The Latest and Greatest on USP 797/800 - An Update

Alyssa Donadio
Baptist Hospital of Miami, AlyssaD@baptisthealth.net
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Alyssa Donadio, Pharm.D., BCPS
PGY-2 Oncology Pharmacy Resident
Baptist Hospital of Miami
alyssad@baptisthealth.net
Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.
Objectives

- Review the scope and purpose of USP <797> and USP <800> and identify key differences between the two chapters

- Describe proposed changes to USP <797> and USP <800> as well as timelines for implementation

- Identify challenges that pharmacies may face in implementing the new standards
USP <797> Scope

- Applies to compounded sterile preparations in all settings
- Describes conditions and practices to prevent harm from:
  - Microbial contamination (non-sterility)
  - Excessive bacterial endotoxins
  - Variability in the intended strength of ingredients
  - Unintended physical and chemical contaminants
  - Ingredients of inappropriate quality in compounded sterile products (CSPs)
USP <797> Proposed Major Changes

<table>
<thead>
<tr>
<th>2008 Version</th>
<th>Proposed 2019 Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three risk levels for CSPs</td>
<td>Simplified compounded sterile preparation (CSP) microbial risk levels</td>
</tr>
<tr>
<td>• <strong>Low risk</strong>: aseptic manipulations within ISO 5 or better hoods; combining 3 or less sterile products into a single bag/vial</td>
<td>• <strong>Category 1 CSPs</strong>: shorter beyond-use date (BUD), may be prepared in an unclassified segregated compounding area (SCA)</td>
</tr>
<tr>
<td>• <strong>Medium risk</strong>: combining &gt; 3 commercial sterile drug products and those requiring complex manipulations</td>
<td>• <strong>Category 2 CSPs</strong>: longer BUD, must be prepared in a cleanroom suite (buffer room with ante-room)</td>
</tr>
<tr>
<td>• <strong>High risk</strong>: non-sterile ingredients, lack effective antimicrobial preservatives, sterile surfaces</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Guidance on use of opened or punctured manufactured products and CSPs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2008 Version</th>
<th>Proposed 2019 Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section on “readying for administration”</td>
<td>Scope of chapter excludes administration of medications</td>
</tr>
<tr>
<td>Investigation in the event of:</td>
<td>Emphasis on conducting investigations and implementing corrective actions in specific situations such as:</td>
</tr>
<tr>
<td>• Sterility test failure</td>
<td>• Media fill failure</td>
</tr>
<tr>
<td>• Recovery of colony-forming units during environmental monitoring</td>
<td>• Personnel qualification failure</td>
</tr>
<tr>
<td>• Facility certification failure</td>
<td>• Out-of-specification results on lab tests</td>
</tr>
<tr>
<td></td>
<td>• Quality-control check failures</td>
</tr>
<tr>
<td></td>
<td>• Complaints indicating CSP quality issue</td>
</tr>
<tr>
<td></td>
<td>• Adverse events</td>
</tr>
<tr>
<td>Radiopharmaceuticals as CSPs</td>
<td>Removal of section on radiopharmaceuticals – Refer to General Chapter &lt;825&gt;</td>
</tr>
</tbody>
</table>

## USP <797> Proposed Major Changes

<table>
<thead>
<tr>
<th>2008 Version</th>
<th>Proposed 2019 Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anti-neoplastics shall not be prepared as immediate-use CSPs</td>
<td>Removal of information related to handling of hazardous drugs – Refer to General Chapter &lt;800&gt;</td>
</tr>
<tr>
<td>• All personnel who compound hazardous drugs shall be fully trained in the storage, handling, and disposal of these drugs – annual verification</td>
<td></td>
</tr>
<tr>
<td>• Storage <em>preferably</em> within a containment area such as a negative pressure</td>
<td></td>
</tr>
<tr>
<td>• Facilities that prepare a “low volume” of HDs may compound in a non-negative pressure room with “two tiers of containment”</td>
<td></td>
</tr>
</tbody>
</table>
USP <800> Scope

- **Purpose:**
  - Describe practice and quality standards for handling hazardous drugs in healthcare settings and help promote patient safety, worker safety, and environmental protection.

- Applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs.

- Applies to both sterile and nonsterile products.
Who is at Risk?

Anyone handling hazardous drugs is at risk of exposure.

- Pharmacists
- Pharmacy Technicians
- Nurses
- Physicians
- Surgeons
- Physician Assistants
- Respiratory Therapists
- Home Health Aides
- Nurses’ Aides
- Housekeeping
- Janitorial Services
- Environmental Services
- Veterinarians
- Veterinarian Technicians
- Veterinarian Assistants

### Hazardous Drug Definitions

<table>
<thead>
<tr>
<th>NIOSH</th>
<th>ASHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenicity</td>
<td>Carcinogenicity in animal models, in the patient population, or in both</td>
</tr>
<tr>
<td>Teratogenicity or developmental toxicity</td>
<td>Teratogenicity in animal studies or in treated patients</td>
</tr>
<tr>
<td>Reproductive toxicity</td>
<td>Fertility impairment in animal studies or in treated patients</td>
</tr>
<tr>
<td>Organ toxicity at low doses</td>
<td>Evidence of serious organ or other toxicity at low doses in animal models or in treated patients</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems)</td>
</tr>
<tr>
<td>Structure and toxicity profile of new drugs that mimic existing drugs determined by hazardous criteria above</td>
<td></td>
</tr>
</tbody>
</table>

History of Hazardous Drug Guidance

- **1983-84** - ASHP Practice Spotlight: safe handling of cytotoxic drugs
- **2004** - NIOSH Alert
- **2006** - ASHP Guidelines on Handling Hazardous Drugs
- **2008** - USP 797 revision in 2008 to harmonize with NIOSH 2004 alert
- **2010** - NIOSH list of antineoplastic and hazardous drugs
- **2016** - USP Chapter 800 Hazardous Drugs—Handling in Healthcare Settings
NIOSH List

National Institute for Occupational Safety and Health

3 groups of drugs:

- **Group 1**: Antineoplastic drugs
- **Group 2**: Non-antineoplastic drugs that meet *one or more of the NIOSH criteria* for a hazardous drug
- **Group 3**: Reproductive risk

Updated every 2 years
Hazardous Drugs List

- Institution-specific HD list must be maintained and reviewed **annually**
- Assessment of new drugs
- Classify investigational agents based on mechanism of action
- Re-categorization as new toxicologic information becomes available
- Consider dosage form
Exposure Risk Points

Managing Waste
Receiving
Cleaning
Transport
Storing
Compounding
Disposal
Dispensing
Spills
Patient Care
Administering

HD Receipt

- Receive HD in sealed, impervious plastic wrap
- Handle with chemotherapy gloves
- Open in neutral or negative-pressure non-sterile area
- Immediately deliver to HD storage area
HD Storage

- HDs **must** be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH)
- Designated hazardous drug sign displayed
- Restricted access
- Antineoplastic HD requiring further manipulation stored separately
  - Dedicated storage refrigerator
- Sterile and non-sterile HD can be stored together

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
HD Sterile Compounding

- **Containment Primary Engineering Control (C-PEC)**
  - Externally vented
  - ISO Class 5 or better air quality
  - Biological safety cabinet (BSC)
    - Class II
    - Lined with plastic-backed mat
  - Compounding Aseptic Containment Isolator (CACI)

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
Biological safety cabinet (BSC) II

Class II, Type B1
Air In-flow 30% Recirculated vs. 70% Exhausted

- HEPA Filtered Air
- Contaminated Worksurface Air
- Contaminated Room Air
HD Sterile Compounding

- **Containment Secondary Engineering Control (C-SEC)**
  - Externally vented
  - ISO Class 7 or better air quality
  - Negative pressure
  - HEPA filter
    - 12 or 30 ACPH

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
HD Sterile Compounding

- Closed-System Transfer Devices (CSTD)
HD Non-sterile Compounding

- **Containment Primary Engineering Control (C-PEC)**
  - Externally vented or redundant HEPA filtered
  - Biological safety cabinet (BSC) class I or II
  - CACI
  - Containment ventilated enclosure (CVE)

- **Containment Secondary Engineering Control (C-SEC)**
  - Externally vented
  - Negative pressure
  - HEPA filter - 12 ACPH
Environmental Quality and Control

Environmental wipe studies for HDs should be performed routinely at least every 6 months.

Surface wipe sampling should include:

- C-PEC and equipment
- Staging or work areas near C-PEC/pass-through
- Areas adjacent to C-PECs (floors)
- Areas outside of buffer room and patient administration areas

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
Personal Protective Equipment (PPE)

- Protection, reduce exposure to HDs aerosolization and drug residue

- **Handling all HDs**: gloves

- **Compounding HDs**: gowns, gloves, head, hair, and double shoe covers
  - Double gloves for sterile compounding

- **Administering injectable HDs**: gloves and gowns
Personal Protective Equipment (PPE)

- **Spills, cleaning under C-PEC work surface, suspected airborne HD exposure:**
  - Chemical cartridge type respirator or powered air-purifying respirator (PAPR)

- **Other activities requiring respiratory protection:**
  - N95 respirator
  - No protection vs. gases/vapors and little protection vs. direct liquid splashes
Hazard Communication Plan

- Institutions must establish policies and procedures for **all aspects** of HD handling

- **Elements of the plan:**
  - **Written plan** on how the standard will be implemented
  - All containers of hazardous chemicals shall be **labeled, tagged, or marked** with identity of the material and appropriate hazard warnings
  - **Safety Data Sheets (SDS)** must be maintained for all hazardous chemical used and accessible to staff
  - **Training program** for staff with potential for exposure
  - Personnel of reproductive capability confirm in writing that they understand **risks** of handling HDs

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
Personnel Training

- Training prior to employee independently handling HDs and reassessed annually

- Must include:
  - Overview of the institution’s list of HDs
  - Review of SOPs related to handling of HDs
  - Proper use of PPE and equipment/devices
  - Spill management
  - Response to known or suspected HD exposure
  - Proper disposal of HDs
Labeling/Packaging/Transport

- **Labeling**: HDs must be labeled as such
- **Packaging**: Use containers to maintain physical integrity, stability and sterility during transport
- **Transport**:
  - Use containers that minimize the risk of breakage/leakage
  - Never use pneumatic tubes to transport antineoplastic HDs
HD Dispensing

- HDs not requiring further manipulation may be dispensed without further requirements for containment, *unless*:
  - Required by manufacturer
  - Visual indicators of HD exposure

- Segregate equipment used for dispensing activities for HD
HD Administration

- HDs must be administered safely using protective medical devices and techniques
- Appropriate PPE worn when administering HDs and disposed properly
- CSTDs must be used for administration of antineoplastic HDs when dosage form allows
- Avoid manipulating HD dosage forms when possible

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
### Deactivating, Decontaminating, Cleaning, Disinfecting

<table>
<thead>
<tr>
<th>Process</th>
<th>Description</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deactivation</td>
<td>Inactivation of HD compounds</td>
<td>Sodium hypochlorite (Bleach)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peroxide</td>
</tr>
<tr>
<td>Decontamination</td>
<td>Physically remove inactivated particles</td>
<td>Sodium hypochlorite (Bleach)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peroxide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Removal of organic/inorganic material</td>
<td>Germicidal detergent</td>
</tr>
<tr>
<td>Disinfection</td>
<td>Inhibit/destroy microorganisms</td>
<td>Sterile alcohol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disinfectant</td>
</tr>
</tbody>
</table>
HD Spills

- Training about proper spill kit use
- SOPs required for spill prevention and cleanup procedures (including use of PPE and respirators)
- Document circumstances of spill
- Immediate medical evaluation for potentially exposed personnel
- Non-employees exposed should report to ED for evaluation

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
HD Disposal

- **Bulk Hazardous Drug Waste**
  - >3% of the capacity of the container
  - Chemotherapy vials (empty or partially full), syringes, materials used to clean

- **Trace-Contaminated Waste**
  - Minimal drug (<3% total capacity)
  - Gowns, gloves, gauze, masks
  - May be incinerated at medical regulated waste facility

- **Sharps**
  - Needles, ampules, syringes

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
Medical Surveillance Program

- Should have the following elements:
  - Baseline assessment of worker’s health and medical history
  - Estimate of workers HD exposure over time
  - Monitoring of organ function at risk for toxicity from HD exposure
  - Follow-up plan for acute and long-term exposure to HDs
## Old vs. New HD Standards

<table>
<thead>
<tr>
<th>2008 Version USP &lt;797&gt;</th>
<th>USP &lt;800&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Storage</strong> <em>preferably</em> within a containment area such as a negative pressure</td>
<td><strong>HDs</strong> <em>must</em> be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH)</td>
</tr>
</tbody>
</table>
| Facilities that prepare a *“low volume”* of HDs may compound in a non-negative pressure room with *“two tiers of containment”* | All facilities that prepare HDs must have a containment secondary engineering control (C-SEC)  
  • Must be externally vented, physically separated, have appropriate air exchange, and have a negative pressure |

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
## Old vs. New HD Standards

<table>
<thead>
<tr>
<th>2008 Version USP &lt;797&gt;</th>
<th>USP &lt;800&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only allows low-risk non-HD Compounded Sterile Preparations (CSPs) with 12 hour or less beyond-use date (BUD) to be prepared in an unclassified segregated compounding area (SCA)</td>
<td>Allows low and medium risk HD CSPs to be prepared in an unclassified containment segregated compounding area (C-SCA)</td>
</tr>
<tr>
<td></td>
<td>• C-SCA required to have fixed walls, be externally vented with 30 ACPH and have negative pressure</td>
</tr>
</tbody>
</table>

*Note differences in terminology and requirements in the SCA in USP <797> and C-SCA in <800>*

USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings
USP Timeline for General Chapter Revisions

- **Public Comment <795>**
  - **March 30, 2018**: Web pre-posting *5/1 publication in Pharmacopeial Forum*
  - **April 20, 2018**: Open Microphone Session
  - **July 31, 2018**: Close of public comment

- **February 2016 <800>**
  - Publication USP-NF

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

- **Sept 5, 2018**: Open Microphone Session

- **Nov 30, 2018**: Close of public comment

- **June 1, 2019 <795>**
  - Intended Publication USP-NF

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

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

Financial/physical plant
- New equipment
- Facility design changes
- Separation of hazardous/non-hazardous compounding
- Storage

Time
- Documentation
- More frequent environmental sampling
Potential Challenges

- Staff training/education
- Lack of evidence
  - Recommendations based on expert panel opinions
- Impact on low volume sites
  - Outpatient clinics, physician offices, etc.
FIGURE 7
Primary Challenge to Achieving USP Compliance

Once again, hospitals find financial restrictions and physical plant limitations to be the top challenges to achieving compliance with the USP compounding chapters.

- Financial/budgetary restrictions: 35%
- Physical plant limitations: 28%
- Time commitment: 10%
- Training resources: 9%
- C-suite lack of knowledge: 6%
- C-suite lack of support: 3%
- Staff resistance to change: 3%
- Other: 5%

## Compliance Rates for General Facility Design

While pharmacy has had some success in eliminating nonessential items and personnel from the compounding area, a variety of design challenges remain.

<table>
<thead>
<tr>
<th>Compliance Rate</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceiling panels are impervious and hydrophobic; caulked around the perimeter of each to seal to frame</td>
<td>44%</td>
</tr>
<tr>
<td>Sink in anteroom (AR) is equipped with hands-free controls for water and soap dispensing</td>
<td>56%</td>
</tr>
<tr>
<td>A line of demarcation in the ante-area or SCA separates the dirty area from the clean area*</td>
<td>56%</td>
</tr>
<tr>
<td>Furniture, equipment, and plant surfaces are smooth and cleanable</td>
<td>68%</td>
</tr>
<tr>
<td>Walls are solid surface or locking panels and are impervious, cleanable, and nonshedding</td>
<td>74%</td>
</tr>
<tr>
<td>Floors are cleanable (heat-sealed wide sheet vinyl or other solid surface) and molding is coved</td>
<td>74%</td>
</tr>
<tr>
<td>Climate of buffer and anterooms is conducive to comfort (ie, 68°+/-)</td>
<td>83%</td>
</tr>
<tr>
<td>No sink drain or water in the buffer room</td>
<td>84%</td>
</tr>
<tr>
<td>Furniture, equipment, and supplies in the buffer room, AR, or SCA are limited to those essential for compounding-related activities</td>
<td>85%</td>
</tr>
<tr>
<td>Access to compounding areas is limited to those performing compounding-related activities</td>
<td>88%</td>
</tr>
</tbody>
</table>

*SCA=segregated compounding area
## TABLE 7

**Environmental Sampling Compliance Rates**

While overall environmental sampling is at 80%, rates for surface sampling are particularly low.

<table>
<thead>
<tr>
<th>Environmental Sampling Compliance</th>
<th>Compliance Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Sampling</td>
<td>74%</td>
</tr>
<tr>
<td>General Viable Air Sampling and Surface Sampling Considerations</td>
<td>75%</td>
</tr>
<tr>
<td>Environmental Sampling Program</td>
<td>77%</td>
</tr>
<tr>
<td>Incubation</td>
<td>77%</td>
</tr>
<tr>
<td>Viable Air Sampling</td>
<td>85%</td>
</tr>
<tr>
<td>Non-Viable Particle Testing</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Total Environmental Monitoring Compliance</strong></td>
<td><strong>80%</strong></td>
</tr>
</tbody>
</table>

### TABLE 8

**Personnel Garbing and Sampling Compliance Rates**
Compliance with gloved fingertip sampling requirements has yet to pass the three-quarter mark.

<table>
<thead>
<tr>
<th></th>
<th>Compliance Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gloved Fingertip Sampling</td>
<td>73%</td>
</tr>
<tr>
<td>Hand Washing and Garbing</td>
<td>83%</td>
</tr>
<tr>
<td>Personnel Media-Fill Challenge Testing</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Total Garbing and Sampling Compliance</strong></td>
<td><strong>82%</strong></td>
</tr>
</tbody>
</table>
FIGURE 10
Compliance with Written SOPs for Equipment Management

Only 58% of hospitals have written SOPs for equipment maintenance, calibration, and cleaning. To be effective, this equipment must be used properly; when used incorrectly, compounding equipment has been proven to have a negative impact on patient safety.

Key
- 90% and up
- 85%-89%
- 75%-84%
- 60%-74%
- Up to 59%
- No relevant data received

Alaska, Hawaii, Puerto Rico insets are not to scale

**Self-Assessment**

- **True/False:** USP <800> applies only to the compounding of sterile hazardous drugs

- **True/False:** USP <797> and USP <800> updates are anticipated to become official on December 1, 2019

- **True/False:** The most common challenge to achieving USP compliance has been identified to be financial restrictions
Summary

- USP 797 sets sterile compounding standards vs. USP 800 sets hazardous drug handling standards
- Updated versions will be enforceable December 1, 2019
- Institutions should determine readiness to meet standards early
- Some standards will require significant investment of time and money
References

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