USP <797> in Nuclear Pharmacy and Medicine I

Overview of USP Chapter <797>
Pharmaceutical Compounding - Sterile Products Preparations

SNM Midwinter Symposium
February 16, 2008
Newport Beach, California

Sam C. Augustine, Pharm.D., FAPhA
Associate Professor
Creighton University
School of Pharmacy and Health Professions
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Disclaimer

Although I am a member of the USP Sterile Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative. The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.
# The 2005-10 USP SCC

<table>
<thead>
<tr>
<th>♦ Dr. Sam Augustine</th>
<th>♦ Mr. Eric Kastango</th>
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<tr>
<td>♦ Dr. Mary Baker</td>
<td>♦ Dr. Dave Newton²</td>
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<tr>
<td>♦ Dr. Jim Cooper</td>
<td>♦ Mr. Keith St. John</td>
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<td>♦ Dr. Don Filibeck</td>
<td>♦ Dr. Laura Thoma</td>
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<tr>
<td>♦ Mr. Larry Griffin</td>
<td>♦ Mr. Larry Trissel³</td>
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<tr>
<td>♦ Mr. Ken Hughes</td>
<td>♦ Mr. Jim Wagner</td>
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</table>

1 Dr. Claudia C. Okeke, [cco@usp.org](mailto:cco@usp.org), is USP staff liaison to the SCC

2 Chairman

3 Vice Chairman
Advisory Panel
Radiopharmaceuticals as CSPs

- Samuel C. Augustine
- David Barnes
- Stephen C Dragotakes
- John Kuperus
- Vivian S. Loveless
- Richard Nickel
- Neil Allen Petry
- Rodney Prosser
- Timothy M. Quinton
- Joseph Hung
Significance

• Patient safety
  – purpose set standards for preparing compounded sterile preparations (CSPs) for the assurance of patient safety
    • Defines compounding differently than the FDA

• Right to Compound
  – go beyond package insert
    • use “professional judgment”
Much more content devoted to **air quality**, e.g., ISO Class 5, for CSP critical sites, than to contact contamination.

Yet, all USP and non-USP experts agree that **contact** is most likely source of clinically significant microbial and non-microbrial contamination; thus, it **is** the **first prevention priority**!
Especially concerned to prevent contact contamination:

- Sterile gloves and IPA reduce the initial microbial bioburden, which reduces gross contamination of critical sites.
- Honest, SCC knows that sterile gloves do not remain sterile, and that sterile 70% isopropanol does not sterilize.
- IPA is not sporicidal, but sporicidal disinfectants have long kill and drying time.
Process timeline:

• May 2006 – January 2007
  – Comment period with Committee review
• late 2007
  – revision bulletin posted on USP’s website
• Spring 2008
  – publication in Pharmacopeal Forum as an Interim Revision Announcement
• June 1, 2008
  – official

- Sep.-Nov. 2005: draft revisions; 1.5-day meeting
  Jan.-Mar. 2006: several 2-hour phone conferences
- Sep.-Nov. 2006: study comments; 1.5-day meeting
- Nov. 2006-Feb. 2007: write and re-re-rewrite revisions
- Since Mar. 2007: rewrite and adopt revisions; begin cleaning/disinfection and “nuke” advisory panels; several 2-hour phone conferences
SCC met q 2 wks by phone since March, 2007

Revision completed based on thorough review and consideration of more than 500 comments during May-June, 2006 regarding In-Process Revision of proposed changes.

SCC aware of delicate balance of practicality issues to compounding practitioners and protecting public health
Introduction Section

- **IMPORTANT NOTE**: pertains to the CSPs prepared for **clinical administration** to patients via application, implantation, infusion, inhalation, injection, insertion, instillation and irrigation

- **General Chapter < 797>** applies to:
  - All persons (nuclear pharmacists & nuclear medicine technologists) involved in the preparation, storage, and transportation of compounded sterile preparations (CSPs)
  - All places (centralized & in-house pharmacies & laboratories) where CSPs are prepared
  - Radiopharmaceuticals & other diagnostic agents are included
It is important to note a statement in the introduction: “The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.”
Responsibility of Compounding Personnel

- Compounding personnel are expected to maintain the high standards for quality, control of processes, components and environments and for workers’ competence, skills and knowledge.
  - Training
  - Ingredient Integrity
  - Integrity of CSPs
Risk Levels

- Immediate – Use CSPs
- Low Risk Level CSPs
  - CSPs with BUDs of 12 hours and less
- Medium Risk Level CSPs
- High Risk Level CSPs
Single-Dose and Multiple-Dose Containers

- Definition
- Expiration
Radiopharmaceuticals as CSPs

• Addresses issues specific to radiopharmaceuticals routinely used in practice
  – Chapter <823>
  – Low Risk Level exemption
  – $^{99}$Mo/$^{99m}$Tc Generator storage & operation
  – Finished radiopharmaceutical storage
  – Visual inspection
  – Contamination – patient care areas
Standard Operating Procedures

Compounding facilities are to have written SOPs for environmental quality.

Procedures provided address:
- Access to the restricted compounding area
- Introduction of supplies in the restricted area
- Preparation of personnel allowed in the compounding area
- Restriction of materials and activities in the compounding area
- Operation of PECs
- Preparation of the DCA
- Compounding procedures in the DCA
- Inspection of finished CSPs
- Removal of used supplies and equipment from the DCA
Environmental Quality and Control

- **Room segregation**
  - Use of positive and negative pressures

- **Placement of devices and objects not essential to compounding**
  - Printers
  - Refrigerators
  - Other devices
## ISO Classes

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Old U.S. Classification</th>
<th>ISO Classification</th>
<th>Old Particles per cubic meters</th>
<th>Old Particles per cubic feet</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Class 1</td>
<td>35.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Class 10</td>
<td>352</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Class 100</td>
<td>3520</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Class 1,000</td>
<td>35,200</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Class 10,000</td>
<td>352,000</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Class 100,000</td>
<td>3,520,000</td>
<td>100,000</td>
<td></td>
</tr>
</tbody>
</table>
Low risk 12 hour or less BUD

Segregated Compounding Area

PEC ISO Class 5

DCA

100 particles/ft³
Low-, Medium- and High-Risk Levels

- **PEC ISO Class 5**
- **Buffer Area ISO Class 7**
- **Ante Area ISO Class 8**

Particles/ft$^3$:
- 100,000
- 10,000
- 100
Additional Personnel Requirements

- Food, drinks, and items exposed in patient care areas are prohibited from buffer areas/rooms, segregated compounding areas and ante-areas/rooms
- Manipulation patient blood derived materials shall be clearly separated from routine CSP preparation activities specific SOPs are required for blood product preparation
- Unpacking of compounding supplies and personnel cleansing and garbing are prohibited from buffer areas or rooms (performed in ante area)
- Shall be a demarcation designation separating buffer areas/rooms and ante-areas/rooms
- Provision for antiseptic hand cleansing and access to sterile gloves in buffer areas/rooms
Environmental Quality & Control

Cleaning and Disinfecting the Compounding Area
Cleaning Policy and Procedure

- Specific requirements *(where, when, who, why and how)*
- Specific cleaning agents and dilution
- Specific areas to be cleaned and frequency
- Protective gear
- Documentation requirements
- Resources *(MSDS forms, CDC literature, etc)*
- Applicable internal forms or policies
## Frequency Recommendations: Best Practice

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty Garbage</td>
<td></td>
<td>All daily activities</td>
<td>All daily activities</td>
</tr>
<tr>
<td>ISO 5 Areas</td>
<td>Walls, windows of cleanroom/anteroom</td>
<td>All weekly activities</td>
<td></td>
</tr>
<tr>
<td>• Interior surfaces</td>
<td>Storage shelving-all surfaces</td>
<td>Ceilings of cleanroom and anteroom</td>
<td></td>
</tr>
<tr>
<td>hood/isolators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Compounders: move ACDs and equipment and clean underneath</td>
<td>Storage bins-remove contents, clean all surfaces and replace</td>
<td>Top of Hoods/Isolators</td>
<td></td>
</tr>
<tr>
<td>Top of carts, stools, or other furniture</td>
<td>All surfaces of carts, stools, other furniture</td>
<td>Inside surface of trash bins</td>
<td></td>
</tr>
<tr>
<td>Floors in cleanroom and anteroom</td>
<td>Outside surface of trash bins</td>
<td>Other equipment: incubator, refrigerator</td>
<td></td>
</tr>
<tr>
<td>Pigs, coolers and other transport containers</td>
<td></td>
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</table>
Elements of Quality Control

- Personnel Training
- Environment
  - Facilities and Equipment
  - Engineering Controls
  - Environmental Sampling
  - Cleaning and Maintenance
Elements of Quality Control

- **Personnel Requirements**
  - Garb – Personnel Protective Equipment
  - Evaluation of Aseptic Work Practice
    - Aseptic Manipulations Assessment
    - Visual Assessment of Personnel Performance
  - Corrective actions
Personnel Cleansing and Garbing

• Clarify garbing process by emphasizing the “dirtiest to cleanest” order

• Discussion of personal garments, cosmetics, jewelry, fingernails (natural and artificial)

• Don garb that covers non-hand areas first, followed by proper hand hygiene, then donning gowns and sterile gloves

• Frequent disinfection of sterile gloves with 70% IPA
Personnel hand hygiene and garbing

- Hair net
- Beard cover and face mask
- Gown
- Gloves
- Shoe covers

End result.
Finished Preparation Release
Checks and Tests

• physical inspection of CSPs includes visual examination for particulate matter

• In the case of radiopharmaceuticals
  – visual inspection should be performed using ALARA exposure techniques
Finished Preparation Release

Checks and Tests

- **Written procedures**
  - double-checking compounding accuracy are recommended for every CSP
    - during preparation
    - immediately prior to release
    - Accuracy measurements of radiopharmaceuticals include measurement of concentration of radioactivity using dose calibrator.
  - Sterility testing/bacterial endotoxin testing not required for radiopharmaceuticals routinely compounded using sterile components
Identity and Strength Verification

- Written procedures
  - verify correct identity & quantity prior to dispensing
  - Labeling including:
    - Correct names and amounts of ingredients
    - Total volume
    - BUD
    - Route of administration
    - Storage conditions
    - Other information for safe use
Identity and Strength Verification

- Methods for comparing original written orders with compounding records
- Confirmation of amounts by required methods
Beyond-Use Dating

The chapter requires that BUDs for CSPs that are prepared strictly in accordance with manufacturers’ product labeling shall be:

- those specified in that labeling
- from appropriate literature sources
- from direct testing
Beyond – Use Dating

When considering a radiopharmaceutical these include:

- the nature of the radiopharmaceutical
- its degradation mechanism
- its packaging or containment
- expected storage conditions
- the intended time of its administration
Conclusion

- Objective
  - Patient protection