Navigating the Regulatory Tides of Compounding

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Learning Objectives

• At the conclusion of this program, the participant will be able to:
  – Interpret current and proposed USP chapters and U.S. Food and Drug Administration guidance that affect the compounding of sterile preparations.
  – Explain the role that the National Association of Boards of Pharmacies has taken in health-system pharmacy topics (i.e., Verified Pharmacy Program, Verified Accredited Wholesale Distributors, etc).
  – Evaluate examples of common findings in health-system pharmacy surveys.
NABP VPP Inspections Review the Pharmacy’s Compounding Compliance With:

A. FDA Good Manufacturing Practices (GMPs)
B. USP Chapter <795>
C. USP Chapters <795> and <797>
D. USP Chapters <795> and <797>, and FDA current GMPs
USP Chapter <800> and the Proposed Changes to USP Chapter <797>:

A. Are the same in regard to risk levels
B. Apply only to sterile compounding
C. Both effective July 1, 2018
D. Handling of hazardous drugs (HDs) is removed from Chapter <797>, cross-referenced to Chapter <800>
VPP Inspections at Institutions Revealed That This Area Has the Highest Number of Findings:

A. Environment
B. Garbing
C. Finished product release checks and tests
D. Cleaning
VPP Process: Application to Completion

*Represents an average applicant and depends on application completion and pharmacy practices

** May be extended due to excessive blackout dates provided by pharmacy
NABP VPP Inspection

• Information and comments obtained in the nonsterile and sterile compounding inspections are based on USP Chapters <795> and <797>.

• Inspections against current Good Manufacturing Practices (cGMPs) are not conducted.

• There may be some overlap in concepts.
What Types of Pharmacies Are We Inspecting?

Types of Pharmacies Inspected in 2017

- Nonsterile Compounding Facility: 25%
- Sterile Compounding Facility: 20%
- NS/Sterile Compounding Facility: 39%
- Nuclear Pharmacy: 5%
- Outsourcing Facility: 1%
Number of Inspections

Through September 1, 2017 – 757 Inspections Performed

- 2013-2014: 205
- 2015: 148
- 2016: 215
- 2017: 189
FDA Guidance Documents

FDA Guidance Documents

FDA Report

Human Drug Compounding Progress Report – January 2017

FDA seeks to strike a balance between preserving access to lawfully marketed compounded drugs for patients who have a medical need for them while protecting patients from risks associated with compounded drugs that are not produced in accordance with the applicable requirements of federal law.
When Will the New USP Chapter <797> Be Released?

• New chapter coming . . . most likely in 2020.
• There currently is another round of responses to questions/concerns being received and evaluated by the expert committee.
• Additionally, Chapter <800> has the same categories as the current Chapter <797>, and a new update would have to follow its release.
Several Proposed Changes to USP Chapter <797>

- Current three risk levels changed to two (distinguished by conditions under which they are made and time within use).
- Quarterly requirement for personnel monitoring (visual observation of hand hygiene and garbing, media fill tests, and gloved fingertip samples).
Several Proposed Changes to USP Chapter <797>

• Beyond-use date (BUD) and storage times changes
• Master formulation and compounding records required for all batch and nonsterile compounding
• New placement requirements on use of isolators
• Removal of HDs handling – cross-reference to USP Chapter <800>
Several Proposed Changes to USP Chapter <797>

- Monthly requirement for viable air and surface sampling
- Introduction and definition of “in-use time”
- New guidance for sterility testing of compounded sterile preparations prepared in batch sizes of less than 40
History of USP Chapter <800>

• The chapter was developed by the USP Compounding Expert Committee with the assistance of the USP Compounding with Hazardous Drugs Expert Panel and government liaisons from FDA and the US Centers for Disease Control and Prevention, including the National Institute for Occupational Safety and Health (NIOSH).

• The chapter was published for the first time for public comment in March 2014.

• Based on the public comments received, the chapter was revised and proposed for another round of public comments in December 2014.

• The chapter was revised again and published in the United States Pharmacopeia and the National Formulary (USP–NF) in February 2016.
Status of USP Chapter <800>

• USP General Chapter <800> was published on February 1, 2016, in the First Supplement to USP 39–NF 34.
• The USP Compounding Expert Committee approved a delayed official implementation date of July 1, 2018.
• This delay allows entities more than two years from publication to implement the new standard.
Purpose of USP Chapter <800>

• Describe the practice and quality standards for handling HDs in health care settings to minimize exposure.

• Goal is to help promote:
  – Patient safety
  – Worker safety
  – Environmental protection
Application of USP Chapter <800>

- Applies to all health care personnel
- Applies to all health care facilities
  - Receipt
  - Storage
  - Preparation
  - Transport
  - Administration
  - Disposal
- Applies to sterile and nonsterile HD products (commercially available) and preparations (compounded)
## Major Differences Between USP Chapters <797> and <800>

<table>
<thead>
<tr>
<th>Chapter &lt;797&gt;</th>
<th>Chapter &lt;800&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applies to sterile compounding only</td>
<td>Applies to sterile and nonsterile compounding</td>
</tr>
<tr>
<td>From receipt of inventory up to drug administration</td>
<td>From receipt of inventory through disposal</td>
</tr>
<tr>
<td>All HDs must be stored separately in area with 12 air changes per hour (ACPH) and 0.01” w.c. negative to the adjacent space</td>
<td>Antineoplastic HDs must be stored separately from non-HDs in an area with 12 ACPH and 0.01” w.c. negative to the adjacent space <strong>unless</strong> coated, final-manufactured dosage forms are clearly labeled as HDs and safety strategies are detailed in policies and procedures</td>
</tr>
<tr>
<td>Exemption for low volume compounding</td>
<td><strong>No</strong> low volume exemption</td>
</tr>
<tr>
<td>No compounding supervisor for HDs</td>
<td>Requirement of compounding supervisor</td>
</tr>
</tbody>
</table>
## Major Differences Between USP Chapters <797> and <800>

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<tr>
<th>Chapter &lt;797&gt;</th>
<th>Chapter &lt;800&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed-system transfer device (CSTD) use is a “should”</td>
<td>CSTD use is a “shall” during administration as long as dosage form permits</td>
</tr>
<tr>
<td>Defines primary engineering controls (PECs) for HD sterile compounding</td>
<td>Defines PECs for nonsterile and sterile HD compounding; allows manipulations of HDs that do not produce aerosols (eg, coated tablets or capsules) outside of containment PEC</td>
</tr>
<tr>
<td>Prohibits segregated compounding area (SCA) for HD compounding; requires biological safety cabinet (BSC) to be housed in ISO Class 7 room that is 0.01” w.c. negative</td>
<td>Permits SCA for HDs provided compounding aseptic containment isolator (CACI)/BSC in area that has 12 ACPH and 0.01” w.c. negative; maximum BUD 12 hours</td>
</tr>
<tr>
<td>Does not require environmental and medical surveillance</td>
<td>Recommends environmental and medical surveillance</td>
</tr>
</tbody>
</table>
What Is an HD?

• An HD is any drug identified as hazardous or potentially hazardous by NIOSH.
• NIOSH list is updated every other year in even-numbered years.
## 2016 NIOSH HD Category Examples

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Table 2</th>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin</td>
<td>Diethylstilbestrol</td>
<td>Acitretin</td>
</tr>
<tr>
<td>Gemtuzumab</td>
<td>Estrogens</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Ganciclovir</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Spironolactone</td>
<td>Misoprostol</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Tacrolimus</td>
<td>Testosterone</td>
</tr>
</tbody>
</table>
Basis for Hazard Classification

- Drugs must be identified by **at least one** of the following six criteria:
  - Carcinogenicity
  - Teratogenicity or developmental toxicity
  - Reproductive toxicity in humans
  - Organ toxicity in low doses in humans or animals
  - Genotoxicity
  - New drugs that mimic existing HDs in structure or toxicity
2016 NIOSH HD Categories

• There are three HD categories in 2016 NIOSH:
  – Table 1: Antineoplastics
  – Table 2: Non-antineoplastic drugs that meet one or more NIOSH criteria for HDs
  – Table 3: Non-antineoplastic drugs that primarily have adverse reproductive effects
Examples of HDs

- Cytotoxic drugs
- Antineoplastic drugs
- Antiviral drugs
- Immunosuppressive drugs
- Some bioengineered drugs
- Some anticonvulsants
- Some steroidal agents
- Any agent that may cause risk to the health care worker or patient
Will There Be Further Changes/Updates?

- Harmonization of language in Chapter <800> with Chapter <795> and the proposed Chapter <797> will be necessary.
  - <800> uses low-, medium-, and high-risk level categories for sterile compounding.
  - Proposed <797> uses Category 1 and Category 2 to describe sterile compounding.
- <800> has very specific requirements for types of personal protective equipment (gowns, masks), while <797> and <795> do not go to this level of specification.
- <800> states a four-step cleaning process, while <797> and <795> do not have this same step-wise process.
Key Points

• Elimination of the low volume allowance for facilities that prepare HDs that permits placement of a BSC in a nonnegative pressure room.
• All HD compounding must be done in a separate area designated for HD compounding.
• Addition of an allowance in Chapter <800> for a containment segregated compounding area (C-SCA), a separate, negative pressure room with at least 12 air changes per hour for use when compounding HDs.
• Low- and medium-risk HD compounded sterile preparation may be prepared in a BSC or CACI located in a C-SCA, provided that the HDs are mixed and given within 12 hours.
Key Points

• Revised section on list of HDs to allow entities to:
  – Perform an assessment of risk for non-antineoplastic drugs and final dosage forms to determine alternative containment strategies and/or work practices.
  – Unpack HDs in either a neutral/normal or negative pressure area.
  – Use external venting or redundant high-efficiency particulate air filtration of containment primary engineering controls (C-PECs) used for nonsterile compounding.
Percentages at Institutions With at Least One Finding in These Areas (N=60)

• Environment – 70%
• Training – 70%
• Environmental monitoring – 57%
• Garbing – 45%
• Compounding procedures – 43%
• Cleaning – 35%
• Finished product release checks and tests – 33%
• Compounding equipment – 18%
• General operations – 18%
• Documentation – 7%
Top Findings – Environment

- Humidity and humidity – excursion monitoring not performed
- Issues with temperature monitoring – room, refrigerator, and freezer
- Ceiling tiles not caulked/sealed
- Ledges/sprinkler heads = areas that are difficult to clean
- No line of demarcation in anteroom
- Wood/porous materials in ante and/or clean/buffer room
- Blood compounding area not separate/distinct from other compounding
Each tablet contains:
Meloxicam, USP ........ 7.5 mg

Usual Dosage: See package insert for complete prescribing information.

Store at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature.
Keep in a dry place.
Dispense in a tight container.

KEEP THIS AND ALL THE DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
India

Distributed by:
Zycus Pharmaceuticals USA Inc.
Pennington, NJ 08534
Top Findings – Training

• Colony forming units not identified down to the genus level
• Lack of proper documentation on media fill (lot number, expiration date, dates incubated, temperature of incubation)
• No initial three gloved fingertip tests for compounding personnel
• No training/lack of training of compounding supervisor(s)
• No initial and/or annual written examinations
• No sign-off for understanding risks of compounding with HDs
Top Findings – Environmental Monitoring

- Viable samples and media fill issues (no growth promotion, if found – no identification of microorganisms, passive air samples, and no outside validation)
- No smoke testing of rooms/pass-throughs
- Pressure monitoring not performed and/or out of range
- Particle counts not performed under dynamic conditions
- No smoke test of PEC under dynamic conditions
- No smoke testing of area around particle generating equipment in ante/buffer rooms
Top Findings – Garbing

• No persistent activity agent in waterless scrub and/or scrub not used
• No nail picks and/or using scrub brush
• Booties on but going across line of demarcation with no shoes
• Hair not completely under bonnet and/or no mirrors
• Jewelry/makeup being worn
• Improper garbing for use with isolators
Top Findings – Compounding Procedures

- Missing data on compounding records
- Improper first air techniques
- Only one pair of gloves on compounding aseptic isolator
- Not spraying hands upon going in/out of PEC
- Not spraying materials before they go into PEC
Top Findings – Cleaning

- Fatigue mats not being cleaned (either daily and/or on both sides)
- PECs too close to walls for proper cleaning
- No sporicidal agent used
- Sterile water for injection not used in cleaning process for PECs
- PEC only cleaned at beginning of shift and not during compounding
- Tools not marked/not stored properly
Top Findings – Finished Product Release Checks and Tests

- No light/dark area to check for particulates (staff are looking but not against both backgrounds)
- Compounding accuracy not documented by verification of steps
- Sterility and endotoxin testing not performed as required for high-risk stock solutions and every batch of finished product
Top Findings – Finished Product Release Checks and Tests
Top Findings – Compounding Equipment

• No automated compounding device (ACD) used in media fill tests
• No record of ACD tubing changes
• Training documentation missing for ACD
Top Findings – Compounding Equipment
Top Findings – General Operation

• HD not stored under negative pressure with at least 12 ACPH
• Quality improvement programs do not include compounding (sterile and nonsterile)
Top Findings – Documentation

• EXP on labels versus BUD
• No or incomplete documentation
  – Unable to perform recalls - IV fluids not tracked
  – Sterility testing documentation incomplete
Top Findings – Documentation

TACROLIMUS ORAL SUSPENSION
1 MG/1 ML
Lot# ________
Exp: ________ Time: ________
Tech: ________ RPh: ________
***SHAKE WELL***
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Key Takeaways

• Key Takeaway 1
  – USP Chapter <800> has a delayed official implementation date of July 1, 2018.

• Key Takeaway 2
  – All CFUs detected from environmental and personnel testing must be analyzed down to the genus, even if the number of CFUs does not exceed an action level.

• Key Takeaway 3
  – If using an ACD, the ACD is used in the media fill testing procedure.
Questions and Answers
Thank You!