USP <797> Pharmaceutical Compounding - Sterile Preparations Proposed Revision: Understanding the Impact to Home Infusion

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Disclaimer

Connie Sullivan is presenting this information solely as a representative of NHIA and is not speaking on behalf of USP or the USP Compounding Expert Committee.
Objectives

By the end of this presentation you should be able to:

1. Identify the proposed changes to USP Chapter <797> that will most impact home infusion providers.
2. Understand how to provide comments to USP regarding the proposed revision to Chapter <797>.
What Didn’t Change

- Shift from low, medium, and high risk to Category 1 and Category 2 classification system
- References to USP <800> for hazardous drugs
- Improved organization and flow
- Procedure boxes
Summary of Major Changes

• Revised *Introduction* and *Scope* sections describing when to apply the chapter
• Elimination of “urgent-use” exemption
• Elimination of “in-use” time terminology
• Changes to required frequencies for personnel qualifications and environmental monitoring
• New section specific to allergen extracts
• Removal of radiopharmaceuticals to a separate chapter
Scope of USP <797>

- **Definition of compounding**
  - Combining, admixing, diluting, pooling, reconstituting, repackaging, altering\(^1\)

- **Definition of administration**
  - Direct and immediate application by injecting, infusing, or otherwise providing a sterile medication in its final form\(^1\)
  - Remains outside the scope of <797>
Administration

• New “immediate-use” provision exempts preparation of a conventionally manufactured, non-hazardous, CSP for a single patient when:
  1. Prepared in accordance with the directions in the approved labeling
  2. Administration starts within one hour of beginning preparation
  3. Administration “should” follow the manufacturer or compounders labeling, and “must” follow applicable laws
  4. Aseptic technique must be used
  5. Discard unused starting ingredients unless labeled as a multiple-dose container
Scope of USP <797>

- Broader list of practitioners & settings including, but not limited to:
  - Pharmacists
  - Technicians
  - Nurses
  - Physicians
  - Veterinarians
  - Naturopaths
  - Chiropractors
  - Dentists
CSP Categories

Two categories of CSPs:
  – Category 1
  – Category 2

• Distinguished by environment in which they are made, probability for microbial growth, and time within which they will be used.
Category 1 CSPs

- Maximum BUD of 12 hours RT, 24 hours REF
- Primary Engineering Control (PEC) not required to be located in a classified area
Category 2 CSPs

- BUD > 12 hour RT, > 24 hour REF
- PEC located in ISO 7 (or better)
- Sterility testing required depending on assigned BUD
  - Endotoxin testing if using non-sterile sources
  - See Table 12 in the proposed revision
## Personnel Qualification

<table>
<thead>
<tr>
<th>Activity</th>
<th>Current Standard</th>
<th>2015 Proposed Revision</th>
<th>2018 Proposed Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual observation of hand hygiene and garbing</td>
<td>Annual</td>
<td>Quarterly</td>
<td>6 Months</td>
</tr>
<tr>
<td>Gloved fingertip and thumb testing</td>
<td>Annual*</td>
<td>Quarterly</td>
<td>6 Months</td>
</tr>
<tr>
<td>Media fill</td>
<td>Annual*</td>
<td>Quarterly</td>
<td>6 Months</td>
</tr>
</tbody>
</table>

*For low and medium risk compounding
Personnel Qualification

- More prescriptive minimum requirements for documenting media fill competency
- Calculations included in minimum principle proficiencies
- Competencies must be complete before an employee can compound “independently”
- Initial gloved fingertip testing 3x, in buffer room or SCA, subsequent in PEC after media fill
- Failures in competency testing require a single successful re-test
- Requalification after a gap in compounding extended to 6 months from 3 in prior proposed revision
Garbing

- No electronic devices (headphones, cell phones) not required for compounding
- Requirement for sterile gown or sterile sleeves is removed
- Garb cannot be re-used once you exit the cleanroom
- Garbing order is based on facility SOP
Facility Requirements

- Humidity below 60%
- Temperature 20 degrees or cooler
- Physically separate “rooms” vs. “areas”
- Introduction of cleanroom “suite” terminology
- HEPA filter placement for both ante and buffer room must be in the ceiling
- Returns low on walls unless otherwise verified by a smoke study
- Minimum requirement of 20 ACPH in the ISO 8 area
Facility Requirements

• “Should” minimize dust collecting overhangs, “must” be easily cleaned
• Pass-through doors “should” be interlocking
• No tacky mats in classified areas
• Access doors “should” be hands-free
• Smoke studies “must” demonstrate proper placement of PEC and compounder ability to maintain first air in the direct compounding area
RABS and Isolators

- RABS – must be placed in an ISO 7 area with cleanroom suite configuration for compounding Category 2 CSPs
- Isolators must be placed in ISO 8 air quality to compound Category 2 CSPs
- Placement confirmed by smoke pattern visualization test every 6 months
Certification and Recertification

• Certification requirements apply to classified areas and PEC
• Nonviable air is included in certification section vs. EM
• Frequency remains initial and every 6 months
• Suggested corrective actions for nonviable when action levels are exceeded
Microbiological Air and Surface Monitoring

- New terminology for viable air sampling
- Frequencies changed from 2015 proposed revision

<table>
<thead>
<tr>
<th></th>
<th>Current</th>
<th>2015 Proposed Revision</th>
<th>2018 Proposed Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viable Air</td>
<td>6 Months</td>
<td>Monthly</td>
<td>6 Months</td>
</tr>
<tr>
<td>Surface</td>
<td>Risk based</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
</tbody>
</table>
Action Level Guidance

• Viable air sample action levels revert to current standard
• Surface sampling action levels condensed vs. varied by work surface or non-work surface as proposed in prior draft
  • Surface action levels for ISO 8 or worse changed to >50 cfu/device or swab
• Modified incubation procedures
• Recover to genus level for excursions, “with assistance of a microbiologist”
Cleaning and Disinfecting

• Performed by trained, garbed personnel
• Sporicidal frequency reduced to monthly from weekly in prior proposed revision (currently not required)
• New table for cleaning frequencies is more specific and user friendly
• Requirement for sterile cleaning tools removed
• No corrugated cardboard in classified areas
Master Formulation Records

Required when:
- Preparing batches for multiple patients
- Compounding from non-sterile ingredients
Master Formulation Record

Must include:

– Name, strength or activity, dosage form of CSP
– Identities and amounts of all ingredients
– Type and size of container systems
– Physical description of final preparation
– Complete instructions including equipment, supplies and compounding steps
– BUD and storage requirements
– Reference to support stability
Compounding Records

- Required for all CSPs
- Identity of all individuals involved in the preparation of the CSP
- Provide traceability of all ingredients
- Cross-reference this requirement with Section 15.1 (line 1783)
## Labels

<table>
<thead>
<tr>
<th>Current</th>
<th>2018 Proposed Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient name</td>
<td>Active ingredients and amounts, activities or concentrations</td>
</tr>
<tr>
<td>Amount or concentrations of ingredients</td>
<td>Volume if not obvious from the container</td>
</tr>
<tr>
<td>Volume</td>
<td>Route of admin if not obvious</td>
</tr>
<tr>
<td>Route of administration</td>
<td>BUD</td>
</tr>
<tr>
<td>BUD</td>
<td>Storage conditions if other than RT</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>Date Prepared</td>
</tr>
<tr>
<td></td>
<td>Statement of compounding</td>
</tr>
<tr>
<td></td>
<td>Contact information of compounding facility</td>
</tr>
<tr>
<td></td>
<td>Special handling or warnings</td>
</tr>
<tr>
<td></td>
<td>If the CSP is multi-dose</td>
</tr>
</tbody>
</table>
Beyond Use Dates (BUDs)

- Category 1: Limited to 12 hrs or less RT, 24 hrs or less REF
- Category 2: Depending on the following:
  - Method of preparation
    - Aseptic or terminal sterilization
  - Sterility of starting components
  - Sterility testing performed
  - Presence of preservatives
  - Storage conditions

NHIA
National Home Infusion Association
Summary of Category 2 BUD Changes

<table>
<thead>
<tr>
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<th>Current Standard</th>
<th>2015 Proposed Revision</th>
<th>2018 Proposed Revision</th>
</tr>
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<tbody>
<tr>
<td>Aseptically prepared from one or more non-sterile starting</td>
<td>24 hours (RT)</td>
<td>4 days (RT)</td>
<td>1 day (RT)</td>
</tr>
<tr>
<td>components, no sterility testing</td>
<td>3 days (REF)</td>
<td>7 days (REF)</td>
<td>4 days (REF)</td>
</tr>
<tr>
<td></td>
<td>45 days (FZ)</td>
<td>45 days (FZ)</td>
<td>45 days (FZ)</td>
</tr>
<tr>
<td>Aseptically prepared from only sterile starting components, no</td>
<td>30-48 hours (RT)*</td>
<td>6 days (RT)</td>
<td>4 days (RT)</td>
</tr>
<tr>
<td>sterility testing</td>
<td>9-14 days (REF)*</td>
<td>9 days (REF)</td>
<td>9 days (REF)</td>
</tr>
<tr>
<td></td>
<td>45 days (FZ)</td>
<td>45 days (FZ)</td>
<td>45 days (FZ)</td>
</tr>
<tr>
<td>Aseptically prepared and successful sterility testing</td>
<td>Based on sterility test results.</td>
<td>28 days (RT)</td>
<td>30 days (RT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42 days (REF)</td>
<td>45 days (REF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 days (FZ)</td>
<td>60 days (FZ)</td>
</tr>
<tr>
<td>Terminally sterilized, successful sterility testing**</td>
<td>Based on sterility test results.</td>
<td>28 days (RT)</td>
<td>45 days (RT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42 days (REF)</td>
<td>60 days (REF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 days (FZ)</td>
<td>90 days (FZ)</td>
</tr>
</tbody>
</table>

*Low risk CSPs are 48 hours RT and 14 days REF, medium risk CSPs are 30 hours RT and 9 days REF. **Assumes no preservative present for comparison to the 2015 proposed revision BUDs.
Release Testing

• No requirement to visually inspect against a lighted white background and a black background for particulates

• If a CSP is assigned a BUD that requires sterility testing, then Sterility Testing <71> applies
  • Exception for batch sizes of 1-39 units
  • Batch sizes of 40+ must use Chapter <71> Table 3

• CSPs may be dispensed before the end of the sterility testing period if (prescriber specifically requests dispensing prior to known sterility results) the facility has procedures to:
  1. Notify prescriber of a testing failure
  2. Determine whether a recall is necessary

*Above requirements are moved to Section 15. Quality Assurance and Control
Changes to In-Use Times Section

• Broken into two new sections based on whether the component is a conventionally manufactured product or a CSP
  • Section 13. Use of Conventionally Manufactured Products
  • Section 14. Use of CPSs as Components
Quality Assurance and SOPs

• Much of the detail is removed from these sections
• Refers to <1163> Quality Assurance in Pharmaceutical Compounding
• Note references to a “designated person” throughout the chapter
Allergenic Extracts

New Section 18 applies when:

1. Simple transfers of conventionally manufactured, sterile components
2. Manipulations are limited to penetrating disinfected stoppers to transfer sterile liquids
3. Use sterile syringes and needles to perform compounding
# Summary of CSP Compounding Requirements and BUDs in the 2018 Proposed Revision

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Category 1 - Segregated Compounding Area (SCA)</th>
<th>Category 2 – Cleanroom Suite (ante-room plus buffer room)</th>
<th>Allergenic Extracts – PEC or AECA</th>
</tr>
</thead>
<tbody>
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<td>Visual observation of hand hygiene and garb competency</td>
<td>6 Months</td>
<td>6 Months</td>
<td>Annual</td>
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<td>Gloved fingertip and thumb sampling</td>
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<td>Annual</td>
</tr>
<tr>
<td>Media Fill Testing</td>
<td>6 Months</td>
<td>6 Months</td>
<td>Annual</td>
</tr>
<tr>
<td>PEC Certification</td>
<td>6 Months</td>
<td>6 Months</td>
<td>Annual</td>
</tr>
<tr>
<td>Secondary Engineering Control Certification</td>
<td>Not required</td>
<td>6 Months</td>
<td>6 Months*</td>
</tr>
<tr>
<td>Microbiological (viable) air sampling</td>
<td>6 Months</td>
<td>6 Months</td>
<td>Not required</td>
</tr>
<tr>
<td>Surface sampling</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Not required</td>
</tr>
<tr>
<td>Maximum BUD under refrigeration for a CSP prepared aseptically from sterile starting ingredients, not sterile tested</td>
<td>24 hours</td>
<td>9 days</td>
<td>1 year, or the shortest expiration date of any individual component</td>
</tr>
</tbody>
</table>

*A PEC is optional for allergenic extracts*
Timeline for Submitting Comments

- Official publication in *Pharmacopeial Forum (PF)* is September 4, 2018
- USP Open Mic Session – September 5, 2018
- Comment period closes November 30, 2018
  - Submit comments to USP [http://www.usp.org/compounding/general-chapter-797](http://www.usp.org/compounding/general-chapter-797)
  - Email to connie.sullivan@nhia.org
- Final publication – June 1, 2019
- Effective date – Dec. 1, 2019
References


3. USP. Proposed revisions to Chapter <797>, September 2015. Available at: www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-
Questions?