Review of the Proposed Revisions to USP Chapter <797>

• Eric S. Kastango, BS Pharm, MBA, FASHP
Disclosure Information

Review of the Proposed Revisions to USP Chapter <797>

Eric S. Kastango, BS Pharm, MBA, FASHP

• I have the following financial relationships to disclose:
  • Consultant for: Wolters Kluwer
  • Grant/Research support from: BD Medical, Equashield
  • Principal of: Clinical IQ, and CriticalPoint, LLC

• I will not discuss off label use and/or investigational use in my presentation.
At the completion of this activity, you will be able to:

• Describe how the changes made to risk levels, going from three levels to two categories of compounded sterile preparations, Category 1 and Category 2 will affect compounding practices

• Explain the Primary and Secondary Engineering Controls and Segregated Compounding Areas as described in the proposed revision of USP Chapter <797>

• Describe the clarified Cleaning and Disinfection section of the chapter
Disclaimer

The presenters are speaking in their individual capacity and not as representatives of any organization or committee regardless of their status, membership or affiliations with any entity.

The views and opinions presented are entirely their own.

They do not necessarily reflect the views of any other organization they may be associated with, nor should they be construed as an “official” explanation or interpretation of any USP chapter or any State Board of Pharmacy rule/law.
USP Compounding Chapters Timeline

- **February 2016**<br>Publication USP-NF

- **March 30, 2018**<br>Web pre-posting *5/1 publication in Pharmacopeial Forum

- **April 20, 2018**<br>Open Microphone Session

- **July 31, 2018**<br>Close of public comment

- **July 27, 2018**<br>Web pre-posting *9/4 publication in Pharmacopeial Forum

- **Sept 5, 2018**<br>Open Microphone Session

- **Nov 30, 2018**<br>Close of public comment

- **June 1, 2019**<br>Intended Publication USP-NF

- **Dec 1, 2019**<br><800><795><797> Intended Official Date

**Note:** The current version of General Chapters <795> and <797> published in USP-NF are official.
Remember

• This is a discussion of many of the proposed revisions released on July 27, 2018.

• Anything discussed may change after public comments are received by USP and the chapter is finalized.

• The version of the chapter released in 2008 is the current version and will be until December 1, 2019.
Remember

• It is critical that you read the chapter in its entirety.
• The 2018 Proposed Revision of the chapter can be downloaded from the USP website
  • http://www.usp.org/compounding/general-chapter-797
• Submit comments by using link on the USP <797> landing web page
Discussion will include…

• Review of Category 1 and Category 2 CSPs
• Personnel Qualifications
• Primary and Secondary Engineering Controls (PEC and SEC) and Segregated Compounding Areas (SCA)
• Viable Environmental Monitoring (EM)
• Cleaning and Disinfection
• Beyond Use Dating (BUD)
Defining Category 1 and Category 2

- Category 1 CSP - based on facility configuration (SCA/C-SCA)
  - BUD of 12 hours or less at controlled room temperature
  - BUD of 24 hours or less when refrigerated
  - Only if made in accordance with applicable requirements for Category 1 CSPs

- Category 2 CSP – based on facility configuration (ISO classified ante and buffer rooms)
  - BUD of greater than 12 hours at controlled room temperature
  - BUD of greater than 24 hours when refrigerated
  - Only if made in accordance with applicable requirements for Category 2 CSPs

- Table 1 provides a summary of the minimum requirements for each category, but many requirements are not in the table because they apply to ALL CSPs.
Personnel Qualifications

Category 1 and Category 2 requirements are the same

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Observation of hand hygiene and garbing</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Gloved fingertip and thumb sampling</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Media fill testing</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Requalification</td>
<td>Every 12 months</td>
</tr>
</tbody>
</table>

Requalification includes the demonstration of core competencies.
Other Personnel

• Training is not just for compounders
• Other personnel handling CSPs or accessing the compounding area
• Must demonstrate competency in proper behavior to maintain the environment
Garbing and Hand Hygiene

• Disposable nail cleaner must be used
• Garbing order is not specified
  • Up to the facility to decide
  • Define in SOP
• Gowns cannot be reused
• CAI and CACI
  • Disposable gloves under gauntlet gloves
  • Sterile gloves over gauntlet gloves
Gloved Fingertip and Thumb Sampling

• No changes to the number of times
• Clarifies that initial GFS is done after “separate and complete hand hygiene and full garbing”
• Box 2-1 indicates that fingers and thumb are rolled over the surface
• Gives multiple options for devices to use
• Provides incubation parameters that are longer and require two temperatures
Failure of any of the following will require successful reevaluation before personnel can resume compounding.

- Hand Hygiene/Garbing
- Aseptic Technique
- GFS
- Media Fill Testing

How will this effect your ability to care for patients if you need to wait 14 days for media fill results?
Facility Requirements

Category 1 = Cleanroom Suite or SCA

Category 2 = Cleanroom Suite

You can no longer compound in a CAI or CACI in an SCA and get full dating!
Defining Cleanroom Suite

- ISO-classified ante-room with fixed walls and doors
- Controls to minimize the flow of lower-quality air into the more controlled areas
- Supply Air *introduced through HEPA filters located in the ceiling*
- Low wall returns unless a visual smoke study is performed
- Pressure-differential monitoring system
- Line of demarcation in the ante-room
Important “shoulds”

- Design of the facility should take into account
  - number of personnel and their movements
  - equipment, supplies, and components
- The cleanroom suite should
  - be at a temperature of 20° or cooler and at a relative humidity below 60%
  - provide comfortable conditions for personnel in required garb
- Pass-through doors
  - should be interlocking
  - that are not interlocking MUST never be opened at the same time
## Air Exchanges

<table>
<thead>
<tr>
<th>Compounding Area</th>
<th>ACPH Requirements (HEPA-filtered supply air)</th>
<th>Pressure Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclassified SCA</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Unclassified C-SCA</td>
<td>$\geq 12$ ACPH (exhaust) No HEPA air required</td>
<td>Negative 0.01 to 0.03” w.c.</td>
</tr>
<tr>
<td>ISO Class 7 Non-HD Buffer Room</td>
<td>$\geq 30$ ACPH (supply)</td>
<td>Minimum Positive 0.02” w.c.</td>
</tr>
<tr>
<td>ISO Class 7 HD Buffer Room</td>
<td>$\geq 30$ ACPH (supply)</td>
<td>Negative 0.01 to 0.03” w.c.</td>
</tr>
<tr>
<td>ISO Class 7 Anteroom</td>
<td>$\geq 30$ ACPH (supply)</td>
<td>Minimum Positive 0.02” w.c.</td>
</tr>
<tr>
<td>ISO Class 8 Anteroom</td>
<td>$\geq 20$ ACPH (supply)</td>
<td>Minimum Positive 0.02” w.c.</td>
</tr>
</tbody>
</table>
Air Exchanges

• Highly controversial part of certification
• Chapter only prescribe minimum ACPH based on HEPA-filtered supply air except for C-SCA (based on exhaust)
• ACPH may need to be higher to maintain a state of control
• Factors effecting needed ACPH
  • number of personnel in the area,
  • number of particulates generated from processes in the area,
  • equipment located in the room,
  • room pressure,
  • and the effects of temperature.
Air Change Specifics

• ISO Class 7
  • ≥30 ACPH
  • ≥15 ACPH from the PEC
  • ≥15 ACPH through the HVAC
  • If the PEC is used to meet the minimum requirements, the PEC must not be turned off except for maintenance.
  • Certification report must have the ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH.

• ISO Class 8
  • ≥20 ACPH
  • Certification report must have total ACPH.

Compounding area must be certified according to the CETA application guide for Sterile Compounding Facilities or an equivalent guideline.
Sink

- Should be hands free
- Cleanroom Suite
  - Inside the anteroom
  - Outside the anteroom
- SCA
  - Accessible
  - At least 1 meter from the PEC
  - Must not be in the SCA perimeter
Viable Environmental Monitoring

For Category 1 and Category 2

Viable Air Sampling
- Every 6 months

Surface Sampling
- Monthly
Section 5 Retitled

Environmental Monitoring (2015)

Microbiological Air and Surface Monitoring (2018)
Media and Incubation

- No longer required to sample in the SCA, only the classified areas
- TSA still the only type of media listed
  - Option given to use two pieces of media for each sample location
  - Open for SDA, MEA, etc.
- One plate of TSA
  - 30 °C to 35 °C for no less than 48 hours and
  - 20 °C to 25 °C for no less than 5 days
- Two plates
  - TSA - 30 °C to 35 °C for no less than 5 days
  - TSA, MEA, SDA - 20 °C to 25 °C for no less than 5 days
### Action Levels

<table>
<thead>
<tr>
<th>Classification</th>
<th>Air Sample (CFU/m³)</th>
<th>Surface Sample (CFU/sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt;1</td>
<td>&gt;3</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>&gt;10</td>
<td>&gt;5</td>
</tr>
<tr>
<td>ISO Class 8</td>
<td>&gt;100</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

Only if the *Action Level is exceeded*, the genus of any microorganism recovered must be identified with the assistance of a microbiologist.
Exceeded Action Levels

• Cause must be investigated and corrective action must be taken.
• Corrective action plan must be dependent on the CFU count and the microorganism recovered.
• The extent of the investigation should be consistent with the deviation and should include an evaluation of trends.
• The corrective action plan must be documented.
What’s missing?

“Highly Pathogenic Organisms”
and
Identification of every CFU
Cleaning and Disinfecting

Cleaning frequency is not dependent on the CSP Category.
Cleaning Agent Classes: EPA Registered One-Step Disinfectant Cleaner

Hydrogen Peroxide Agents
- No residues, no rinsing, not corrosive
- Effective against yeast, fungi, bacteria, virus and spores based on concentration
- Easy to store and stable

Peroxyacetic Acid & Hydrogen Peroxide Agents
- Broad-spectrum; sporicidal at low concentrations and ambient temperatures
- Inactivates gram+, gram-, fungi, yeasts, viruses and spores
- Not inactivated by organics and enhance their removal; Byproducts: oxygen, acetic acid and water

Phenolic Agents
- Many of these also EPA registered disinfectants on environmental surfaces
- Based on dilution are fungicidal, virucidal and bactericidal
- Unpleasant odor; leave gummy residue that requires rinsing; may damage surfaces

Quaternary Ammonium Compounds
- Never sporicidal; poor activity against mycobacterium; poor activity against hydrophilic viruses
- Must be rinsed; may be irritating to eyes
- Efficacy reduces by hard water and organic material
These are NOT Cleaning Agents!

- Sodium hypochlorite (Bleach)
  - Bleach is not a cleaning agent
  - Has sporicidal properties
  - Does not have surfactant or detergent
  - Has undesirable effects on most finishes over time

- Isopropyl Alcohol (IPA)
  - IPA is a disinfectant
  - Does not have surfactant or detergent
  - Is a *disinfectant* when applied immediately after cleaning
  - Is a *sanitizer* when applied throughout the day but not immediately after cleaning
Cleaning Tools

• Material should be disposable
• Reusable tools MUST be
  • Cleanable
  • Cleaned before and after each use
  • Dedicated for use in the classified area or SCA
• Tools must be in good condition and replaced as needed
Cleaning the PEC (Table 8)

Cleaning

• Horizontal work surface at the beginning and end of each shift, after spills, and when surface contamination is known or suspected.
• Ceiling, walls, bars and any equipment inside the PEC on each day that compounding is performed and when contamination is known or suspected.

Disinfecting

• All interior surfaces of the PEC at the beginning and end of each shift, after spills, and when surface contamination is known or suspected.
• The horizontal work surface at least every 30 minutes while compounding if the compounding process takes 30 minutes or less.

Sporicidal Application

• Monthly
## Cleaning the SEC & in the SCA Perimeter (Table 8)

<table>
<thead>
<tr>
<th>Site</th>
<th>Cleaning</th>
<th>Disinfecting</th>
<th>Sporicide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface of sink</td>
<td>Daily</td>
<td>Daily</td>
<td>Monthly</td>
</tr>
<tr>
<td>Pass-through</td>
<td>Daily</td>
<td>Daily</td>
<td>Monthly</td>
</tr>
<tr>
<td>Work surface</td>
<td>Daily</td>
<td>Daily</td>
<td>Monthly</td>
</tr>
<tr>
<td>Floor</td>
<td>Daily</td>
<td>Daily</td>
<td>Monthly</td>
</tr>
<tr>
<td>Walls, doors</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Storage</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
</tbody>
</table>
Disinfecting the Critical Site

• Specifies sterile 70% IPA and wiping in one direction
• No mention of the type of wiper
  • Prep pads
  • Critical site wiper
• Revision reads as long as wiper is sufficiently wet, it can be used on multiple sites
• The critical site must be dry before puncturing the stopper/septum or breaking the necks of ampules.
Beyond Use Date

• Defined as…
  • Either the date or hour and date after which a CSP must not be used or administration must not begin.
  • The BUD is determined from the date/time that preparation of the CSP is initiated.

• Must be established based on Table 11 and Table 12 in the chapter
• Tables are based on microbial contamination risk, assuming the compound will be physically and chemical stable, and will maintain package integrity
• BUD must not exceed shortest remaining expiration date
## Category 1 Requirements – no change from 2015

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEC placement</td>
<td>Not in ISO classified area</td>
</tr>
<tr>
<td>Sterility Testing</td>
<td>Not required</td>
</tr>
<tr>
<td>Endotoxin Testing</td>
<td>Not required</td>
</tr>
<tr>
<td>BUD</td>
<td>( \leq 12) hours room temperature or ( \leq 24) hours refrigerated</td>
</tr>
</tbody>
</table>
**PEC placement**
Placed in ISO classified air

**Sterility Testing**
Based on BUD Assignment below

**Endotoxin Testing**
Required if nonsterile components

**Storage**
> 12 hour room temperature or > than 24 hours refrigerated

<table>
<thead>
<tr>
<th>BUD Assignment</th>
<th>Method</th>
<th>Sterility Testing</th>
<th>Preservative Added</th>
<th>Controlled Room</th>
<th>Refrigerated</th>
<th>Frozen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptically Prepared CSPs</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Made from 1 or more non sterile components</td>
<td>4 days</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Made with sterile components</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>6 days</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td></td>
<td>Yes (USP 51)</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (USP 51)</td>
<td>42 days</td>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminally Sterilized CSPs</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>14 days</td>
<td>28 days</td>
<td>45 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (USP 51)</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (USP 51)</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (USP 51)</td>
<td>42 days</td>
<td>45 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2015 Proposed Category 2

www.ivpnsymposium.org
PEC placement | Placed in ISO classified air
---|---
Sterility Testing | Based on BUD Assignment below
---|---
Endotoxin Testing | Required if nonsterile components and if assigned a BUD that requires sterility testing
---|---
Storage | > 12 hour room temperature or > than 24 hours refrigerated
---|---

<table>
<thead>
<tr>
<th>BUD Assignment</th>
<th>Method</th>
<th>Sterility Testing</th>
<th>Controlled Room</th>
<th>Refrigerated</th>
<th>Frozen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aseptically Prepared CSPs</td>
<td>No</td>
<td>Made from 1 or more non sterile components</td>
<td>1 days*</td>
<td>4 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Made with sterile components</td>
<td>4 days*</td>
<td>9 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>30 days</td>
<td>45 days</td>
<td>60 days</td>
</tr>
<tr>
<td></td>
<td>Terminally Sterilized CSPs</td>
<td>No</td>
<td>14 days</td>
<td>28 days</td>
<td>45 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>45 days</td>
<td>60 days</td>
<td>60 days</td>
</tr>
</tbody>
</table>

2018 Proposed Category 2
*lowered from 2015 version

www.ivpnsymposium.org
Achieving Sterility

- **Aseptic Preparation**
  - Compounding with only sterile starting ingredient(s), or
  - Compounding with nonsterile ingredient(s) followed by sterilization by filtration

- **Terminal Sterilization**
  - Compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization
  - *CSP sterilized in its final container*
  - The process is intended to achieve an Sterility Assurance Level (SAL) of $10^{-6}$
  - Dry heat, steam, or irradiation
Sterility Testing

- Table 12 indicates whether sterility testing is needed
- Testing done according to USP Chapter <71>
- Deviations from the batch size are now allowed
  - If between 1 and 39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number.
  - If 1 is compounded, 1 additional would be prepared.
- 40 or more in a single batch follows <71>
“By failing to prepare, you are preparing to fail.”

Benjamin Franklin
Polling/ Assessment Questions

All of the following requirements must be completed every 6 months except for…

a. visual observation of hand hygiene and garbing
b. gloved fingertip and thumb sampling
c. media fill testing
d. **demonstration of core competencies**
ISO Class 8 Anteroom requires Air Changes Per Hour (ACPH) of

a. ≥ 20 ACPH
b. ≥ 30 ACPH
c. ≥ 12 ACPH
d. no ACPH requirement
Category 1 CSPs have a beyond-use date (BUD) of 12 hours or less at controlled Room Temperature (RT), while Category 2 CSPs have BUD of greater than 12 at controlled RT.

A. True
B. False
Which of the following is not a cleaning agent?

a. hydrogen peroxide agent  
b. sodium hypochlorite  
c. phenolic agent  
d. quaternary ammonium compound