- Employs sterile fluid bacterial culture media transfers with sterile syringes, needles, vials, etc.
- Represents most challenging or stressful conditions actually encountered for a low- and medium-risk level or when sterilizing high-risk level CSPs
- High-risk level compounding simulations are also used to verify the capability of the compounding environment and process to produce a sterile preparation
Media-Fill Challenge Testing (2)

- Commercially available sterile fluid culture media
  - Soybean-Casein Digest Medium – Sterility Tests <71>
    - Shall promote exponential colonization of bacteria most likely to be transmitted to CSPs from compounding personnel and environment
- Media-fill vials incubated a minimum of 14 days
  - Incubation at 20\(^\circ\) C - 25\(^\circ\) C or 30\(^\circ\) C - 35\(^\circ\) C
    - If two incubation temperatures are used, media-fill sample containers should be incubated for at least 7 days at each temperature
    - Failure is indicated by visible turbidity in the medium on or before 14 days
Recommended Media Fill Procedure (Overview)

1. Draw 0.8 mL of media from Kit
2. Repeat process 4 times for a total of 24 incubation vials
3. Incubate 4 vials at 20-35º C
Radiopharmaceuticals as CSPs (1)

• Production of PET RPs
  » USP Chapter <823> Radiopharmaceuticals for Positron Emission Tomography – Compounding supersedes USP Chapter <797>
  » However, upon release of a PET RP as a finished drug product* from a production** facility, the further handling, manipulation, or use of the product will be considered compounding, thus the content of this section and chapter is applicable

* product → commercially manufactured  ** production → commercial manufacturing
Radiopharmaceuticals as CSPs (2)

- RPs 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 shall be designated as, and conform to, the standards of Low-Risk Level CSPs.
- These RPs shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 PEC located in an ISO Class 8 or cleaner air environment to permit compliance with special handling, shielding and negative air flow requirements.
Radiopharmaceuticals as CSPs (3)

- RP vials designed for multi-use, compounded with Tc-99m, exposed to ISO Class 5 environment, and punctured by needles with no direct contact contamination may be used up to the time indicated by manufacturer’s recommendations.

- Storage and transport of properly shielded vials or radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO designation.
Radiopharmaceuticals as CSPs (4)

- Tc-99m / Mo-99 generator systems shall be stored and eluted under conditions recommended by manufacturers and applicable state and federal regulations.
- Such generator systems shall be eluted in an ISO Class 8 or cleaner air environment to permit special handling, shielding, and air flow requirements.
- To limit acute and chronic radiation exposure of inspecting personnel, direct visual inspection of RP CSPs containing high concentrations of radioactivity shall be conducted in accordance with the ALARA concept.
Radiopharmaceuticals as CSPs (5)

- RPs prepared as Low-Risk Level CSPs with 12-Hour or Less BUD shall be prepared in a “segregated compounding area”
- A line of demarcation defining the segregated compounding area shall be established
- Materials and garb exposed in a patient care and treatment area shall not cross a line of demarcation into the segregated compounding area
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
While labeling of patient blood products must be done under sterile/aseptic conditions, the blood itself is not sterile.

Patient blood and blood products are considered a biohazardous risk to operators.

During the labeling procedure sterility controls must be carefully balanced against the control of biohazards.

Manipulations of blood products must be clearly separated from “routine” CSP activities in such a manner that cross-contamination cannot occur.

One case of failure to do so had catastrophic results.

Standards in the chapter are intended to apply to all places where CSPs are prepared

- Hospitals and other healthcare institutions
- Patient treatment clinics
- Pharmacies and nuclear pharmacies
- Physicians’ practice facilities
- Other locations and facilities in which CSPs are prepared, stored and transported

Although not specifically stated, these standards do in fact apply to nuclear medicine “hot labs”
Significance of Sterile Compounding Facilities

- Optimally designed and functioning facilities provide:
  - Highly controlled particle free work environments
  - Means to effectively and efficiently remove personnel and process generated particles / contaminants
  - Free and comfortable movement pathways to facilitate a variety of aseptic processing support tasks
  - Means to limit potential negative impact of critical site touch contamination following the necessary touching of sanitized but nonsterile packages, PEC surfaces, equipment, other objects during aseptic processes
Figure 1. Conceptual representation of the placement of an ISO Class 5 PEC in a segregated compounding area used for low-risk level CSPs with 12-hour or less BUD.

Figure 2. Conceptual representation of the arrangement of a facility for preparation of CSPs categorized as low-, medium-, and high-risk level.

Nuclear Medicine Clinic Model  Nuclear Pharmacy Model
Conceptual Representation of USP Chapter <797>
Nuclear Pharmacy Facility Requirements

Figure 2. Conceptual representation of the arrangement of a facility for preparation of CSPs categorized as low-, medium-, and high-risk level.
Physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites

Shall provide a comfortable and well-lighted working environment, which typically includes a temperature of 20°C or cooler to maintain comfortable conditions for compounding personnel when attired in required aseptic compounding garb

PECs provide unidirectional (i.e., laminar) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites

Clean rooms for nonhazardous and nonradioactive CSPs are supplied with HEPA air that enters from ceilings with return vents low on walls, and provide not < 30 air changes per hour
Buffer areas maintain 0.02 to 0.05 inch water column positive pressure, and do not contain sinks or drains.

Air velocity from buffer rooms or zones to ante-areas is at least 40 feet per minute.

PECs placed within a buffer area in such a manner as to avoid conditions that could adversely affect their operation.

PECs placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross-drafts.

HEPA-filtered supply air introduced at the ceiling.

Activities / tasks carried out within buffer area limited to only those necessary when working within a controlled environment.
USP Chapter <797> - Facility Design “Shalls” (3)

- Only furniture, equipment, supplies, and other material required for compounding activities to be performed brought into room
- Surfaces and essential furniture in buffer rooms or zones and clean rooms shall be nonporous, smooth, non-shedding, impermeable, cleanable, and resistant to disinfectants
- Surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in buffer area shall be smooth, impervious, free from cracks and crevices, and non-shedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate
- Surfaces shall be resistant to damage by disinfectant agents

Appendix I, USP Chapter <797>, December 2007
- Junctures of ceilings to walls coved or caulked to avoid cracks and crevices where dirt can accumulate
- Ceiling tiles caulked around each perimeter to seal them to the support frame
- Exterior lens surface of ceiling lighting fixtures smooth, mounted flush, and sealed
- Any other penetrations through the ceiling or walls sealed
- Buffer area contains no sources of water (sinks) or floor drains
- Buffer area work surfaces constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected
Carts shall be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility.

Storage shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and disinfectable.

Their number, design, and manner of installation the items above shall promote effective cleaning and disinfection.
If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic.

Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided.

Air returns should be mounted low on the wall creating a general top-down dilution of room air with HEPA-filtered make-up air.
Nuclear Pharmacy
Sterile Compounding Facilities

- Should be designed to provide adequate space for the workload anticipated and for future expansion.
- Expansion space should be provided and, as the service demands and compounding volume increases, the ability to maintain environmental and process controls must not be compromised by overcrowding.
- Must be designed with due consideration of scope of operation and the microbial risk-levels associated with the compounding services to be provided.
- ALARA mandated radiation shielding and safety must be accommodated.
Factors Influencing Pharmacy Design

- CSP volumes and risk-levels
- Types of CSPs prepared (hazardous, radioactive)
- Staffing levels and work patterns
- Dose and waste return programs
- Internal / external distribution
- Other planned remodeling
- Current facility and physical plant
- Current organizational practices and plans
Conceptual Representation of USP Chapter <797>
Nuclear Medicine Clinic Facility Requirements

Figure 1. Conceptual representation of the placement of an ISO Class 5 PEC in a segregated compounding area used for low-risk level CSPs with 12-hour or less BUD.
Nuclear Cardiology – Hot Lab Floor Plan

- Designated Room
  - Eliminate extraneous activities / materials
- Restrict use to low-risk level CSPs with 12-hr or less BUD
- Add demarcation line
- Delete window
- Add shielded BSC (PEC)
  - ISO Class 5 air
  - CSP, personnel, and environment protection
- Add ceiling HEPA units?
- Comply with standards
  - Hygiene
  - Gowning / Garbing
  - Other

> 100 Square feet
< Limited-use
Nuclear Medicine – Hot Lab Floor Plan

- Plan?
- TBA
- Target Area?

< 100 Square feet
> Multi-multi-use
References (1)


- ASHP Compounding Resource Center
  » http://www.ashp.org/SterileCpd/
References (2)

- Access to the Revised General Chapter <797>
- Access to the Sterile Compounding Committee's Response to Comments