Review of requirements for sterile compounding - USP 797 and 800

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Objectives

- **Objectives for the Pharmacists:**
  - Describe the differences in the requirements for USP 797 and USP 800
  - Summarize the key concerns for non-compliance to hazardous drugs requirements
  - Discuss action plans to ensure compliance with the updated recommendations in USP 800

- **Objectives for the technicians:**
  - Discuss the types of exposure and responsibilities of personnel handling hazardous drugs
  - List the changes in the risk categories of compounded sterile preparations
  - Identify requirements for personal protective equipment for Personnel

Disclosure

- Speaker has no disclosure

Introduction

- The United States Pharmacopeia (USP) convention:
  - Non-profit scientific organization
  - Provides public with quality standards regarding drugs, excipients and supplements
  - Standards originate from sponsors, undergoes public comments, revised and approved by expert committee
  - USP is not an enforcing body
  - Standards are enforceable by other agencies
Introduction

- Enforcing Bodies:
  - Mandate compliance with USP general chapters
  - Mandates compliance with USP to ensure compounded products are not adulterated
  - Does not survey for compliance with USP standards but USP could be used to prepare for TJC survey

USP <1160> Pharmaceutical Calculations in Prescription Compounding
USP <1163> Quality Assurance in Pharmaceutical Compounding
USP <1176> Prescription Balances & Volumetric Apparatus
USP <795> Pharmaceutical Compounding Non-sterile Preparations
USP <797> Pharmaceutical Compounding Sterile Preparations
USP <800> Hazardous Drugs: Handling in Health Care Settings

USP <797>
Standards for Pharmaceutical Compounding Sterile Preparations (CSPs)

USP <797>

- Definition of Compounded Sterile Products (CSP):
  - Prepared according to the manufacturer’s labeled instructions and other manipulations that expose contents to potential contamination
  - Containing nonsterile ingredients or employ nonsterile components or devices that must be sterilized before administration
USP <797>: Scope

- Injections
- Aqueous bronchial inhalations
- Baths and soaks for live organs and tissues
- Irrigations for internal body cavities (i.e., any space that does not freely communicate with the environment outside of the body)
- Ophthalmics
- Implants

USP <797>: Goal

- To prevent potential patient harm or death that could result from:
  - Microbial contamination (Non-sterility)
  - Excessive bacterial endotoxins
  - Chemical and physical contaminants
  - Large content errors in the strength of correct ingredients
  - Incorrect ingredients

Briefing of Proposed Changes

- Reorganized, redundancies eliminated, and requirements clarified
- New terminology
  - Primary Engineering Controls
  - Risk Levels
- Increased frequency for personnel and environmental monitoring
- Changes in establishing beyond-use dates
- Requirements for handling hazardous drugs removed and cross-references added to USP <800>

Definitions

- **In-use time**: The time before which a conventionally manufactured product or a CSP must be used after it has been opened or needle punctured
- **Beyond Use Dates**: included on the label of each CSP to indicate the date or date and hour after which the CSP must not be used, because its required quality characteristics cannot be ensured
  - Term “expiration date” is not appropriate
Definitions and Practice Issues

- Proprietary vial/bag systems
  - Docked and immediately administered → a function of medication administration
  - Docked in batches for future activation → <797> applies

- Reconstitution and dilution
  - For one patient for immediate administration → a function of medication administration
  - Batched → <797> applies

- Repackaging → <797> applies

Personnel Qualifications

Training, Qualification and requalification:

- Greatest risk of contamination: failure of personnel in following quality standards
- All personnel involved in compounding must undergo training and annual refreshers
- All trainings qualifications and re-qualifications must be documented
- Supervisors of compounding personnel should observe compounding activities on a daily basis and take immediate corrective action if deficient practices are observed

Personnel Qualifications - Core Competencies

- Hand hygiene and garbing
- Cleaning and disinfection
- Measuring and mixing
- Aseptic manipulation
- Proper cleanroom behavior
- Methods of sterilization and depyrogenation, if applicable
- Use of equipment
- Documentation of the compounding process (e.g., master formulation and compounding records)
- Understanding the direction of the HEPA-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of PECs
- The potential impact of personnel activities such as moving materials into and out of the compounding area

Personnel Qualifications

<table>
<thead>
<tr>
<th>Personnel Qualifications</th>
<th>Current &lt;797&gt; Qualifications</th>
<th>Proposed Qualification</th>
</tr>
</thead>
</table>
| Media fill testing       | • Annually if only low/medium risk compounded
                          | • Semiannually if high risk compounded | • Quarterly

Retrain and re-qualify personnel:

- After a change in cleaning and disinfecting procedures
- After a pause in compounding: Personnel who have not compounded CSPs in more than 3 months must be re-qualified in all core competencies before resuming compounding duties
Buildings and Facilities

• Buildings and facilities used in compounding must be designed to prevent airborne contamination of the area in which sterile compounding occurs.

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Particle Count./m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>35.2</td>
</tr>
<tr>
<td>4</td>
<td>352</td>
</tr>
<tr>
<td>5</td>
<td>3,520</td>
</tr>
<tr>
<td>6</td>
<td>35,200</td>
</tr>
<tr>
<td>7</td>
<td>352,000</td>
</tr>
<tr>
<td>8</td>
<td>3,520,000</td>
</tr>
</tbody>
</table>

Limits for number of particles ≥0.5 μm measured under typical operating conditions.

Primary Engineering Controls (PECs)

• Laminar Air Flow Systems
  – Laminar Air Flow Workbenches
  – Laminar Air Flow Zones
  – Biological Safety Cabinets (BSC)

• Restricted Access Barrier Systems (RABS)
  – Compounding aseptic isolator (CAI)
  – Compounding aseptic containment isolator (CACI)

• Isolators
  – Transfer ports
  – Sporicidal chemical decontamination
  – Constant overpressure requirement

Buildings and Facilities

• DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY:

<table>
<thead>
<tr>
<th>Classified Areas</th>
<th>Operations Performed</th>
<th>Minimum ISO Class Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ante Areas</td>
<td>Hand hygiene and garbing procedures, staging of components, order entry and CSP Handling</td>
<td>ISO Class 8 Standards</td>
</tr>
<tr>
<td>Buffer Room</td>
<td></td>
<td>ISO Class 7 Standards</td>
</tr>
<tr>
<td>Compounding Room</td>
<td>Intended for CSP Preparation</td>
<td>ISO Class 5 Standards</td>
</tr>
</tbody>
</table>

Facility Design and Environmental Controls

• Well Lit
• The room must be maintained at a temperature of 20° or Cooler
• Humidity below 60% at all times

Temperature and humidity must be controlled through an efficient heating, ventilation, and air conditioning (HVAC) system.
### Environmental Monitoring

<table>
<thead>
<tr>
<th>Environmental Sampling</th>
<th>Current Frequency</th>
<th>Proposed Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonviable air sampling</td>
<td>Every six months</td>
<td>Every six months</td>
</tr>
<tr>
<td>Viable air sampling</td>
<td>Every six months</td>
<td>Monthly</td>
</tr>
<tr>
<td>Surface sampling</td>
<td>Periodic</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

### Secondary Engineering Controls

**Category 1 CSPs**
- Segregated Compounding Area (SCA)

**Category 2 CSPs**
- Positive pressure buffer room with access through a positive pressure anteroom
- To meet Category 2 requirements, the PEC must be in an ISO Class 7 area

### Establishing Beyond-Use Dates (BUDs)

Changes in BUDs are based on increasing the frequency of monitoring personnel and the environment:

1. Aseptically-prepared or terminally-sterilized?
2. Sterility test performed?
3. Preservative added?
4. Only sterile components or any nonsterile component?
5. Storage temperature
   - A. Controlled Room Temperature
   - B. Refrigerator
   - C. Freezer

### Beyond-Use Dates (BUDs)

<table>
<thead>
<tr>
<th>Facility Design</th>
<th>Current &lt;797&gt; BUDs</th>
<th>Proposed &lt;797&gt; BUDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segregated Compounding Area</td>
<td>12 hours</td>
<td>Room Temp – 12 hours Refrigerated – 24 hours</td>
</tr>
<tr>
<td>Cleanroom (aseptically prepared, no sterility testing, no preservatives)</td>
<td>Room Temp – 48 hours Refrigerated – 14 days</td>
<td>From sterile components only: Room Temp – 6 days Refrigerated – 9 days</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Room Temp – 30 hours Refrigerated – 9 days</td>
<td></td>
</tr>
<tr>
<td>Med Risk</td>
<td>Room Temp – 24 hours Refrigerated – 3 days</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>Room Temp – 24 hours Refrigerated – 3 days</td>
<td>From any nonsterile component: Room Temp – 4 days Refrigerated – 7 days Endotoxin testing</td>
</tr>
</tbody>
</table>
Summary USP <797>
- Change from three risk levels (low, medium, and high) based on the components and processes to categories based on the facility type and BUD assignment
- Increased monitoring frequency of personnel and environment
- Stratified BUD assignment

Introduction
- What are Hazardous Drugs?
  - Organ toxicity at low doses in humans or animals
  - Carcinogenicity
  - Genotoxicity
  - Teratogenicity or developmental toxicity
  - Reproductive toxicity in humans
  - New drugs that mimic existing hazardous drugs

USP <800>
Hazardous Drugs Handling in Healthcare Settings

Introduction
- Current Hazardous Drug References
  - American Society of Health-System Pharmacists
  - National Institute for Occupational Safety and Health (NIOSH)
  - Occupational Safety and Health Administration (OSHA)
  - Oncology Nursing Society (ONS)
  - US Pharmacopeia (USP)
Introduction

NIOSH List

- Not all drugs on NIOSH list are hazardous
- Some dosage forms defined as hazardous may not pose a significant risk of direct occupational exposure because of their dosage formulation (coated tablets, capsules)

USP <800> Bottom Line

- Comprehensive approach to prevent exposure to
  - Personnel
  - Environment

Introduction

Objectives of USP Chapter <797>

1. Protect personnel and the environment
2. Includes, but not limited to receipt, storage, mixing, preparing, compounding, dispensing, administering, disposing, and otherwise altering, counting, crushing, or pouring HDs
3. Includes both non-sterile and sterile products and preparations
4. Standards apply to all personnel who compound HDs preparations and all places where HDs are prepared, stored, transported, and administered

Introduction

Entity Requirements

- Engineering controls
- Compounding Supervisor
- Competent personnel
- Robust work practices
- Availability of appropriate Personal Protective Equipment (PPE)
- Medical surveillance program
**Containment and Engineering Controls**

- **Containment Primary Engineering Control (C-PEC)**
  - Externally vented

- **Containment Secondary Engineering Control**
  - Separate room
  - Externally vented
  - Negative pressure
  - Appropriate air changes per hour

**Compounding Supervisor**

- Designated individual
- Develops and implements appropriate procedures
- Oversees facility compliance with this chapter and other applicable laws, regulations, and standards
- Ensures competency of personnel
- Assures environmental control of the compounding areas
- Must be knowledgeable about the standards

**Receiving HDs**

- Antineoplastic HDs must be unpacked in an area that is neutral/normal or negative pressure relative to the surrounding areas.

- HDs must not be unpacked from their shipping containers in sterile compounding areas or in positive pressure areas.
Storage of HDs

- Must be stored separately from non-HDs (USP <797)
- Restricted access storage room must be:
  - negative pressure
  - externally vented
  - have at least 12 air changes per hour
- Injectable HDs may be stored in negative-pressure buffer room used for sterile preparations if all particle generating packaging is removed prior to storing
- Refrigerated antineoplastic must be stored in a HD-dedicated refrigerator

Compounding HDs

- Must be performed in a containment primary engineering control (C-PEC)
  - Within a separate room that provides personnel protection
  - A restricted-access room under negative pressure
  - Externally vented
  - Has an appropriate number of air changes per hour based on the type of compounding and the C-PEC in which it is being done
  - Applies to sterile and non-sterile compounding

Compounding HDs

- C-PECs include:
  - Containment ventilated enclosures (commonly called a powder hood)
  - Class I biological safety cabinets (BSC)
  - Class II BSC dedicated to use for non-sterile compounding.
- Allows occasional use of the sterile designated C-PEC provided mitigating steps are taken to safely return the use of the BSC or compounding aseptic containment isolator (CACI) to sterile compounding.
- <800> removed exemption that permitted low-volume sterile compounding sites to use a BSC or CACI in a positive pressure room.

Compounding HDs

- However, a containment segregated compounding area (C-SCA) can be created.
  - Currently not allowed by <797>, but a BSC can be placed in the C-SCA if a facility meets these criteria:
  - Prepares only low- to medium-risk HD compounded sterile preparations
  - Finds a limit of a 12-hour beyond-use time acceptable
Three Possible Designs for Compounding HDs

<table>
<thead>
<tr>
<th>Function</th>
<th>Containment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEC</td>
<td>Area</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Compounding Sterile HD in a cleanroom</td>
<td>BSC or CACI</td>
</tr>
<tr>
<td>Compounding Sterile HD in a CACI that meets the requirements of &lt;797&gt;</td>
<td>CACI</td>
</tr>
<tr>
<td>Compounding medium or low risk sterile HD in a BSC</td>
<td>BSC</td>
</tr>
</tbody>
</table>

Administering HDs

- <800> extends consideration to all personnel in healthcare settings, including HD administration.
- Use of closed-system drug transfer devices (CSTDs) are supplemental engineering controls are required during HD administration and recommended for compounding processes.

Dispensing HDs

- Oral and topical HDs must be in unit-dose or unit-of-use packaging that do not require any manipulation other than counting before delivery to the patient.
- If the healthcare facility’s policies permit, non-antineoplastic HDs that require only transfers from the manufacturer’s package to a prescription container may be dispensed without any further requirement for containment unless required by the manufacturer.

Personal Protective Equipment

- Gloves
  - ASTM-tested chemotherapy gloves
  - Sterile gloves for sterile HD CSPs
- Gowns (Impervious)
- Head, hair, and sleeve covers
- Eye and face protection
- Respiratory protection
Take home points

• Become familiar with requirements of USP Chapter <797> and <800>
• Update the list of hazardous drugs in your facility
• Evaluate facility designs
• Review PPE used
• Review and reemphasize policies

Self-Assessment Questions

• Primary Engineering control (Chemo Hoods) used for preparation of sterile antineoplastic compounded sterile preparations must be placed in a room that has
  a. Positive pressure to surrounding areas
  b. Negative pressure to surrounding areas
  c. Neutral or normal pressure to surrounding areas
  d. Placement is not defined in proposed USP General Chapter <800>

Self-Assessment Questions

• Proposed USP General Chapter <800>
  a. Replaces USP Chapter <795>
  b. Replaces USP Chapter <797>
  c. Replaces USP Chapter <795> and <797>
  d. Supplements USP chapters <795> and <797>

References

• Proposed changes to USP chapter <797>: http://www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision [accessed on January 12, 2016]
• ASHP guidelines on compounding sterile preparations. AM J Health-Sys Pharm. 2014; 71 (2): 145-166
Questions