Meeting Notice  
Missouri Board of Pharmacy  
Sterile Compounding Sub-Committee  
Conference Call  
March 16, 2018 2:00 p.m.  

Division of Professional Registration  
3605 Missouri Boulevard  
Jefferson City, MO 65109  

Notice is hereby given that designated members of the Board will be meeting to review proposed changes to the sterile compounding rule via conference call on March 16, 2018. The full Board will not be meeting. However, public notice of the meeting is being provided as detailed herein to ensure compliance with Chapter 610, RSMo.

If any member of the public wishes to attend the meeting, s/he should be present at the Division of Professional Registration, Executive Conference Room, 3605 Missouri Boulevard, Jefferson City, Missouri, at approximately 2:00 p.m. on March 16, 2018. Alternatively, participants may participate in the conference call by joining the meeting online on March 16, 2018 at 2:00 p.m. at: https://global.gotomeeting.com/join/139214789. Pre-registration is not required. Once you join online, a conference call number and access code will be provided to allow you to join the call.

Notification of special needs as addressed by the Americans with Disabilities Act should be forwarded to the Missouri Board of Pharmacy, P O Box 625, 3605 Missouri Blvd., Jefferson City, Missouri 65102, or by calling (573) 751-0091 to ensure available accommodations. The text telephone for the hearing impaired is (800) 735-2966. Please see the attached tentative agenda for this meeting.
Meeting Notice
Missouri Board of Pharmacy
Sterile Compounding Sub-Committee
Conference Call
March 16, 2018 2:00 p.m.

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3605 Missouri Boulevard
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1. Review of 20 CSR 2220-2.200 Emergency Rule
   a. Discussion of Required Remedial Actions When a Highly Pathogenic Microorganism is Detected
      i. Draft Language
      ii. Critical Point Comments
      iii. Truman Medical Center/St. Luke’s/UMKC Comments
   b. Nuclear Pharmacy Beyond-Use Date/In-Use Times
      i. Draft Language

2. Future Meeting Topics/Dates

3. Adjourn
(B) For ISO-5 classified areas: If a highly pathogenic microorganism is detected or if the CFU count exceeds USP 797 action levels in any ISO-5 classified area as outlined below, no further sterile compounding shall be performed in that specific ISO-5 classified area until resampling shows a suitable state of microbial control.

Pharmacies with clean room designs consisting of custom built (non-commercially manufactured) “open” ISO Class 5 designs, including integrated vertical flow ISO Class 5 work benches (vertical benches) should not resume compounding until proper remediation is proven by repeat environmental –microbiology reports demonstrating results within acceptable levels.

(C) For ISO-7 classified areas: If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels as outlined below sterile compounding may continue while the pharmacy conducts the remedial investigation and resampling. However, if the resampling fails to show a suitable state of microbial control, the pharmacy must cease sterile compounding activity until further resampling shows such a suitable state has been achieved.

1) Upon receipt of an action level environmental monitoring result as outlined below, a pharmacy may resume compounding for low and medium risk level CSP’s if:
   a) The current above action level does not represent the third consecutive sampling report with the below action level results for specific classified space; and
   b) The pharmacy has immediately assessed the above action level environmental monitoring results, developed and implemented a remediation plan, and scheduled repeat monitoring; and
   c) The pharmacy has evaluated preparation risk and implemented an appropriate risk mitigation plan (i.e. reduced beyond use dates); and
   d) A pharmacy should not resume compounding of low and medium risk level CSP’s if the environmental monitoring data indicates three consecutive sampling reports with above action levels results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results within acceptable levels

2) Upon receipt of an action level monitoring result as outlined below, a pharmacy may resume compounding for a high level risk CSP’s if:
   a) The current above action level does not represent the second consecutive sampling report with the below action level results for specific classified space; and
   b) The pharmacy has immediately assessed the above action level environmental monitoring results, developed and implemented a remediation plan, and scheduled repeat monitoring; and
   c) The pharmacy has evaluated preparation risk and implemented an appropriate risk mitigation plan (i.e. reduced beyond use dates); and
   d) A pharmacy should not resume compounding of high risk CSP’s if the environmental monitoring data indicates two consecutive sampling reports with above action levels results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results within acceptable levels
(D) For ISO-8 classified areas: If a highly pathogenic microorganism is detected or if the CFU count exceeds USP 797 action levels as outline below sterile compounding may continue while the pharmacy conducts the remedial investigation and resampling as outlined above under (C) (1) and (2).

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(E) Beyond Use Date modification during remediation – A pharmacy choosing to resume compounding of CSP’s during remediation of above action level results should limit beyond use dates to 24 hours at room temperature or three days refrigerated until the repeat environmental monitoring reports demonstrate results within acceptable levels. A pharmacy should not freeze any CSP upon receipt of an above action level environmental monitoring results until repeat monitoring reports demonstrate results within acceptable levels.

(F) The pharmacy shall 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. The pharmacy shall provide the board a final reporting outlining the completed remediation plan, including the microbiology report from repeated environmental monitoring within 21 days of submission of the original notification report.
Dear Missouri Board of Pharmacy:

We understand that the MO Board of Pharmacy discussed a possible emergency rule language in February that would address concerns that have been raised regarding terminating sterile compounding activities if a highly pathogenic microorganism is discovered during testing or if the CFU count exceeds 797 action levels. Board members requested input from stakeholders regarding the language that would be incorporated into 20 CSR 2220-2.200. The attached document reflects input from CriticalPoint and ClinicalIQ. The person recording the comments is Abby Roth, the Director of Microbiology for ClinicalIQ but reflects the opinion of Eric Kastango, myself and others in our organization.

Thank you for the opportunity to provide comment.

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The CriticalPoint Peer Network – Now Available!
Sign up to access the latest Sterile Compounding Resources
(B) **For ISO-5 classified areas.** If a highly pathogenic microorganism is detected or if the CFU count exceeds USP 797 action levels in any ISO-5 classified area as outlined below, no further sterile compounding shall be performed in that specific ISO-5 classified area until resampling shows a suitable state of microbial control.

Pharmacies with clean room designs consisting of custom built (non-commercially manufactured) “open” ISO Class 5 designs, including integrated vertical flow ISO Class 5 work benches (vertical benches) should not resume compounding until proper remediation is proven by repeat environmental –microbiology reports demonstrating results within acceptable levels.

(C) **For ISO-7 classified buffer areas.** If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels as outlined below sterile compounding may continue while the pharmacy conducts the remedial investigation and resampling. However, if the resampling fails to show a suitable state of microbial control, the pharmacy must treat the ISO-7 buffer area as a Segregated Compounding Area and assign the appropriate beyond use dating cease sterile compounding activity until further resampling shows such a suitable state has been achieved.

1) Upon receipt of an action level environmental monitoring result as outlined below, a pharmacy may resume compounding for low and medium risk level CSP’s if:
   a) The current above action level does not represent the third consecutive sampling report with the below action level results for specific classified space; and
   b) The pharmacy has immediately assessed the above action level environmental monitoring results, developed and implemented a remediation plan, and scheduled repeat monitoring; and
   c) The pharmacy has evaluated preparation risk and implemented an appropriate risk mitigation plan (i.e. reduced beyond use dates); and
   d) A pharmacy shall not resume compounding of low and medium risk level CSP’s if the environmental monitoring data indicates three consecutive sampling reports with above action levels results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results within acceptable levels.

2) Upon receipt of an action level monitoring result as outlined below, a pharmacy may resume compounding for a high level risk CSP’s if:
   a) The current above action level does not represent the second consecutive sampling report with the below action level results for specific classified space; and
   b) The pharmacy has immediately assessed the above action level environmental monitoring results, developed and implemented a remediation plan, and scheduled repeat monitoring; and
   c) The pharmacy has evaluated preparation risk and implemented an appropriate risk mitigation plan (i.e. reduced beyond use dates); and
   d) A pharmacy should shall not resume compounding of high risk CSP’s if the environmental monitoring data indicates two consecutive sampling reports with above action levels results until remediation is completed and proven by

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**Comment [AR1]:** The first instance of an exceeded level or recovery of an organism of concern does not necessarily indicate the ISO 5 area is not properly functioning. The area must be cleaned and resampled but does not need to be shut down. Reducing the BUD of CSPs may be appropriate. If the resample comes back exceeded, need to cease compounding in that PEC or if it is the only PEC, perform a triple clean, reduce the BUD to 12 hours and contact the certifier to evaluate the PEC.

**Comment [AR2]:** Use the room as an SCA with 12-hour RT and 24-hour refrigerated dating if there is a second excursion. It is better to continue operation as an SCA than shutting down and limiting patient access to needed CSPs.
microbiology reports of repeat environmental monitoring demonstrating results within acceptable levels

(D) For ISO-7 and 8 classified ante areas: If a highly pathogenic microorganism is detected or if the CFU count exceeds USP 797 action levels as outline below sterile compounding may continue while the pharmacy conducts the remedial investigation and resampling. In the event, remediation has been unsuccessful in returning the area to a state of microbiol control after the third sampling, the adjoining ISO 7 buffer rooms must be treated as Segregated Compounding Areas and assign the appropriate beyond use dating, as outlined above under (C)(1) and (2).

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(E) Beyond Use Date modification during remediation – A pharmacy choosing to resume compounding of CSP’s during remediation of above action level results should limit beyond use dates to 24 hours at room temperature or three days refrigerated until the repeat environmental monitoring reports demonstrate results within acceptable levels. A pharmacy should not freeze any CSP upon receipt of an above action level environmental monitoring results until repeat monitoring reports demonstrate results within acceptable levels.

(F) The pharmacy shall 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. The pharmacy shall provide the board a final reporting outlining the completed remediation plan, including the microbiology report from repeated environmental monitoring within 21 days of submission of the original notification report.

Comment [AR3]: The benefit of contacting the BOP with every exceeded action level or recovery of a “highly pathogenic organism” is unclear. An exceeded action level or recovery of one of those organisms is not a direct measure of CSP sterility assurance. EM data cannot be used as a sterility assurance measure. This is discussed in USP <1116>. Notifying the board with repeated incidence of exceeded level in the class 5, or three-time incidence in the room is more reasonable and would be clearer indication of a true loss of the microbial state of control in the controlled environment. If the pharmacy exceeds and remediation works, there is no need for the board to be notified.
Kim,

Thank you for the opportunity to comment. These comments are the result of a collaborative effort between St. Luke’s Health System, Truman Medical Centers and The University of Kansas Health System.

The drafted changes to 20 CSR 2220-2.200 are a step in the right direction to improve public safety and limit the delays and interruptions to patient care while maintaining the safety of sterile compounding.

We do feel it is important to consider that the requirement to cease compounding for above action level viable samples, whether on the first or subsequent samples, is not required by USP 797 or Current Good Manufacturing Practice (CGMP) making Missouri’s rule stricter than the well-established standards governing sterile compounding for both pharmacies and 503B compounders. In contrast, Missouri’s rule allows compounding of Risk Level 1 products in a controlled area where USP 797 only allows low risk products with a BUD of less than 12 hours to be compounded in a segregated compounding area. This discrepancy in standards imposes unnecessary hardships on compounding pharmacies that have elected to compound risk level 1 products in ISO classified spaces even though compounding in ISO classified spaces improves patient safety.

In the email attachments, we have included comments and track changes for consideration as well a clean version of what we propose to be a compromise on rule language if the board feels strongly that they wish to establish some points at which compounding would cease. Thank you for the opportunity to comment and help ensure the continued care and safety of the Missouri Public.

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Meredith Wills, PharmD
Oncology and Investigational Drug Services Pharmacy Manager
Hello All:

As you may know, the Board discussed possible emergency rule language in February that would address concerns that have been raised regarding terminating sterile compounding activities if a highly pathogenic microorganism is discovered during testing or if the CFU count exceeds 797 action levels. The Board formed a sub-committee to draft sample language which met on 2/23. Board members requested input from stakeholders regarding the attached language that would be incorporated into 20 CSR 2220-2.200. The Board has shortened its review period. Therefore, please return comments as soon as you can. Thanks all.

Kimberly A. Grinston, J.D.
Executive Director
Missouri Board of Pharmacy

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For ISO-5 classified areas: If a highly pathogenic microorganism is detected or if the CFU count exceeds USP 797 action levels on a viable air sample in any ISO-5 classified area as outlined below, no further sterile compounding shall be performed in that specific ISO-5 classified area until resampling shows a suitable state of microbial control.

For ISO-5 classified areas: If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels on a viable surface sample in any ISO-5 classified area as outlined below, sterile compounding may continue while the pharmacy conducts the remedial investigation and resampling.

1) Upon receipt of an action level environmental monitoring result as outlined below, a pharmacy may continue compounding for risk level 1 and 2 CSP’s if:
   a) The current above action level does not represent the third consecutive sampling report with the same above action level CFU results for the ISO-5 space; and
   b) The pharmacy has immediately cleaned the ISO-5 area three times with a disinfectant that demonstrates activity against the identified CFUs and has documented such cleaning, and scheduled repeat monitoring; and
   c) A pharmacy should not continue compounding of risk level 1 and 2 CSP’s if the environmental monitoring data indicates three consecutive sampling reports with the same above action level CFU results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results below the action levels listed below

2) Upon receipt of an action level environmental monitoring result as outlined below, a pharmacy may continue compounding for risk level 3 CSP’s if:
   a) The current above action level does not represent the second consecutive sampling report with the same above action level CFU results for the ISO-5 space; and
   b) The pharmacy has immediately cleaned the ISO-5 area three times with a disinfectant that demonstrates activity against the identified CFUs and has documented such cleaning, and scheduled repeat monitoring; and
   c) A pharmacy should not continue compounding of risk level 3 CSP’s if the environmental monitoring data indicates second consecutive sampling reports with the same above action level CFU results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results below the action levels listed below

Pharmacies with clean room designs consisting of custom built (non-commercially manufactured) “open” ISO Class 5 designs, including integrated vertical flow ISO Class 5 work benches (vertical benches) should not resume compounding until proper remediation is proven by repeat environmental—microbiology reports demonstrating results within acceptable levels.

Comment [AS1]: Above action level viable air samples could indicate problems with the ISO-5 PEC or HEPA filters and compounding should cease until those problems are remediated

Comment [AS2]: Above action level viable surface samples are more easily remediated through cleaning with a disinfectant. Thorough cleaning of the ISO-5 area three times (a triple clean) will ensure continued safe compounding while resamples are incubating.

Comment [AS3]: USP uses low and medium risk MO has defined risk levels as 1,2,3 Change to level 1 and 2

Comment [AS4]: Viable sampling is a snap shot in time and is dependent on many factors such as time of day, number of people in the room, etc. On subsequent re-sampling, it is possible to identify a new above action level result, representing a new issue that requires remediation even if you have successfully remediated the original issue. Therefore, we suggest adding that the same CFU would need to be identified 3 times which would represent that you have a persistent issue that you have not successfully remediated.

Comment [AS5]: Viable sampling is a snap shot in time and is dependent on many factors such as time of day, number of people in the room, etc. On subsequent re-sampling, it is possible to identify a new above action level result, representing a new issue that requires remediation even if you have successfully remediated the original issue. Therefore, we suggest adding that the same CFU would need to be identified 3 times which would represent that you have a persistent issue that you have not successfully remediated.

Comment [AS6]: We think this is sufficiently covered by the previous paragraph and does not need to be called out separately.
(C) For ISO-7 classified areas: If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels as outlined below sterile compounding may continue while the pharmacy conducts the remedial investigation and resampling. However, if the resampling fails to show a suitable state of microbial control, the pharmacy must cease sterile compounding activity until further resampling shows such a suitable state has been achieved.

1) Upon receipt of an action level environmental monitoring result as outlined below, a pharmacy may resume compounding for low and medium risk level 1 and 2 risk level CSP’s if:
   a) The current above action level does not represent the third consecutive sampling report with the below same above action level CFU results for a specific classified space; and
   b) The pharmacy has immediately assessed the above action level environmental monitoring results, developed and implemented a remediation plan, and scheduled repeat monitoring; and
   c) The pharmacy has evaluated preparation risk and implemented an appropriate risk mitigation plan (i.e. reduced beyond use dates); and
   d) A pharmacy should not resume compounding of low and medium risk level 1 and 2 risk level CSP’s if the environmental monitoring data indicates three consecutive sampling reports with the same above action level CFUs results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results within acceptable levels below the action levels listed below

2) Upon receipt of an action level monitoring result as outlined below, a pharmacy may resume compounding for high risk risk level 3 CSP’s if:
   a) The current above action level does not represent the second consecutive sampling report with the same above action level CFU results for a specific classified space; and
   b) The pharmacy has immediately assessed the above action level environmental monitoring results, developed and implemented a remediation plan, and scheduled repeat monitoring; and
   c) The pharmacy has evaluated preparation risk and implemented an appropriate risk mitigation plan (i.e. reduced beyond use dates); and
   d) A pharmacy should not resume compounding of high risk risk level 3 CSP’s if the environmental monitoring data indicates two consecutive sampling reports with the same above action level CFUs results until remediation is completed and proven by microbiology reports of repeat environmental monitoring demonstrating results within acceptable levels below the action levels listed below

(D) For ISO-8 classified areas: If a highly pathogenic microorganism is detected or if the CFU count exceeds USP 797 action levels as outlined below sterile compounding may continue while
the pharmacy conducts the remedial investigation and resampling as outlined above under (C) (1) and (2).

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(E) Beyond Use Date modification during remediation – A pharmacy choosing to resume compounding of CSP’s during remediation of above action level results should limit beyond use dates to 24-48 hours at room temperature or three seven days refrigerated until the repeat environmental monitoring reports demonstrate results within acceptable levels. A pharmacy should not freeze any CSP upon receipt of an above action level environmental monitoring results until repeat monitoring reports demonstrate results within acceptable levels.

(F) The pharmacy shall 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. The pharmacy shall provide the board a final reporting outlining the completed remediation plan, including the microbiology report from repeated environmental monitoring within 21 days of submission of the original notification report.

Comment [AS13]: I do not think the Board intends for pharmacies to have to cease compounding for above action level results in ISO-8 areas as this is not in the rule today. However, referencing back to (C) (1), (2) could imply that compounding would cease after the third / second consecutive above action level test. I think deleting this part would be appropriate.

Comment [AS14]: This is stricter than BUDs for Risk Level 1 products. The current rule allows compounding of Risk Level 1 products in a non-ISO classified controlled area that is likely to have more air contamination than an ISO Class 7 room whose CFU count exceeds USP 797 action levels.

The board should not reduce BUDs to less than Risk Level 1 BUDs when they allow Risk Level 1 products to be compounded in controlled areas that are not ISO certified.
PURPOSE: This rule establishes standards for the handling, labeling, distribution, and dispensing of compounded sterile preparations by licensed pharmacies, pursuant to a physician’s order or prescription.

(9) Aseptic Technique and Preparation. Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique.

(D) Single-dose vials/containers and pharmacy bulk vial/containers exposed to ISO Class 5 or cleaner air may be used in compounding until the assigned in-use time which shall not exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer. For multiple-dose vials/containers with no antimicrobial preservative used in the preparation of radiopharmaceuticals whose beyond-use dates are twenty-four (24) hours or less, the in-use time shall not exceed eighteen (18) hours, unless otherwise specified by the manufacturer. Opened single-dose ampules shall not be stored for any time period. The in-use time must be placed on the vial/container.

(E) Unless otherwise specified by the manufacturer, multiple-dose vials/containers with an antimicrobial preservative may be used in compounding until the assigned in-use date which shall not exceed twenty-eight (28) days after initially entering or opening the vial/container (e.g., needle-puncture). The in-use date must be placed on the vial/container.
Kim,

Jubilant Draximage Radiopharmacies, Inc, DBA: Triad Isotopes who operates two Class E pharmacies in Missouri appreciates the opportunity to comment on drafted changes to 20 CSR 2220-2.200.

The drafted changes to 20 CSR 2220-2.200 will help to improve patient safety and limit the delays and interruptions to patient care while maintaining the safety of compounded sterile products. We believe a few more changes are needed to ensure access as well as patient safety.

The requirement to cease compounding for above action level for viable samples in a secondary engineering control such as a cleanroom or segregated compounding area is not required by USP <797> or Current Good Manufacturing Practice (CGMP). Missouri Board of Pharmacy should reconsider the rule to ceasing compounding in any secondary control for exceeding action levels. Such a rule would prevent necessary care from being provided to Missouri patients.

Concerning in-use-time (IUT) for radiopharmaceuticals the differentiation between beyond-use-date (BUD) and in use time are essentially the same due to the short half-life of a compounded radiopharmaceutical. Compounded Tc99m diagnostic radiopharmaceutical kits are multi-dose; residual vial activity after initial compounding should have in-use-time that matches the max beyond-use -date/time of twenty-four (24) hours. Any IUT less than 24 hours would greatly reduce access to radiopharmaceuticals for patients in Missouri.

In the email attachment, we have included comments and tracked changes for your consideration for section #2 Nuclear Language.
Thank you for the opportunity to comment and help ensure the continued care and safety of the patients served in Missouri.

Don Warner, R.Ph. (MO 043635)
Triad Isotopes
Senior Director, Pharmacy Development
p. 214-769-8417
DWarner@triadisotopes.com
PURPOSE: This rule establishes standards for the handling, labeling, distribution, and dispensing of compounded sterile preparations by licensed pharmacies, pursuant to a physician’s order or prescription.

(9) Aseptic Technique and Preparation. Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique.

(D) Single-dose vials/containers and pharmacy bulk vial/containers exposed to ISO Class 5 or cleaner air may be used in compounding until the assigned in-use time which shall not exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer. For multiple-dose vials/containers with no antimicrobial preservative used in the preparation of radiopharmaceuticals whose beyond-use dates are twenty-four (24) hours or less, the in-use time shall not exceed twenty-foureighteen (2418) hours, unless otherwise specified by the manufacturer. Opened single-dose ampules shall not be stored for any time period. The in-use time must be placed on the vial/container.

(E) Unless otherwise specified by the manufacturer, multiple-dose vials/containers with an antimicrobial preservative may be used in compounding until the assigned in-use date which shall not exceed twenty-eight (28) days after initially entering or opening the vial/container (e.g., needle-puncture). The in-use date must be placed on the vial/container.

Commented [DW1]: Radiopharmaceuticals compounded, dispensed and administered with 24 hours are not a risk to patient safety if the standards of this rule are followed.

Commented [DW2]: The statement “unless otherwise specified by the manufacturer” is not necessary.
March 14, 2018

Missouri Board of Pharmacy,

The Nuclear Pharmacy Working Group is responding to the request by the Board at the February 28 meeting and provides this summary letter with the consensus position of the nuclear pharmacies licensed in Missouri on a specific contemplated rule interpretation we believe is inconsistent with accepted industry practice, USP <797> standards as well as negatively impacting patient access to diagnostic radiopharmaceuticals and timely patient care in Missouri.

**Relevant Highlight of the Nuclear Pharmacy Industry**

Radiopharmacies prepare sterile injectable radiopharmaceuticals from commercially manufactured sterile lyophilized drug “kits” and sterile radioactive solutions eluted from commercially manufactured generators. All prescription drugs compounded and dispensed are commercially available drugs approved by the U.S. FDA. These drugs are obtained from manufacturers who manufacture them in accordance with their new drug application (NDA) or abbreviated new drug application (aNDA) in drug manufacturing facilities that are licensed, registered and inspected by the FDA. All radiopharmaceuticals prepared meet the USP <797> definition as low risk compounded preparations. The 2012 revision of USP <797> states; “For the purposes of this chapter, radiopharmaceuticals compounded from sterile components in closed sterile containers and with a volume of 100 mL or less for a single dose injection or not more than 30 mL taken from a multiple-dose container (see Injections <1>) shall be designated as, and conform to, the standards for Low-Risk Level CSPs.”

**Beyond Use Dates (BUD) and In-Use Times (IUT) for radiopharmaceuticals**

The concept of an “In-Use” time is not present in the current 2012 revision of USP <797>. We disagree with the Board’s verbally communicated rule interpretation that an additional limiting BUD and IUT relating specifically to discrete single and multi-dose containers should be applied to already established rules governing CSPs of radiopharmaceuticals reagent kits prepared consistent with the manufacturer’s package insert with short-lived radionuclides. We strongly believe that the BUD and IUT storage periods of these radiopharmaceuticals undergoing a compounding and/or preparation process in an ISO Class 5 PEC should follow the time limitations already adequately specified under: “Low-Risk Level CSPs” of USP <797> and similarly described in subparagraph (1)(GG)1 of the Missouri State Board of Pharmacy rules 20 CSR 2220-2.200 Sterile Compounding. Accordingly, appropriate Missouri rules are already established governing the preparation of radiopharmaceuticals. Our position is based on the following premises:

1. From the start, the process of preparing a radiopharmaceutical reagent kit with short-lived radionuclides constitutes a CSP-classified as Risk Level 1 of the Missouri rules and Low-Risk Level under USP <797>.

2. All manipulations are performed in an ISO Class 5 PEC and, as required or deemed necessary, within an ISO Class 7 cleanroom.

3. Radiopharmaceuticals are prepared in small volumes based on physician prescriptions/orders or in anticipation of recurring prescriptions/orders for a small number of patients over a short period of time. Importantly, all prepared radiopharmaceuticals are 100% subjected to end product quality assurance testing in accordance with manufacturers’ specifications.

4. The BUD of a Risk Level 1 CSP, by its in-process nature (i.e., undergoing compounding activities), should not be conflated with other regulations for single and multi-dose containers which relate to discrete commercially available, non-compounded products which may be dispensed directly
for patient use or used as component drug in the preparation of a CSP. In other words, once CSP drug manipulations begin (in appropriate ISO Class 5 PECs) the process must, by its compounding nature, fall under CSP standards and the rules set forth by USP <797> and the Missouri Board of Pharmacy for beyond-use dating of compounded sterile preparations become applicable.

5. The arbitrary assignment of a non-CSP related BUD (i.e., for discrete non-compounded containers) to a radiopharmaceutical CSP will have a dramatically detrimental impact on hospital nuclear medicine professionals and their ability to immediately address the dynamic needs of Missouri citizens from their daily CSP inventory, particularly in-patient diagnostic imaging.

**Active Revision of USP Standards**

The USP is actively revising Chapters <795> and <797> with public comment periods for both General Chapters coming up in the very near future.

Excerpted from USP’s website ([http://www.usp.org/compounding/updates-on-standards](http://www.usp.org/compounding/updates-on-standards)):

To provide a unified approach to quality compounding, USP intends to align the timing and content of General Chapters <795>, <797>, and <800>. General Chapters <795> and <797> are in the active revision process.

The three chapters (<795>, <797>, and <800>) are anticipated to be official and aligned on December 1, 2019.

It is important to note that the current published versions of USP-NF General Chapters <795> and <797> are official until the revised Chapters become official. (Emphasis added)

The public comment period for <797> will occur between July 28 and November 30, 2018 but it will be “pre-posted” on the USP website on July 28, 2018. Additionally, the public comment period for <795> will occur between March 30 and July 31, 2018 but it will be “pre-posted” on the USP website on March 30, 2018.

In addition, USP has identified a need for the compounding of radiopharmaceuticals (sterile and non-sterile) to have a separate chapter. They have identified this Chapter as <825>. Please see the notification at: [http://www.uspnf.com/notices/825-compounding-radiopharmaceuticals](http://www.uspnf.com/notices/825-compounding-radiopharmaceuticals). This chapter will also be released for public comment in the near future.

In light of the impending changes to USP <795>, <797>, the development of Chapter <825>, and that current Missouri rules adequately specify accepted industry standards for radiopharmaceuticals, we strongly believe the proposed changes to regulations effecting radiopharmaceuticals by the Missouri Board are unwarranted. Additionally, the implications of such proposed change would greatly reduce the citizens of Missouri access to safe and effective radiopharmaceuticals.

Sincerely,

Cardinal Health
PharmaLogic Holdings Corp.