How USP Chapter <797> affects Nuclear Medicine
Disclosures

• Speaker is currently employed by Cardinal Health Nuclear Pharmacy Services
• Views expressed are those of the speaker and not of Cardinal Health
Objectives

• STATE the influence of the USP on sterile drug compounding and rulemaking
• IDENTIFY requirements for compliance with USP Chapter <797> standards
• STATE what USP <797> does not cover
• LIST conditions under which certain compounding activities are exempt from USP Chapter <797>
What is the USP?

• United States Pharmacopeia

• Establishes legally enforceable, national drug standards

• Private, nonprofit standard-setting body for pharmacy and medicine

• Enforceable when recognized and incorporated into laws and regulations
USP Who, What, and Why?

- **Who:** MD’s, RPh’s, RN’s, etc.

- **What:** Private, nonprofit standard-setting body for pharmacy and medicine & the drug manufacturing industry

- **Why:** Enforceable when recognized and incorporated into laws regulations

- **Two official compendia:** USP and NF
The USP “promotes public health and benefits practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other health care technologies, and related practices used to maintain and improve health and promote optimal health care delivery.”
Birth of USP Chapter <797>

- Precursor was General Information Chapter <1206>, *Sterile Products for Home Use*

- USP Chapter <797> initially in effect 2004

- Over 500 comments resulted in significant revision in 2007, effective June 1, 2008

- Object of the Chapter: Compounded Sterile Preparations (CSPs)

- Sterile Compounding Committee formed
Sterile Compounding Committee

• Sterile Compounding Committee (SCC)
  “This is all about patient safety. The purpose is to protect patients. Protect them from microbial contaminated preparations, ensure correct drug identities, amounts of ingredients, etc.”

• Applies to:
  – All persons who prepare CSPs
  – All places where CSPs are routinely prepared

This includes you!
Intent of USP Chapter <797>

• FDA pressured health care institutions to approach drug manufacturers’ standards for sterile compounding (cGMP)

• Goals:
  – Prevent Harm: Non-sterile products, endotoxins, errors in calculation, incorrect, impure ingredients
  – Maintain Sterility: Establish methods to keep sterile products sterile
  – Assure Sterility: Establish methods to confirm sterility for products made from nonsterile ingredients or employing nonsterile devices
Enforcement of USP Chapter <797>

- FDA could enforce, but FDA seldom visits pharmacies, hospitals or clinics without cause.

- Some Boards of Pharmacy are enforcing and some have promulgated regulations in parallel.

- The Joint Commission is inspecting for compliance during some accreditation visits.

- These bodies reference USP standards for developing their statutes and regulations.
Many Factors in Product Sterility

- Operating Environment
- Good Hygiene
- Equipment
- Facility Design
- Personnel
- Cleaning
- HVAC
- Traffic Flow
- Training

Sterility of Final Product

This includes radiopharmaceuticals.
### USP <797> Major Sections

<table>
<thead>
<tr>
<th>Responsibilities of Compounding Personnel</th>
<th>Radiopharmaceuticals as CSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSP Risk Levels</td>
<td>Storage &amp; Beyond Use Dating</td>
</tr>
<tr>
<td>Verification of Compounding Accuracy &amp; Sterility</td>
<td>Maintaining Quality After Product Dispensing</td>
</tr>
<tr>
<td>Personnel Training &amp; Evaluation in Aseptic Manipulation Skills</td>
<td>Patient or Caregiver Training</td>
</tr>
<tr>
<td>Environmental Quality &amp; Control</td>
<td>Finished Preparations &amp; Release Checks &amp; Tests</td>
</tr>
<tr>
<td>Equipment</td>
<td>Adverse Event Reporting</td>
</tr>
<tr>
<td>Immediate – Use CSPs</td>
<td>Quality Assurance Program</td>
</tr>
</tbody>
</table>
Definitions

- Aseptic Processing
- Beyond-Use Date (BUD)
- Critical Site
- Direct Compounding Area (DCA)
- Preparation
- Product
- Segregated Compounding Area
Air Quality Standards

- Environmental air quality standards apply to the handling of CSPs
- ISO is an internationally-recognized body of standards
- ISO class is limited by number of particles 0.5 micron in size per unit volume of air
- For example, a Laminar Flow Workbench (LAFW) must be certified to have ISO Class 5 air quality

<table>
<thead>
<tr>
<th>ISO CLASS</th>
<th>PARTICLES /m³</th>
<th>PARTICLES /ft³</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3,520</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>352,000</td>
<td>10,000</td>
</tr>
<tr>
<td>8</td>
<td>3,520,000</td>
<td>100,000</td>
</tr>
</tbody>
</table>
Air Quality

- “Dirty” air enters from room
- Pre-filtered then through HEPA
- Flows down over work area
- Drawn back through work surface, up the back then recycled
- First air to Direct Compounding Area (DCA)
- Must not obstruct clean airflow when possible

LAFW Hood
USP-Defined CSP Risk Levels

- **High Risk**
  - CSPs prepared with initially nonsterile ingredients and/or equipment, which are later sterilized

- **Medium Risk**
  - CSPs that are prepared for administration to multiple patients or involving complex compounding

- **Low Risk**
  - CSPs prepared from initially sterile ingredients; minimal manipulation
Radiopharmaceuticals: Low Risk Level

- Radiopharmaceuticals are designated as Low-Risk Level CSPs if:
  - Compounded from sterile components in closed sterile containers with volumes of 100 mL or less for a single-dose injection
  - Not more than 30 mL taken from a multiple-dose container

- $^{99m}$Tc kit preparations are therefore considered Low-Risk Level

- Radiopharmaceutical CSPs prepared in a segregated compounding area with a Laminar Air Flow Workstation (LAFW) are to be used within 12 hours
Radiopharmaceuticals as CSPs

- All manipulations with exposure of vial’s critical sites must be performed in LAFW.

- Some environmental considerations are modified for radiopharmaceuticals as CSPs:
  - LAFW may be located in a room with ISO Class 8 air environment
  - Shielded storage anywhere with restricted access
  - Generator elution allowed in ISO Lcass 8 air environment

- Operating procedures to prevent cross-contamination between patient care or blood-labeling and sterile drug compounding areas must be in place!
Blood is **Not Sterile**

- $^{111}$In or $^{99m}$Tc leukocytes

- $^{99m}$Tc labeled red blood cells
  - UltraTag® kit
  - The finished dose to be injected is not sterile, therefore this is not a CSP, not subject to USP <797> other than required separation of preparation areas, implements
LAFW is the Primary Engineering Control (PEC)

- LAFW filters air through HEPA filter
- Must be certified to assure ISO Class 5 conditions
- CSPs must be compounded a PEC
- Training in proper cleaning and handling techniques within LAFW is required
Environmental Maintenance

- Ante area: ISO Class 8 air; for cleaning of supplies and equipment, hand washing and sanitizing and donning appropriate compounding garb

- Buffer area: ISO Class 8 air; LAFW and generators must be located here

- Smooth, cleanable wall and ceiling surfaces, counters and furniture; minimal equipment and supplies

- SOPs for cleaning, validation of employees required
Environmental Maintenance (continued)

• Regular cleaning and disinfecting of compounding areas and adjacent surfaces is required

• This is the mandated schedule

• It is best to minimize clutter and keep equipment and supplies at a bare minimum

<table>
<thead>
<tr>
<th>Compounding Area</th>
<th>Frequency of Cleaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAFW</td>
<td>Each shift</td>
</tr>
<tr>
<td>Counters</td>
<td>Daily</td>
</tr>
<tr>
<td>Floors</td>
<td>Daily</td>
</tr>
<tr>
<td>Walls</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Monthly</td>
</tr>
<tr>
<td>Shelving</td>
<td>Monthly</td>
</tr>
</tbody>
</table>
Aseptic Technique Training / Evaluation

- Compounders must be trained in the theory and practice of aseptic preparation

- Must maintain high standards for CSP quality, workers’ competence, skills and knowledge

- Must assure radiopharmaceutical integrity, accuracy of measurement, correct mixing and dilution

- Review of written texts, videos or computer-based learning modules are examples of resources used to convey theoretical principles

- Media challenges using bacterial growth media used to evaluate aseptic techniques

- Both didactic and practical tests must be done at least annually for low- and medium-risk activities
Personnel Requirements

- Careful hand washing and good personal hygiene
- No jewelry, artificial nails, cosmetics in compounding area; wear non-shedding appropriate compounding garb
- Use of gloves and frequent reapplication of 70% isopropyl alcohol to gloves during compounding process
- Annual reevaluation of compounders’ aseptic technique is required
- Sterile bacterial growth media is manipulated under actual-use conditions that simulate the relevant compounding activity
  - Media vials in shielded containers
  - Syringes handled with syringe shields
Standard Operating Procedures

• Written SOPs required for:
  – Access to the compounding area restricted
  – Introduction of supplies in the compounding 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
Finished Preparation Checks

• Radiopharmaceuticals have obvious restrictions on their visual examination

• ALARA must prevail when visually examining finished preparations

• Compounding accuracy checks may be documented on written records

• Final assay of finished preparation is made in the dose calibrator

• Comparison of orders against finished products
Beyond-Use Dates

• Not the same as expiration date

• Beyond-Use Date may deviate from manufacturer labeling and be extended based on:
  – Relevant stability information in published literature
  – Storage conditions
  – Intended time of administration
  – Packaging

• Common example: $^{99m}$Tc sestamibi BUD of 12 or 18 hours vs. 6 hours in package insert
Immediate-Use Provision of USP <797> exempts emergent, unplanned compounding if:

1. Transfer of not more than three pharmaceutical products from the manufacturers’ original containers with not more than two entries into any one container.
2. The continuous compounding process does not exceed one hour.
3. Aseptic technique is followed in the preparation of the CSP.
4. The administration of the CSP to a single patient is begun within one hour following the start of the preparation.
5. The CSP must be labeled with the one patient’s identification information and the initials of the preparer unless it is immediately & completely administered as witnessed by the preparer.
6. If the CSP is not administered within one hour following the start of its preparation, it must be “promptly, properly and safely discarded.”
Immediate-Use CSPs: Important Considerations

- If you make an emergency kit for 1 patient from $^{99m}\text{TcO}_4^-$ and use it within the hour, then USP Chapter <797> does not apply
  - No LAFW needed, for example

- Remaining unused $^{99m}\text{TcO}_4^-$ labeled drug vial and the $^{99m}\text{Tc}$ sodium pertechnetate MUST be discarded

- Single-dose and multi-dose vials are subject to same restriction

- Consider increasing unit-dose deliveries, have after hours $^{99m}\text{TcO}_4^-$ delivered in syringes
Compliance with USP <797> Means:

- Adherence to:
  - Personnel training requirements
  - Validation of aseptic technique
  - Environmental cleaning standards
  - Air quality standards
  - Compounding accuracy standards
  - Pre-release quality checks
  - CSP adverse event reporting/review
Impact of USP Chapter <797>

• Major impact on nuclear pharmacies and nuclear medicine departments

• Administrators will need to reevaluate current procedures for compliance with the new requirements

• Retraining of personnel and regular maintenance and validation of environmental quality is a significant challenge

• Meeting USP Chapter <797> requirements is expensive and time consuming

• Future accreditation and regulatory compliance impact
Three Options

- Full Unit Dose System
- Hybrid Unit Dose System
- Generator System
Full Unit Dose System

• Exempts department from USP <797> Standards

• Designated area for labeling blood preparations

• A separate designated compounding area for sterile preparations

• Designated dose calibrator dipper/well liner sleeve for blood preparations

• A separate designated dose calibrator dipper/well liner sleeve for sterile preparations

• Policies and Procedures describing training in aseptic technique for all employees
Hybrid System

- Mostly patient ready unit doses
- $^{99m}\text{Tc}$ pertechnetate delivered in vials and/or syringes for stats
- Must use within one hour to be “exempt from <797>”
- Must perform quality control on preparations
- Same five recommendations under full unit dose must be implemented (i.e., designated areas for blood preparations, separate dippers, aseptic training)
Generator System

- Full USP <797> compliance
- ISO Class 8 buffer and ante areas
- ISO Class 5 PEC (i.e., LAFW)
- Aseptic training and validation
- Environmental monitoring
- Daily, weekly, and monthly cleaning
- Development of SOP’s
If You Decide to Compound CSPs…

• You must comply fully with USP Chapter <797>
  – All training requirements
  – All personnel aseptic technique validations
  – All equipment certification and testing
  – All environmental quality standards
  – All adverse event review and reporting standards
  – All recordkeeping to support your activities
Thank you