



# The Missouri Board of Pharmacy

## STERILE COMPOUNDING RULE IMPLEMENTATION GUIDE

The Board has filed an interim emergency rule to revise the Board's sterile compounding rule, 20 CSR 2220-2.200. The emergency rule will be effective on **August 4, 2016**. A permanent rule has also been filed that is scheduled to be effective in **March of 2017**. This guidance document is being provided by the Board to summarize key rule changes.

*This document does not constitute a comprehensive review of all changes in the emergency and amended rules. Licensees should review the rules in their entirety to ensure compliance. The text of the emergency and amended rules are available on the Board's website.*

### Why Now?

The Board began working with licensees and stakeholders in 2014 to update its sterile compounding rule to be more consistent with USP Chapter 797. Recent inspections prompted the Board to file an emergency rule to address gaps in the Board's current regulation. The Board's goal was to update the rule to better protect the public while minimizing compliance costs that could adversely affect the availability of sterile compounding services in the state.

### Did the Board adopt USP 797?

USP is in the process of revising Chapter 797. Accordingly, the Board chose not to adopt USP Chapter 797 at this time. However, the interim emergency rule and the amended rule incorporate relevant portions of current USP Chapter 797 that the Board determined were more immediately needed to protect the public. The Board intends on revising 20 CSR 2220-2.200 again after USP Chapter 797 is finalized.

### Implementation

The interim emergency rule will become effective on August 4, 2016 while the amended rule will likely be effective in March of 2017. Board inspectors will help to educate licensees on the new

compliance requirements during the initial implementation stages. The Board will also be hosting a series of free webinars to explain the new rules. Webinar dates/times will be posted on the Board's website and e-mail alerts.

### What's Been Changed?

The Board updated the rule to reflect current terminology and to clarify rule language that may have been inconsistent or confusing. The following major changes are summarized in this Guidance:

- Compounding definitions (equipment and classified areas)
- Risk level classifications
- Garbing requirements
- Training requirements
- Cleaning & disinfection requirements
- Environmental Monitoring
- End-preparation evaluation
- Remedial investigations/Recalls

Significantly, no facility/structural changes are required in the emergency/amended rule. The Board will reassess these requirements after USP Chapter 797 is revised. <sup>1</sup>

<sup>1</sup>Sterile compounders must also comply with the Board's general compounding rule, 20 CSR 2220-2.400. The Board intends on merging the rules during the next revision after USP Chapter 797 is finalized.

## Compounding Definitions

The following major definitions have been changed/included in the rule:

	Definitions
Buffer Area	An ISO Class 7 or better area where the primary engineering control (PEC) is physically located. The terms “clean room” and “clean zone” have been deleted throughout the rule.
Class 100/Class 10,000 area	Renamed to an ISO Class 5 or ISO class 7 area to match current ISO classifications.
Controlled Area	A separate room designated for preparing sterile preparations or an area designated for preparing sterile preparations that is separated from other activities/operations by a line of demarcation that clearly separates the area from other operations.
Isolator/Barrier Isolator	These terms have been deleted and changed to a “restricted access barrier system” or “RABS” ( <i>see definition below</i> ).
Primary Engineering Control (PEC)	A system that provides an ISO 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but are not limited to, horizontal/vertical laminar airflow hoods, biological safety cabinets or a restricted access barrier system (RABS). <i>All sterile compounding must occur in a PEC or in an ISO Class 5 environment.</i>
Restricted Access Barrier System (RABS)	A PEC that is comprised of a closed system made up of four (4) solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a compounding aseptic isolator (CAI) or a compounding aseptic containment isolators (CACI)

## Compounding in Controlled Areas:

In lieu of an ISO classified buffer area, both the emergency and amended rule allow licensees to compound sterile preparations in a PEC that is located in a “controlled area.” The controlled area does not have to be a separate room. Instead, a controlled area can be a separate room **or** an area of the pharmacy that is clearly separated from other pharmacy activities/operations by a line of demarcation. **NOTE: Risk Level 2 and 3 preparations can only be compounded in a controlled area if a RABS is used.**

Controlled areas must be cleaned and disinfected as required by the rule (*see cleaning chart below*). Similar to current requirements, a sink with hot and cold running water must be near, but not in, the controlled area. Traffic flow in or around the controlled area must also be minimized and controlled to prevent contamination.

Significantly, pharmacy staff compounding in a controlled area must now be **garbed** as required by the rule for all risk levels (*see garbing chart below*). This requirement will be new for many pharmacies. Pharmacy staff should be educated and instructed on how to properly garb.

## Compounding Risk Levels

The sterile compounding risk level definitions have been clarified in both the emergency and amended rule. Specifically, sterile compounding risk levels are now defined based on the assigned beyond-use date; references to the administration time have been removed as follows:

Risk Level	Current Rule	Emergency & Amended Rule
Risk Level 1	<ul style="list-style-type: none"> <li>• Products stored at room temperature and <u>completely administered</u> within 48 hours after preparation</li> <li>• Products stored under refrigeration for ≤7 days before <u>complete administration</u> to a patient over a period that does not exceed 48 hours.</li> <li>• Products stored frozen for ≤30 days or less before <u>complete administration</u> to a patient over a period that does not exceed 48 hours.</li> </ul>	<ul style="list-style-type: none"> <li>• Preparations stored at controlled room temperature and assigned a beyond-use date of 48 hours or less</li> <li>• Preparations stored under refrigeration and assigned a beyond-use date of 7 days or less</li> <li>• Preps stored frozen and assigned a beyond-use date of 30 days or less</li> </ul>

Risk Level 2	<ul style="list-style-type: none"> <li>Any product stored &gt;7 days under refrigeration, &gt;30 days frozen or administered beyond 48 hours after preparation</li> <li>Batch-prepared products without preservatives intended for use by more than 1 patient</li> <li>Products compounded by complex or numerous manipulations of sterile ingredients by using closed-system aseptic transfer</li> </ul>	<ul style="list-style-type: none"> <li>Preparations stored at controlled room temperature and assigned a beyond-use date greater than 48 hours</li> <li>Preparations stored under refrigeration and assigned a beyond-use date greater than 7 days</li> <li>Preparations stored frozen and assigned a beyond-use date greater than 30 days</li> </ul>
Risk Level 3	<ul style="list-style-type: none"> <li>Products compounded from nonsterile ingredients or compounding with nonsterile components, containers or equipment before terminal sterilization</li> <li>Products prepared by combining multiple ingredients (sterile or nonsterile) by using an open-system transfer or open reservoir before terminal sterilization.</li> </ul>	<ul style="list-style-type: none"> <li>No Change</li> </ul>

Licenseses may now be able to change risk levels for some preparations since administration time is no longer included within the storage/ beyond-use parameters.

## Garbing Requirements

The following garbing requirements are included in both the emergency and amended rule:

Risk Level	Current Rule	Emergency/Amended Rule
Risk Level 1	No garbing required	Non-shedding gowns, hair cover, face mask, beard cover and gloves
Risk Level 2	Hair cover, beard cover, gown, mask and gloves	Non-shedding gowns, hair cover, face mask, beard cover, shoe covers and sterile gloves
Risk Level 3	Hair cover, beard cover, gown, mask, gloves and shoe covers	Non-shedding gowns, hair cover, face mask, beard cover, shoe covers and sterile gloves

If a RABS is used for Risk Level 2 & 3 compounding, sterile gloves must be donned over RABS gloves. Garbing is required even if staff is compounding in a controlled area that is not ISO classified or a RABS is used.

## Training Requirements

Education and training of compounding staff is a vital part of maintaining sterility and preventing contamination. The emergency/amended rules require all compounding staff to complete the following initial and ongoing [aseptic technique skill assessment](#) for all risk levels that includes media-fill testing:

	Current Rule	Emergency/Amended Rule
Requirement	Compounding staff must receive suitable and didactic training. A “process validation” test is also required.	Compounding staff must take <b>and pass</b> an aseptic technique skill assessment that includes a <b>direct visual observation/evaluation</b> of aseptic competency during a process simulation. The process simulation must represent the most challenging or stressful condition the individual encounters or performs (e.g. the highest risk or largest batch process).
Frequency	Before compounding	Before compounding
Re-assessment/ Re-training (after initial training)	Process validation required annually	Risk Level 1 & 2 (annually) Risk Level 3 (every 6-months)

The required aseptic technique skill assessment must include a visual observation of:

1. Proper aseptic technique, including use of first air
2. Cleaning & disinfection
3. Hand hygiene, gloving and garbing
4. Identifying, weighing and measuring ingredients
5. Maintaining sterility in ISO Class 5 areas
6. Labeling & inspecting CSPs for quality.

Individuals who fail any written test or media-fill test or who fail to pass a visual observation of hand hygiene, garbing or aseptic technique must be retrained and pass three (3) successive reevaluations in the deficient area before beginning or resuming sterile compounding. Training dates and testing/re-testing results must be documented in the pharmacy's records.

All new hires after the effective date of the rule (August 1, 2016) must take and pass the required aseptic technique skill assessment. For current staff compounding Risk Level 1 & 2 preparations, the required aseptic technique skill assessment should occur at their next annual process validation date that would have been required under the current 20 CSR 2220-2.200(8). For staff compounding Risk Level 3 preparations, the aseptic technique skill assessment should occur within six (6) months of the effective date of this rule or during their next annual process validation date that would have been required under the current 20 CSR 2220-2.200(8), if earlier.

## Media-Fill Testing

Media-fill testing must be conducted in accordance with USP Chapter 797 and as referenced below:

	Current Rule	Emergency/Amended Rule
Frequency	<ul style="list-style-type: none"> <li>• Before compounding*</li> <li>• If the quality assurance program yields an unacceptable result or unacceptable techniques are observed</li> <li>• When microbial growth is detected</li> </ul>	<ul style="list-style-type: none"> <li>• Before compounding*</li> <li>• If the quality assurance program yields an unacceptable result or unacceptable techniques are observed</li> <li>• If the staff's risk level of sterile activity changes (e.g., staff begins compounding Risk Level 3)</li> <li>• If there's a change in compounding methods</li> </ul>
Reevaluation	Annually (all risk levels)	<ul style="list-style-type: none"> <li>• Risk Level 1 &amp; 2 (annually)*</li> <li>• Risk Level 3 (every 6-months)*</li> </ul>
# of Media-Fill Tests	Not specified	<ul style="list-style-type: none"> <li>• Initial training (3 media-fill tests)</li> <li>• Ongoing (1 media-fill test)</li> </ul>

\* As part of the required aseptic technique skill assessment

Individuals who fail media-fill testing must pass three (3) successive media-fill tests before staff begins or resumes sterile compounding.

## Cleaning & Disinfection

Both the emergency and amended rule require controlled areas and buffer areas to be cleaned & disinfected in accordance with USP Chapter 797. This would include the following requirements for all risk levels:

Site	Emergency/Amended Rule
ISO Class-5 PEC	<ul style="list-style-type: none"> <li>• Daily cleaning; germicidal agent followed by <a href="#">sterile alcohol</a></li> <li>• Frequent disinfection throughout the day using <a href="#">sterile alcohol</a> (prior to compounding, between batches and after spills/surface contamination)</li> </ul>
Counters & Work Surfaces	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage Shelving	Monthly

- 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.
- If compounding occurs less frequently than the required timeframes, cleaning/ disinfection must occur prior to each compounding session.

## Environmental Sampling

Both the emergency and amended rule require all sterile compounding pharmacies to establish and follow proper controls to ensure environmental quality, prevent environmental contamination and to maintain air quality in ISO classified areas. The emergency and amended rules also include the following requirements:

	Current Rule	Emergency Rule	Amended Rule
Risk Level 1	Not specified	<ul style="list-style-type: none"> <li>• Must establish and follow proper environmental controls as identified above</li> </ul>	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air and surfaces</li> <li>• Air sampling before initial compounding and then every six (6) months</li> </ul>
Risk Level 2	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air &amp; surfaces</li> </ul>	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air and surfaces</li> </ul>	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air and surfaces</li> <li>• Air sampling before initial compounding and then every six (6) months</li> <li>• Surface sampling every six (6) months</li> </ul>
Risk Level 3	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air &amp; surfaces</li> </ul>	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air and surfaces</li> </ul>	<ul style="list-style-type: none"> <li>• Applicable environmental monitoring of air and surfaces</li> <li>• Air sampling before initial compounding and then every six (6) months</li> <li>• Surface sampling every thirty (30) days</li> </ul>

## End-Preparation Evaluation

The emergency rule and amended rules retain the current end-preparation evaluation/testing requirements. Specifically, all final preparations must be inspected by a pharmacist to verify that the preparation was compounded accurately. Additionally, Risk Level 3 preparations must be tested for sterility, pyrogens/endotoxins and potency as provided by the rule.

To ensure appropriate testing, the emergency and amended rules incorporate specific USP chapters for Risk Level 3 end-preparation testing. Specifically:

- **Sterility:** Risk Level 3 preparations must be sterilized using a method recognized by USP Chapter 1229. The preparation must be subsequently tested for sterility using a USP Chapter 71 recognized method. **All Risk Level 3 preps must be tested for sterility.**
- **Pyrogen/Endotoxin** testing must be conducted for parenteral sterile preps using a method recognized by USP Chapter 151 (pyrogen) or USP Chapter 85 (endotoxin)
- **Potency** testing is required for all sterile preparations with a BUD >30 days.

**Emergency Dispensing:** The Board's requirements for emergency dispensing of Risk Level 3 preparations have not changed.

## Remedial Investigations/Recalls

All sterile compounding pharmacies are now required to conduct a remedial investigation if:

- (1) Any required sampling or testing demonstrates a colony forming unit (CFU) count that exceeds USP Chapter 797 recommended action levels for the type of sampling/testing (e.g., air/surface sampling), or
- (2) A highly pathogenic microorganism is detected in any preparation or ISO classified area (e.g., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

Compounded sterile preparations and any compounding ingredients used must be quarantined until the investigations results are known. Additionally, all affected areas must be resampled to ensure a suitable state of microbial control prior to further compounding. Licensees must notify the Board in writing within seven (7) days if any preparation or environmental monitoring/testing detects a highly pathogenic microorganism, regardless of CFU count.

**Recalls:** A recall must be initiated if a sterile preparation is deemed to be misbranded, adulterated or non-sterile or if end-preparation testing results are out of specification. The following notifications must be made in the event of a recall:

Prescriber	Must be notified of the nature of the recall, the identified problem(s) and any recommended actions
Patient(s)	Must receive the same notification as the prescriber if the CSP has the potential to harm the patient
Board	Must be notified within three (3) business days of the recall.

The pharmacy must document their activities related to the recall. Board notifications should be e-mailed to: [compliance@pr.mo.gov](mailto:compliance@pr.mo.gov) or mailed to the Board office.



Once again, this Guidance document does not summarize all compliance requirements. Licensees should review both the emergency and amended rule to ensure compliance.

Compliance questions should be addressed to: Inspector Katie DeBold at [Katie.DeBold@pr.mo.gov](mailto:Katie.DeBold@pr.mo.gov) or (636) 825-7011.