Missouri Board Of Pharmacy
An Update on Sterile Compounding Regulations

September 10, 2016

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Inspector
At the end of this activity, participants should be able to:

- Discuss the updated requirements of the emergency sterile compounding rule
  - 20 CSR 2220-2.200: Sterile Compounding

- Discuss the updated requirements of the amended sterile compounding rule
  - 20 CSR 2220-2.200: Sterile Compounding

- Implement the identified rule and compliant sterile compounding practices to protect patients from harm
Introduction

- Why now?
- Did the board adopt USP 797?
- Emergency vs Amended Rule. What’s the difference?
  - Emergency rule effective 8/4/16
  - Amended rule effective 3/2017 (anticipated)
- Future plans? USP 800?
Who does this rule apply to?

* All Missouri Board of Pharmacy permit holders with Class H or E on their license

* Is this rule applicable to hospitals? IT DEPENDS
  * Is your hospital doing sterile compounding for inpatient use only?
    * DHSS regulates all sterile compounding for inpatient use. This rule does not apply to you!

* This rule applies to hospitals that hold a Class B, H permit and are sterile compounding for “outpatient” type activities. Examples include:
  * Compounding TPNs or antibiotics to be sent home with patients
  * Off-site infusion centers (depending upon the location)
Overview of the Major Changes

* No changes to facility or structural design

* Major changes:
  * Training & media fill testing
  * Garbing
  * Clarification regarding controlled areas vs buffer areas
  * Increased cleaning & disinfection requirements
  * Environmental Sampling (eventually)
  * Remedial Investigations
Compounded sterile medications may include, but are not limited to:

1. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must be sterile when they are administered to patients. Including, but not limited to the following dosage forms:

   - Baths and soaks for live organs and tissues
   - Epidural and intrathecal solutions
   - Bladder/wound solutions
   - Injectable, intravenous solutions, parenteral solutions
   - Implantable devices and dosage forms
   - Inhalation solutions
   - Irrigation solutions
   - Ophthalmic preparations
   - Repackaged sterile preparations
   - Assembly of point-of-care systems
Terminology Changes

* Replaced Class 100 & Class 10,000 terminology with ISO classifications

* Addition of buffer area definition – ISO Class 7 or better area where the primary engineering control (PEC) is physically located.

* Clarification of controlled area definition
  
  * Controlled area refers to pharmacies that do not have an ISO classified area for the placement of their PEC
  
  * A room or area designated for sterile compounding. The area is separated from other activities/operations by a line of demarcation.
Removal of “isolator” terminology

- Isolator is a type of PEC with an automated system for built in decontamination.
- RABS = Restricted Access Barrier System
  - New terminology for the types of PECs that people currently refer to as “gloveboxes” and “isolators”. Includes CAI & CACI
- CAI: Compounding Aseptic Isolator
  - Used for non-hazardous compounding
- CACI: Compounding Aseptic Containment Isolator
  - Used for hazardous compounding
Risk Levels

Risk level stratification is mostly unchanged. Administration time removed from storage/beyond use dating parameters.

How to determine your risk level?

1. Sterility of drugs/equipment
   a. If compounding with any ingredients or supplies that are non-sterile = Risk Level 3

2. Batching preparations that are intended for more than 1 patient? Automated compounding device?
   1. Risk Level 2

3. Assignment of beyond use dates

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Current Rule</th>
<th>Emergency/Amended Rule</th>
</tr>
</thead>
</table>
| Risk Level 1 | - Product stored at room temp and **completely administered** within 48 hours after prep.  
- Stored in the fridge for 7 days or less before **complete administration** to a patient over a period not to exceed 48 hours.  
- Frozen storage for 30 days or less and **complete administration** not to exceed 48 hours | Room temp: assigned a beyond-use date (BUD) of 48 hours or less.  
Fridge storage: BUD of 7 days or less  
Frozen: BUD of 30 days or less |
| Risk Level 2 | Any product stored >48 hours at room temp, >7 days under refrigeration, >30 days frozen or **administered beyond 48 hours after preparation.** | Room temp: BUD >48 hours  
Fridge storage: BUD >7 days  
Frozen: BUD >30 days |

Risk Level 3: **N/A**  
Risk level 3 is determined via sterility of compounding ingredients (Non-sterile to sterile compounding)
Section 2: Policies & Procedures

* No changes within this section.
* Specific policy and procedure requirements are referenced throughout the rest of the rule
* Annual review of sterile compounding policy is still required
## Section 3: Personnel Education, Training, and Evaluation

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Current Rule</th>
<th>Emergency/Amended Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Risk Levels</td>
<td>Suitable didactic and experiential training</td>
<td>Specific competencies and assessments. Reference Section 10: Aseptic Technique Skill Assessment</td>
</tr>
<tr>
<td>Risk Level 2</td>
<td>Assessment of competency in all risk level 2 procedures</td>
<td>No change</td>
</tr>
<tr>
<td>Risk Level 3</td>
<td>Specific education in risk level 3 procedures such as sterilization, aseptic processing, end-preparation testing etc.</td>
<td>No change</td>
</tr>
</tbody>
</table>

* **Additional training required for changes in risk level or compounding methods**

* **Policy and procedure is required for staff training and assessment**
Section 4: Storage & Handling

- Minor changes for all risk levels:
  - Addition of daily incubator temperature documentation, if applicable
  - Reference to section (21) regarding recall procedures
Facility requirements clarified. No changes to physical structure or room design.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Emergency/Amended Rule</th>
</tr>
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<tbody>
<tr>
<td>Risk Level 1</td>
<td>Preparations must be prepared in a PEC located in a controlled area defined by a line of demarcation</td>
</tr>
<tr>
<td>Risk Level 2</td>
<td>Preparations must be prepared in a PEC located in an ISO Class 7 buffer area or in a RABS located within a controlled area</td>
</tr>
<tr>
<td>Risk Level 3</td>
<td>Preparations must be prepared in a PEC located in an ISO Class 7 buffer area or in a RABS located within a controlled area</td>
</tr>
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</table>
Section 5: Facilities & Equipment

* All cleaning requirements moved to Section (17): General Cleaning and Disinfection Requirements

* Risk Level 3 preparations shall at a minimum remain Risk Level 3 for the life of the preparation. Same is true for Risk Level 2 preps

* Automated compounding device calibration:
  * Calibration to occur prior to initial and daily use. Test results shall be reviewed by the pharmacist and documented in the pharmacy’s records.

* Pressure differential monitoring: No requirement to install a pressure monitoring device. However, if the pharmacy currently has one installed, the results must be monitored and documented daily.
Frequency of certification is unchanged – All PEC and ISO classified areas certified initially and every 6 months

Re-certification must occur when:

* Any major changes or service to PEC or ISO classified area
* PEC or room is relocated or the physical structure of the ISO classified area has been altered

Certification results must be reviewed by a pharmacist and documented in the pharmacy’s records

Deficiencies or failures shall be investigated and corrected prior to further compounding which may include recertification of the PEC/ISO classified area.

* Corrections may include, but are not limited to, changes in the use of the affected PEC or ISO classified area or initiating a recall.
Section 6: Primary Engineering Controls (PEC)

* New section to provide guidance on proper usage of PECs

* PEC placement: must be located out of traffic patterns and away from conditions that could adversely affect their operation or disrupt intended airflow patterns (e.g., ventilation systems or cross-drafts)

* PECs shall maintain ISO Class 5 or better conditions and provide unidirectional flow

* Establish a recovery time for PECs and identify it in the pharmacy policies and procedures
Section 7: Controlled Area

* Controlled area requirements:
  * For non ISO classified areas – a line of demarcation to designate the area used for sterile compounding
  * Must be clean, well-lit, free of infestation by insects and rodents
  * Trash disposed of at least daily
  * Furniture, carts, supplies and equipment cleaned and disinfected with sterile alcohol before entering ISO classified areas.
  * All personnel entering controlled and buffer areas need to be appropriately garbed (See Section 8)

* Items PROHIBITED in the controlled/buffer areas
  * Tacky mats
  * Food, gum, eating, drinking, smoking
  * Particle shedding items such as: pencils, corrugated cardboard paper towels, cotton items (ex-gauze pads)
  * Shipping or other external cartons
  * Non-essential supplies or equipment
## Section 8: Garbing & Hand Hygiene

<table>
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<tr>
<th>Risk Level</th>
<th>Current Rule</th>
<th>Emergency/Amended Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Level 1</td>
<td>No garbing required</td>
<td>Non-shedding gowns, hair cover, face mask, beard cover and gloves</td>
</tr>
<tr>
<td>Risk Level 2</td>
<td>Hair cover, beard cover, gown, mask, &amp; gloves</td>
<td>Non-shedding gowns, hair cover, face mask, beard cover, shoe covers, and <strong>sterile</strong> gloves</td>
</tr>
<tr>
<td>Risk Level 3</td>
<td>Hair cover, beard cover, gown, mask, gloves, &amp; shoe covers</td>
<td>Non-shedding gowns, hair cover, face mask, beard cover, shoe covers, and <strong>sterile</strong> gloves</td>
</tr>
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</table>

* All Risk Levels: Gloves shall be disinfected before use and frequently thereafter
* No exemptions for RABS. Garb is donned according to risk level.
* Risk Level 2 & 3: If using a RABS, sterile gloves must be donned over the RABS gloves
Section 9: Aseptic Technique & Preparation

* Specific requirements for handwashing:
  * Hands and forearms washed for 30 seconds with warm water
  * Debris removed from underneath fingernails.

* Risk Level 3: sterilization methods need to be USP recognized
Section 9: Aseptic Technique & Preparation

* In-Use Time: the time/date before which a conventionally manufactured product or a CSP must be used after it has been opened or needle-punctured.

* All vials/containers must be dated/timed after initial needle puncture.

* Single dose vials/containers – Maximum in-use time is 6 hours unless otherwise specified by the manufacturer

* Multiple dose vials/containers – Maximum in-use time of 28 days unless otherwise specified by the manufacturer

* Ampules must be used immediately and cannot be stored
Section 10: Aseptic Technique Skill Assessment

- Aseptic technique skill assessment consists of:
  - Media fill testing
  - Direct visual observation of the following competencies:
    - Proper aseptic technique and work practices
    - Cleaning/disinfection
    - Hand hygiene, gloving, and garbing
    - Identifying, weighing, and measuring of ingredients
    - Maintaining sterility in ISO Class 5 area
    - Labeling and inspecting preparations

- Who needs the assessment? All sterile compounding personnel

- How often?
  - Risk Levels 1 & 2: Prior to initial compounding and every 12 months thereafter
  - Risk Level 3: Prior to initial compounding and every 6 months thereafter
  - All Risk Levels: Reassessment when appropriate (ex-risk level changes)
Media Fills

* Policy and procedure required for media fill testing

* Media fill testing shall comply with USP Chapter 797’s procedures and methods
  * Incubation temperature & duration, type of media etc.

* Process must simulate the most challenging or stressful conditions encountered

* During initial media fill testing, a minimum must be completed.
Section 11: Record Keeping

* Few additions/clarifications

* Training records must include the dates and results of the aseptic technique skill assessment and media fill testing

* Incubator temperatures need to be recorded (if applicable)

* Certification records for both PEC and ISO classified area

* Pressure recordings (if applicable)
  * If a continuous monitoring system is used, the system must be able to maintain pressure recordings and alerts. These need to be reviewed and documented daily

* All records/reports need to be kept for 2 years
* **One label change:**

  * Label must include a designation indicating hazardous drugs if applicable

* **No changes to beyond-use dating section other than clarifications**

* **One recommendation added to cytotoxic drug section:**

  * The use of a closed system transfer device
Section 14: End-Preparation Evaluation

* Risk Level 1 & 2: No changes

* Risk Level 3: Addition of USP Chapters
  * Sterility testing must be conducted according in USP Chapter 71
  * Pyrogen testing must be conducted according to USP Chapter 151
  * Endotoxin testing must be conducted according to USP Chapter 85
  * All sterile preparations must be tested for sterility
  * All parenteral sterile preps must be tested for pyrogens
  * Potency testing required for sterile preps with BUD >30 days

* Emergency dispensing:
  * Risk level 3 compounded prep is dispensed prior to sterility/pyrogen test results
  * Requires physician authorization for each emergency dispensing. This authorization and the need for the emergency dispense must be documented in the prescription record
Section 16: Point of Care Assembled Systems

* Assembly of point of care assembled systems is considered Risk Level 1 sterile compounding.

* Examples: addEASE, ADD-Vantage, Mini-Bag Plus, Vial-Mate, Vial2Bag, etc.

* All systems that are assembled by the pharmacy shall be assigned two beyond-use dates. Both dates need to be recorded in the compounding log.

* BUD for the non-activated state according to the manufacturer.

  * If no manufacturer documentation, beyond-use date is limited to 15 days

* BUD for the activated state according to drug stability. (Risk Level 1 maximums apply)
Cleaning & Disinfection of controlled and buffer areas shall be performed according to Chapter 797

### Section 17: General Cleaning & Disinfection

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISO Class 5 - PEC</strong></td>
<td>• Daily cleaning: germicidal agent followed by sterile alcohol</td>
</tr>
<tr>
<td></td>
<td>• Frequent disinfection throughout the day (prior to compounding,</td>
</tr>
<tr>
<td></td>
<td>between batches and after spills/surface contamination): sterile</td>
</tr>
<tr>
<td></td>
<td>alcohol</td>
</tr>
<tr>
<td>Counters &amp; Work Surfaces</td>
<td>Daily</td>
</tr>
<tr>
<td>Floors</td>
<td>Daily</td>
</tr>
<tr>
<td>Walls</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Monthly</td>
</tr>
<tr>
<td>Storage Shelving</td>
<td>Monthly</td>
</tr>
</tbody>
</table>
* If compounding occurs less frequently than the specified timeframes, cleaning/disinfection must occur prior to each compounding session

* Policy and procedure required for all aspects of cleaning/disinfection

* All cleaning tools must be low-lint and dedicated for use in the controlled or buffer area.

* Sterile water for irrigation must be used for dilution of germicidal agents that will be used in the PEC
Emergency Rule: No changes

* Risk levels 2 & 3: Applicable environmental monitoring of air and surfaces must be conducted.

Amended Rule: New Section (18)

* Air Sampling:
  * All risk levels: must occur every 6 months

* Surface sampling:
  * Risk Level 2: must occur every 6 months
  * Risk Level 3: must occur every 30 days
**Section 20: Remedial Investigations**

* **Remedial investigation is required if:**

  * Any required sampling or testing results in a CFU count that exceeds 797 action levels
  * The pharmacy detects a highly pathogenic microorganism in any preparation or ISO classified area.

  * Ex- Gram-negative rods, coagulase positive staph, molds, fungus/yeast
  * Microorganism identification is NOT mandatory. However, if a pharmacy chooses to conduct this testing, a remedial investigation needs to occur for highly pathogenic microorganisms.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Air Sample (cfu per 1000 L of air per plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>&gt;10</td>
</tr>
<tr>
<td>ISO Class 8 or worse</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Surface Sample (cfu per plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt;3</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>&gt;5</td>
</tr>
<tr>
<td>ISO Class 8 or worse</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Section 20: Remedial Investigations

* **CSPs and any ingredients that are part of the remedial investigation shall be quarantined.**

* **All affected areas shall be resampled prior to further compounding**

* **Pharmacy shall notify the Board in writing within 7 days if any preparation or environmental monitoring detects a highly pathogenic microorganism, regardless of CFU count**
A recall is required when:

* A CSP is deemed to be misbranded or adulterated
* A CSP is non-sterile
* End-preparation testing results are out of specification

Actions required by the pharmacy:

* Notify the prescriber
* If CSP has the potential to harm the patient, notify all patients
* Any recall shall be reported to the board, in writing, within 3 business days
* Document all activities related to the recall
Amended Rule

Anticipated to be effective March 2017

* Main difference from the emergency rule is the environmental sampling requirements

Public comments will be accepted for the amended rule

Watch the Board of Pharmacy website for updates and how to submit comments!
Contact Info

Email or call with questions!

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