Overview of Chapter <797> for Surveyors and Inspectors

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Polling Question

In what year did USP <797> first become official?

1. 2000
2. 2004
3. 2008
4. 2010
USP Chapter <797>

- Enforceable by the FDA and 23 State Boards of Pharmacy
- Based on current scientific information and best sterile compounding practices
- Recognized as the national standard of practice
- Included in TJC and other accreditation organization requirements if their standards address sterile compounding
- **Minimum** practice and quality standards for compounding sterile preparations
Who does the chapter apply to?

- Applies to all persons who prepare CSPs
- Applies to all places where CSPs are prepared
- Applies to pre-administration manipulations of CSPs including storage, compounding, and transport
- Does not apply to administration!
- Specific chapter language:
  - “shall” is a requirement
  - “should” is a recommendation
Mission of Chapter: To Prevent Harm

• Microbial contamination
• Excessive bacterial endotoxins
• Variability in intended strength that exceed monograph limits
• Use of ingredients of inappropriate quality
• Unintended physical and chemical contaminants

This is an image of the fungus growing from a sample taken from a patient’s spinal fluid.
Microbial Contamination Risk Levels

- USP categorizes 3 risk levels
- Low, Medium and High
- Immediate-use is considered a special type
- Low Risk is subset of low risk with 12 hour BUD

What is a Microbial Contamination Risk Level?

A microbial contamination risk level is an assignment given a particular type of CSP according to its potential for the introduction of contamination during the compounding process.

The assignment of risk level is based on multiple factors including the type of components used, the environment in which compounding occurs and the complexity of the compounding process.
CSP Microbial Risk Levels

- True emergency situations
- Compounded outside of a hood
- Expectations: Handwashing
- 6 Criteria which *all* must be met

**High Risk**

**Medium Risk**

**Low Risk**

**Low Risk with 12 h BUD**

**Immediate Use**

- 1. Simple transfer of ≤ 3 commercially manufactured non hazardous products
- 2. Not > 2 entries into any container
- 3. Compounding continuous and not > 1 hour
- 4. Aseptic technique is followed
- 5. Admin begins ≤ 1 hour from start compounding
- 6. Labeled

*Example: initial dose of norepinephrine drip in ICU after pharmacy hours*

*Nurses prepare 14.7% of IV doses from vials and ampules (29% < 50 beds, 8% > 50 beds)*

*2011 ASHP National Survey Dispensing and Administration*
CSP Microbial Risk Levels (continued)

- **High Risk**
  - Segregated Compounding Area
    - CSPs made in a LAFW that is not placed in a cleanroom
  - Cannot be used for HDs
  - Expectations still include
    - Hand hygiene and garbing
    - Daily & monthly cleaning
    - Environmental sampling

- **Medium Risk**

- **Low Risk**

- **Low Risk with 12 h BUD**

- **Immediate Use**

*Example: Initial dose of norepinephrine compounded in satellite pharmacy in the ER*
CSP Microbial Risk Levels (continued)

- **High Risk**
  - Not > 3 sterile drug packages used (including diluent)
  - Using sterile equipment
  - Compounded in an ISO Class 5 device usually in an ISO Class 7 environment

- **Medium Risk**
  - Limited, basic, closed-system aseptic transfers and manipulations

- **Low Risk**
  - Expectations: all QA components with annual aseptic media fill and GFS

- **Low Risk with 12 h BUD**

- **Immediate Use**

*Example: 1 dose of 1000 mL D5W with 30 mEq potassium chloride added*
CSP Microbial Risk Levels (continued)

- Using 4 or more sterile ingredients, complex aseptic manipulations
- No bacteriostatic additive and administered over several days

- 1 dose for multiple patients (anticipatory batch compounding)
  OR
- 1 patient on multiple occasions (patient-specific batch)

Example: Parenteral Nutrition or Batch of IV minibags/syringes
CSP Microbial Risk Levels (continued)

- Made with non-sterile ingredients and/or using non-sterile containers, devices or equipment
- Prepared from sterile ingredients but exposed to < ISO Class 5 air
- > 6 hour delay from compounding to sterilization
- Purity of components is assumed but cannot be verified by documentation

Example: Morphine sulfate from nonsterile powder for PCA
Polling Question

You are inspecting a traditional home infusion pharmacy that provides IV antibiotics, TPN and other CSPs to patients. They use sterile components from FDA manufacturers. Home Infusion pharmacies generally dispense enough doses to the patient for 1 week. Just knowing that information tell you that most of their formulations will be what risk level?

1. Low risk with 12 hour BUD
2. Low risk
3. Medium risk
4. I have no idea
Beyond-Use Date (BUD) Limits

• BUDs are based on the chemical stability & microbial risk level *whichever is shorter*.

• There is no single iron-clad determination of risk-levels except that any CSP prepared from non-sterile ingredients is always considered high risk level compounding.

• Have a mechanism where stability is documented and once compounding methodology is locked down, then risk level can be determined and BUD established.
Storage by Risk Level

Here’s a visual summary of the risk levels and their corresponding BUDs to review. It’s important to adhere to these BUD limits unless sterility testing (by membrane filtration per USP Chapter <71>) is performed on each and every batch for which limits are exceeded.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>BUD at Room Temperature (20 to 25° C)</th>
<th>BUD under Refrigeration (2° to 8° C)</th>
<th>BUD with Frozen Storage (-25 to -10° C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Use</td>
<td>1 hour</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Low Risk with 12h BUD</td>
<td>12 hours</td>
<td>12 hours</td>
<td>N/A</td>
</tr>
<tr>
<td>Low Risk</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Medium Risk</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High Risk</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>
## SDVs, MDVs, PBP and Point of Care Activated

<table>
<thead>
<tr>
<th>Container Type</th>
<th>Preservatives</th>
<th>BUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose Ampule</td>
<td>No</td>
<td>N/A because not stored</td>
</tr>
<tr>
<td>Single Dose Vial* (SDV)</td>
<td>No</td>
<td>6 hours if opened in ISO class 5 OR 1 hour if opened is air worse than ISO 5*</td>
</tr>
<tr>
<td>Multiple Dose Vial (MDV)</td>
<td>Yes</td>
<td>28 days from initial puncture or per manufacturer’s package insert</td>
</tr>
<tr>
<td>Pharmacy Bulk Package (PBP)</td>
<td>No</td>
<td>6 hours or shorter if opened in ISO class 5</td>
</tr>
<tr>
<td>Point-of-Care Activated Systems</td>
<td></td>
<td>• ADD-Vantage™, MINI-BAG PLUS, addEASE®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Attaching/activating these not considered compounding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acceptable for nursing to attach and activate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Use manufacturer’s instructions for storage and stability</td>
</tr>
</tbody>
</table>

*The CDC advised on a more conservative approach to further safeguard patients. The CDC stipulates that the remaining contents must be discarded at the end of the procedure/case and it is not to be stored.*
Hazardous Drug Preparation

- Chapter <797> is consistent with NIOSH guidelines
- Must be prepared in separate room from non-hazardous compounding
- HD buffer area must be 0.01 w.c. negative to anteroom
- Drugs stored in a room with at least 12 ACPH
- Potential exception: low volume of hazardous drug preparations
  - Must use closed-system transfer device if BSC is in the same room as the LAFW
- PPE specified
- Disposal according to local, federal and state regulations
Facility Design and Equipment

- Classified space function and design
- Primary engineering controls
- Buffer area
- Ante area
- Air supply
  - HEPA
  - ACPH
  - Pressure Differentials
- Segregated compounding area
- Equipment, surfaces, and supplies
## Primary Engineering Controls

<table>
<thead>
<tr>
<th></th>
<th>Non Hazardous</th>
<th>Hazardous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional</strong></td>
<td>Laminar Air Flow Workbench <strong>LAFW</strong></td>
<td>Biological Safety Cabinet <strong>BSC</strong></td>
</tr>
<tr>
<td><strong>Isolators</strong></td>
<td>Compounding Aseptic Isolator <strong>CAI</strong></td>
<td>Compounding Aseptic Containment Isolator <strong>CACI</strong></td>
</tr>
</tbody>
</table>
Secondary Engineering Controls

Non Hazardous Buffer Area
- ISO Class 7
- Positive Pressure

Ante Area
- ISO Class 7 or 8
- Must be ISO Class 7 if it serves a negative pressure HD buffer area
- Positive Pressure

Hazardous Buffer Area
- ISO Class 7
- Negative Pressure

General Pharmacy and Storage area
Segregated Compounding Area

- Typical scenario
  - Pharmacy without a cleanroom
  - Satellite pharmacy
- Only ISO Class space is the PEC
- Requires dedicated space
- Garbing, Cleaning and ES requirements still apply
Special CSP Types: Radiopharmaceuticals

• Three sections apply
  – Radiopharmaceuticals as CSPs
  – Low risk level CSPs with 12 hour BUDs
  – Immediate use CSPs
• Must be prepared in an ISO 5 PEC in ISO 8 environment or cleaner
• Low risk level includes isotopes of 100 mL or less for single dose or 30 mL or less for multiple dose
• **USP <823>** applies to Positron Emission Tomography (PET)
• Further manipulation of PET is compounding and must comply with USP <797>
Special CSP Types: Allergen Extracts

- Collaboration with American Academy of Otolaryngic Allergy (AAOA) and Joint Council of Allergy, Asthma, and Immunology (JCAAI)
- Preparation Guidelines at www.jcaai.org

- Preservative-free allergen extracts must fully comply with all aspects of USP <797>.
- Preserved intradermal and subcutaneous SDVs and MDVs are exempt from personnel, environmental and storage requirements if all criteria are met.

- For single patient only; labeled; not stored
- Compounded by simple aseptic transfer
- Hand hygiene is performed
- Garb: hair/beard covers, gown, mask, sterile gloves
- Gloves are intermittently disinfected w/ sterile IPA
- Vial stoppers and ampule necks are disinfected
Polling Question

Having a physical plant that is compliant with USP <797> requirements is the most important determinant to reducing the risk of contamination to CSPs.

1. True
2. False
Environment vs. Personnel

“The most important variable affecting microbial contamination of admixtures was the *aseptic technique of personnel*, not the environment in which the drugs were compounded.* ”

Personnel Training

- Initial and ongoing
- Didactic, written and hands on components
- Required competencies
  - Hand hygiene and garbing (GFS)
  - Cleaning and Disinfection
  - Aseptic Technique and Aseptic Media Fill Test
- Surface Sampling is also a personnel metric
<table>
<thead>
<tr>
<th>Garb Requirement</th>
<th>Immediate Use</th>
<th>Low, Medium and High Risk Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makeup/Jewelry restrictions</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Hand hygiene</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Hair/facial cover</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Shoe covers</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Low-shed gown</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Sterile Gloves</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Masks</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>
Garbing with Isolators

- All cleaning and garbing requirements apply to compounding in isolators, unless the isolator manufacturer provides written documentation of statistically validated testing supporting any garbing components that are not required.

- Sterile gloves are required when working in an isolator!
Garbing Order

1. Hair cover, facemask and beard/eye cover (in any order)
2. Shoe covers (donned 1 at a time stepping over LOD)
3. Hand hygiene (30 seconds, use nail pick)
4. Don low-linting gown (does not have to be sterile)
5. Perform hand cleaning with alcohol based surgical hand scrub with persistent activity
6. Don sterile gloves
Polling Question

Skip lot testing (sterility testing of representative batches of CSPs made using the same compounding methods) is a USP <797> compliant practice.

1. True
2. False
# Release Checks and Tests

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Inspection</td>
<td>• Immediately after compounding and upon release</td>
</tr>
<tr>
<td></td>
<td>• Inspect for visible particulates/discoloration</td>
</tr>
<tr>
<td></td>
<td>• Container and closure integrity</td>
</tr>
<tr>
<td>Compounding Accuracy &amp; Verification of Ingredients</td>
<td>• Double check systems</td>
</tr>
<tr>
<td></td>
<td>• Check labels</td>
</tr>
<tr>
<td></td>
<td>• Reconciliation of components</td>
</tr>
<tr>
<td>Sterility Testing</td>
<td>• Any risk level CSP if USP storage limits exceeded</td>
</tr>
<tr>
<td></td>
<td>• Batches of &gt;25 high risk CSPs</td>
</tr>
<tr>
<td></td>
<td>• CSPs that wait longer than 6 hours before being sterilized</td>
</tr>
<tr>
<td>Bacterial Endotoxin Testing</td>
<td>• Batches of &gt;25 high risk CSPs</td>
</tr>
<tr>
<td></td>
<td>• CSPs that wait longer than 6 hours before being sterilized</td>
</tr>
<tr>
<td>Filter Integrity Test</td>
<td>• Every time a filter is used to sterilize a solution</td>
</tr>
</tbody>
</table>
Cleaning and Disinfecting

- **Cleaning**
  - Removes solids
  - Most common agent: Sterile water

- **Disinfecting**
  - Sanitizes surfaces
  - Sterile 70% isopropyl alcohol (sIPA)

- Designed to reduce bioburden in compounding areas
Cleaning Procedures

• Clean from cleanest to dirtiest
  – ISO 5 PEC
  – Buffer area
  – Ante area
  – General supply area
• Use suitable dedicated mops and cleaners
• Must use germicidal detergent everywhere including PEC
## Cleaning Frequency Requirements

<table>
<thead>
<tr>
<th>Location</th>
<th>Minimum Frequency</th>
</tr>
</thead>
</table>
| PEC: Work Surface (deck)      | • Beginning of each shift  
                               | • Before each batch  
                               | • Every 30 minutes when compounding  
                               | • After spills  
                               | • When surface contamination is known or suspected |
| PEC: All inside surfaces      | Daily                                                                             |
| Easily cleanable horizontal surfaces | Daily                                                                            |
| Floors                        | Daily                                                                             |
| Walls                         | Monthly                                                                           |
| Ceilings                      | Monthly                                                                           |
| Shelving                      | Monthly                                                                           |
| Supply bins                   | Monthly                                                                           |
Environmental Sampling

• Designed to demonstrate that
  – 1° & 2° engineering controls,
  – cleaning procedures &
  – work practices
  work together to result in a suitable environment for aseptic compounding

State of Control
Environmental Sampling (continued)

Personnel Related Metrics

• Surface Sampling
• Gloved Fingertip Sampling
• Media-Fill Testing

Facility Related Metrics

• Non Viable Sampling
  – Temperature/humidity
  – Pressure/Velocity
  – Particle Sampling
• Viable Sampling
  – Volumetric Air Sampling
Standard Operating Procedures (SOPs)

- Requires formalized policies, processes and procedures used in preparing CSPs
- One element of quality that may not be routinely performed in pharmacies is documentation, or written “proof” that compounding occurring properly
- Appendix I in the Chapter is list of SOPs
Polling Question

A pharmacy must be able to produce information that substantiates the assigned beyond-use dating of its CSPs by documenting which of the following?

1. Chemical stability
2. Microbial Contamination Risk Level
3. Both
A written QA procedure includes 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
  - pH
- labeling accuracy and completeness
- assignment of BUD
- packaging and storage requirements
Quality Assurance Program

- Equipment-related activities
  - Written procedures identify:
    - equipment calibration
    - annual maintenance
    - monitoring for proper functioning
- Inspection of Solution and review of compounding procedures
  - Preparation records are inspected for accuracy
It’s all about the patient...
USP <797> Compliance Study

- 2011, 2012 and 2013
- Results published in PPPMag which is a great resource
- Infusion results were published in INFUSION
- [www.pppmag.com](http://www.pppmag.com) to register
- Only study of its kind
- Uses web-based tool
- Generates customized Action Plan for each participant
- Available all year long
Overall Compliance by Year

- **2011**:
  - Overall: 73.9%
  - Hospitals: 72.4%
  - Home Infusion: 83.5%

- **2012**:
  - Overall: 77.7%
  - Hospitals: 76.3%
  - Home Infusion: 85.3%

- **2013**:
  - Overall: 77.2%
  - Hospitals: 76.4%
  - Home Infusion: 82.6%
Overall Compliance Score based on Length of Participation in Study

- Participation = 1 yr:
  - 2012: 74.3%
  - 2013: 73.7%

- Participation ≥ 2 years:
  - 2012: 83.3%
  - 2013: 84.9%
Great Free Resource for all Pharmacies!
Register at http://797study.criticalpoint.info/