Proposed USP General Chapter for Radiopharmaceutical Compounding

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USP General Chapters

- General chapters # ≥ 1000
  - Informational general chapters
- General chapters # <1000
  - Enforceable general chapters
USP General Chapter Specifically Designated for Radiopharmaceutical Compounding

- <823> Radiopharmaceuticals for Positron Emission Tomography – Compounding
Other USP General Chapters Specifically Designated for Radiopharmaceuticals

- <821> Radioactivity
- <1015> Automated Radiochemical Synthesis Apparatus
Other USP General Chapters Related to Pharmaceutical Compounding

- <795> Pharmaceutical Compounding – Nonsterile Preparations
- <797> Pharmaceutical Compounding – Sterile Preparations
- <1075> Good Compounding Practices
- <1163> Quality Assurance in Pharmaceutical Compounding

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Categories of Compounding

Category 6

- Radiopharmaceuticals
- Preparation of radiopharmaceuticals
<797> Pharmaceutical Compounding – Sterile Preparations

- <797> has a section titled “Radiopharmaceuticals As CSPs”
- Is <797> a suitable general chapter for radiopharmaceutical compounding?
<797> & Radiopharmaceuticals

- <797> applies to compounded radiopharmaceuticals
  - The FDA states that “Compounding does not include …reconstituting…in accordance with the directions contained in approved labeling.”
- <823> supersedes <797> in the case of production of PET radiopharmaceuticals
- “Radiopharmaceuticals As CSPs”
- “Segregated Compounding Area”
Low-Risk Level CSPs

- ISO Class 5 PEC (primary engineering control) located in an at least ISO Class 7 air environment
- \( \leq 3 \) sterile products & \( \leq 2 \) entries
- Simple aseptic manipulations
- Storage
  - 48 hours at room temperature
  - 14 days at a cold temperature
  - 45 days between -10° and -25°
Low-Risk Level Compounded Radiopharmaceutical Preparations

- Volume
  - ≤ 100 mL for single-dose injection
    - There is no volume restriction for other non-radioactive low-risk level CSPs
  - ≤ 30 mL for multiple-dose container
    - A multiple-dose container for articles or preparations intended for parenteral administration only and usually containing antimicrobial preservatives.
      - $^{67}\text{Ga}$-citrate
      - $^{201}\text{TI}$-chloride

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ISO Class 5 PEC located in an at least ISO Class 8 air environment

Other non-radioactive CSPs have to be compounded in an ISO Class 5 PEC located in an at least ISO Class 7 air environment

Molly generator shall be eluted in an at least ISO Class 8 air environment

Penetrating disinfected stoppers on vials of other non-radioactive CSPs must be carried out in an ISO Class 5 air environment
Low-Risk Level Compounded Radiopharmaceutical Preparations

- Comply with special handling, shielding, and negative air flow requirements
Segregated Compounding Area

- Radiopharmaceuticals prepared as *Low-Risk Level CSPs with 12-Hour or Less BUD*
  - ISO Class 5 PEC cannot be located within an ISO Class 7 buffer area
  - A line of demarcation in a segregated compounding area or room shall be established

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Segregated Compounding Area (SCA)

- **Demarcation Line**
  - It is a common practice to use the principle of “displacement airflow” in which it utilizes a low pressure differential & high airflow principle to move “dirty” air from SCA across the demarcation line into a non-SCA area.
  - However, the above concept is only workable if the demarcated SCA has a positive-airflow pressure to the adjacent non-SCA area which is contrary to the negative-airflow requirement for compounding radiopharmaceuticals as CSPs.
Segregated Compounding Area (SCA)

- SCA may not work with certain radiopharmaceuticals that have a BUD > 12 hours
  - $^{99m}$Tc-mebrofenin (18 hours)
  - $^{67}$Ga-citrate (7 days)
  - $^{201}$Tl-chloride (4 days)
Mayo Clinic Approaches to Meet United States Pharmacopeia <797> Requirements for Facility Design and Environmental Controls of Nuclear Pharmacy

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According to the United States Pharmacopeia (USP) General Chapter <797> (USP <797>), “Pharmaceutical Compounding—Sterile Preparations,” the compounding facility must be physically designed and environmentally controlled to minimize airborne contamination from existing critical sites. The goal of the project was to evaluate the appropriateness and effectiveness of our approach to meeting <797> requirements. Methods: USP <797> standards, radiation safety concerns, and work-flow casters were the focal points in our assessment of four laboratories. Of the nuclear pharmacy laboratories that engage in preparing sterile (low-, medium-, and high-risk levels), non sterile, or possibly hazardous radioactive drugs and two other laboratories in which only low-risk-level preparations are involved. Results: Each laboratory was constructed with a physically secured International Organization for Standardization Class 7 barrier room and clean room to allow us to maintain an appropriate air quality, a consistent operation, and a desirable flexibility. An isolated area within the barrier area was designated for preparing radioactive products. Higher air change per hour was used in the areas with higher traffic or smaller space. Laboratory safety cabinets (BSCs) were segregated and used depending on the risk category of the preparations. In laboratory 1, the exhaust flow for the BSC was too great, and a lead lined compounding aseptic containment isolation (CAC) was installed. Air in the BSC and CAC was 100% exhausted to the atmosphere. 68Co56Co63Ni generators were placed in the negative-pressure clean room to ensure a more efficient operation and cleaner air environment. Clean-room equipment (i.e., keyboards, printers, and telephones) was installed, and refrigerators or freezers and the central-processing unit of each computer were placed outside clean room. Conclusion: Our wide-range preparations of sterile, non sterile, or potentially hazardous radiopharmaceuticals, coupled with the limited space of each laboratory and existing antiquated mechanical systems, presented a challenge. Nonetheless, we successfully remediated each nuclear pharmacy laboratory to meet USP <797> requirements for facility design and environmental controls.

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


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

Per USP <797>, the compounding facility must be physically designed and environmentally controlled to minimize airborne contamination from existing critical sites. Our nuclear pharmacy laboratories, operated under the practice of medicine, have operated in a semilaminar setup since 1989. Each laboratory has had a continuous space, with various designated areas (e.g., radiopharmaceutical-
Immediate-use CSPs are exempt from the requirements described for Low-Risk Level CSPs if

- Administration begins not later than 1 hour following the start of the preparation of the CSP
- \( \leq 3 \) sterile products \& \( \leq 2 \) entries
  - \(^{99m}\)Tc-mertiatide
  - \(^{99m}\)Tc-tetrofosmin
  - \(^{99m}\)Tc-sulfur colloid
  - \(^{99m}\)Tc-red blood cells via UltraTag® RBC

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<1165> Radiopharmaceutical Quality Assurance and Compounding
Timeline

- March 2001
  - *Nuclear Pharmacy Compounding* developed by Section of Nuclear Pharmacy Practice, APhA
- August 2001
  - *Nuclear Pharmacy Compounding* submitted to USP RMI
- November 2002
  - “a very controversial matter” USP staff liaison assigned to RMI
Timeline

- March 2004
  - “regulatory and political implications” USP RMI Chair
    - Definition of compounding
    - References to FDAMA and FFDCA
    - Publication of <797>

- 2008-2009
  - <1017> <1165> Radiopharmaceutical Quality Assurance and Compounding in development

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<1165> & <1167>

- <1165> Radiopharmaceuticals Quality Assurance - Compounding
- <1167> Quality Assurance in Pharmaceutical Compounding
Radiopharmaceuticals Quality Assurance - Compounding

- QA of Individual Patient Doses of a Commercially Procured Radiopharmaceutical
- QA of Radiopharmaceuticals Prepared from Commercially Available Kits and Generators
- QA of Radiopharmaceuticals Involving Deviations from Manufacturer’s Instructions
- QA of Radiopharmaceuticals Involving Extemporaneous Compounding
- Special Considerations

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Individual Patient Doses of a Commercially Procured Radiopharmaceutical

- Commercially procured final-dosage-form radiopharmaceuticals
  - Finished radiopharmaceuticals obtained from manufacturers – $^{201}\text{Tl}$, $^{67}\text{Ga}$
  - Unit-dose radiopharmaceuticals obtained from commercial nuclear pharmacies
QA of Individual Patient Doses of a Commercially Procured Radiopharmaceutical

- Radionuclide (dose) calibrator QC
- Visual inspection of product
- Verification of each patient dose
- Record keeping
Radiopharmaceuticals Prepared from Commercially Available Kits and Generators

- USP monographs for reconstituted radiopharmaceuticals
  - $^{99m}$Tc (25) except
    - Tc 99m sodium pertechnetate injection
  - $^{111}$In (6) except
    - In 111 chloride solution
  - $^{90}$Y (1)
QA of Radiopharmaceuticals Prepared from Commercially Available Kits and Generators

- Radionuclide (dose) calibrator QC
- $^{99m}$Tc generator QC - $^{99}$Mo breakthrough & aluminum breakthrough
- Visual inspection of product
- Radiochemical purity
- Verification of MAA particle size
- Labeling
- Verification of each patient dose
- Microbiological controls – retrospective sterility tests on randomly selected batches of products

Record keeping
Deviations from manufacturer’s preparation instructions for commercially available kits and generators may be necessary in cases relating to safety or efficacy considerations.
QA of Radiopharmaceuticals Involving Deviations from Manufacturer’s Instructions

- Radionuclide (dose) calibrator QC
- $^{99m}$Tc generator QC
- Visual inspection of product
- Radiochemical purity
- Verification of MAA particle size & number
- Stability of beyond-use dating
- Labeling
- Verification of each patient dose
- Microbiological controls – sterility & pyrogen tests at regular periodic intervals
- Record keeping

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Prescriber-directed extemporaneous compounding of radiopharmaceuticals may be necessary for providing optimum care to some patients.

The desired product is unavailable commercially.

Liability aspects relate to responsibility for the product and any adverse consequences therefrom.
QA of Radiopharmaceuticals Involving Extemporaneous Compounding

- Radionuclide (dose) calibrator QC
- $^{99m}$Tc generator QC
- Visual inspection of product
- Radiochemical purity
- Verification of MAA particle size & number
- Stability of beyond-use dating
- Labeling
- Verification of each patient dose
- Microbiological controls
- Record keeping

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QA of Radiopharmaceuticals Involving Extemporaneous Compounding

- Organization & Personnel
- Nuclear Pharmacy Facilities
- Sources of Compounding Drug Components
  - Active Pharmaceutical Ingredient
  - Excipient
    - A component of an approved drug product
    - USP or NF grade
    - AR, ACS, FCC grade
Special Considerations

- Cell Radiolabeling Practices in an Open System
- Intrathecally Administered Radiopharmaceuticals
- Dilutions and Compatibility
Proposed 3-Stage Plan
Stage 1

- Revise <797>
  - SCA with “displacement airflow”
  - SCA & radiopharmaceutical with a BUD > 12 hours?
  - Accept SNM’s proposal of revising Immediate-Use CSPs provision
    - If radiopharmaceuticals conform to the standards for Low-Risk Level CSPs and are administered within on hours of the start of compounding, they may be compounded under the Immediate-Use CSPs provisions.
- Revise <821> Radioactivity
  - It is a “mandatory” (enforceable) general chapter
  - However, <821> is written likes an informational chapter - “textbook” information
- Renumber <821> Radioactivity
  - A general chapter numbered ≥ 1000
Stage 3

- Consult & work with other USP ECs
- Rename <821> to Radiopharmaceuticals – Compounding and Quality Assurance
  - Cancel the development of proposed <1165> Radiopharmaceutical Quality Assurance and Compounding
  - Relocate the draft content of <1165> to <821>
  - State in the first sentence of <821> that the compounding and QA issues of PET radiopharmaceuticals are described in <823>
The following related USP general chapters must be consulted since the requirements may be applied to all pharmacies and compounders by regulatory agencies:

- <795> Pharmaceutical Compounding – Nonsterile Preparations
- <797> Pharmaceutical Compounding – Sterile Preparations
- <1075> Good Compounding Practices
- <1163> Quality Assurance in Pharmaceutical Compounding