MEETING NOTICE
Missouri Board of Pharmacy

Missouri Council of School Administrator’s Conference Center
3550 Amazonas Drive
Jefferson City, MO 65109

June 23, 2017
8:30 a.m.

OPEN SESSION

1. Call to Order: Christina Lindsay, PharmD, President

2. Roll Call

3. Agenda Additions & Corrections

4. General Administration Report
   a. 2017 Legislation
   b. Future Webinars
   c. 2017 Patient Safety Conference/Joint Opioid Safety Conference
   d. Tri-Regulators Meeting
   e. Dist. 6, 7 and 8 Meeting
   f. Governor’s Boards and Commissions Task Force
   g. Sterile Compounding Committee Update
   h. Long-Term Care Working Group Update
   i. General Office Updates

5. UMKC/STLCoP Site/Preceptor Approval

6. Intern Special Sites/Preceptor Applications

7. Public Comments on 20 CSR 2220-2.200 (Sterile Compounding): This rule is currently under review by the Board of Pharmacy’s Sterile Compounding Sub-Committee. The Board will be taking public comments on the rule for Sub-Committee consideration. Due to time constraints and other agenda items, comments may be limited to three (3) minutes.

8. Rules Under Review
   a. Rule review status report
   b. 20 CSR 2220-2.010 (Pharmacy Standards of Operation)
   c. 20 CSR 2220-2.012 (Pharmacy Supervision- NEW)
   d. 20 CSR 2220-2.025 (Non-Resident Pharmacies)
   e. 20 CSR 2220-2.090 (Pharmacist-In-Charge Rule)
f. 20 CSR 2220-2.650 (Class-J Shared Services Rule- EMERGENCY & PROPOSED)
g. 20 CSR 2220-6.040 (Administration by Medical Prescription Order)
h. 20 CSR 2220-6.050 (Immunization by Protocol)

9. 2018 Proposed Legislation
   a. Pharmacy Technician Training/Scope of Practice (§ 338.013, RSMo)
   b. 3PL Licensing
   c. Pharmacist Continuing Education
   d. Charitable Pharmacy
   e. Civil Penalties
   f. Other proposed legislative suggestions

10. Strategic Planning Report for FY 18-19

11. Future Meeting Topics/Dates

12. Public Discussion

13. The Board may go into closed session at any point during the meeting and all votes, to the extent permitted by law, pertaining to and/or resulting from this closed meeting will be closed under Section 610.021(1), (5), (7), and (14) and under Section 324.001.8, and .9 RSMo. The Board will return to open session at the conclusion of discussion on closed session items.

14. Adjournment
#5 UMKC/STLCOP Site Preceptor Lists
- UMKC Sites
- UMKC Preceptors
- STLCOP Sites
- STLCOP Preceptors
Applications for Intern Training Special Site/Non-Pharmacist Preceptor

- Astellas Pharma Global Development
- Ayder Referral Hospital
- Clement J. Zablocki VA Medical Center
- Mercy Hospital
- Nelson Mandela Metropolitan University
- Pharmacy & Retail Operations- Walgreens Corporate Office
- ProPharma Group
- Rite Aid District Office
- US Food and Drug Administration
- Washington County Memorial Hospital
Comments on MO BOP 20 CSR 2220-2.200 Sterile Compounding Rule
Introduction and Executive Summary

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 and are intended to provide feedback to the Board of Pharmacy about 20 CSR 2220-2.200 Sterile Compounding. To explain our concerns, we will be citing a section of the rule, providing suggested language, citing references with rationale, indicating a priority level, and describing the impact to patient safety.

Public safety is the first priority for the Board of Pharmacy, and the Sterile Compounding Rule makes significant progress in regulating an area of high risk. Because of that, we have identified areas and provided comments to promote public safety. Because USP 797 is the industry standard for safe sterile compounding, our comments will reflect differences between Board of Pharmacy Rules and USP 797.

In addition to public safety, Executive Order 17-03 requires that all regulations have a positive cost-benefit, are essential, minimally restrictive, and scientifically based, and do not adversely affect the public. Our comments are submitted in light of these principles. When Missouri Board of Pharmacy rules contradict existing regulations it can be difficult for pharmacies to design appropriate systems to comply with the varying requirements. Class H Pharmacies owned by health systems are subject to regulations from regulatory bodies like the FDA, the Joint Commission, DHSS, CMS and professional organizations like the American Society of Health-System Pharmacists. Adopting the language proposed below would make compliance with all of those organizations more feasible, ensuring that the rules do not interfere with the public’s access to medications.

Thank you for your consideration.

Executive Summary of Proposed Changes

- **Comment 1**: Immediate cessation of sterile compounding for viable results above action level in ISO 7 areas does not increase patient safety, but rather decreases it because it creates dangerous interruptions in care for the public and discourages thorough evaluation of microbial contamination risk. The Board of Pharmacy should promote thorough viable sampling that allows for the identification of issues and continual improvement of compounding facilities and practices, without putting the public at risk through unnecessary disruptions.

- **Comment 2**: The definition of a controlled area should be amended to allow pharmacies to employ ISO-7 facility features in controlled areas to reduce non-viable and viable burden, increase cleanliness and improve patient safety.

- **Comment 3**: Board of Pharmacy inspectors have marked our Pharmacies as non-compliant with garbing when sterile gloves were NOT donned in the ante room. However, donning sterile gloves in the ante room leads to contaminated gloves, which puts the public at risk. Pharmacies should be allowed to don gloves in a manner that is safe.

- **Comment 4**: A RABS unit is a closed system that protects the compounding area from contamination. The garbing requirements for RABS should be different from the requirements for an open hood due to the different risks in contamination. Requiring the same level of garbing is unnecessary and results in barriers to providing safe care to the public.
Comment 5: The completion of 1 media fill test is a sufficient indicator of safe sterile technique. Requiring the completion of 3 tests creates an undue burden without any corresponding safety improvements.
COMMENT #1

Current Language: Section (20): “If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels in any ISO-5 or ISO-7 classified area, no further compounding shall be performed until resampling shows a suitable state of microbial control”

Suggested Language: “If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels in any ISO-5 classified area, no further compounding shall be performed in the ISO-5 area until resampling shows a suitable state of microbial control. If a highly pathogenic microorganism is detected, or if CFU count exceeds USP 797 action levels in any ISO-7 classified area, the beyond use date for all compounded sterile product made in the ISO-7 area shall not exceed the BUDs for Risk Level 1 products until resampling shows a suitable state of microbial control.”

References:
- USP 797 does not require facilities to immediately cease compounding, but rather advises a prompt re-evaluation of operations and facilities including the assistance of a competent microbiologist, infection control professional or industrial hygienist followed by cleaning and re-sampling of failed results.
- The current sterile compounding 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. In these two scenarios the risk to a patient receiving a Risk Level 1 product is the same.
- See additional comments presented by Alison Smith at the Board of Pharmacy Meeting, April 19th, 2017.

Priority: HIGH

Patient Safety Impact:
- Delays and interruptions in the provision of timely and life sustaining compounded sterile preparation (CSPs) to patients are unavoidable if this rule remains unchanged. Incubation time/temperature for viable samples is 30°C to 35°C for 48 hours to 72 hours followed by 26°C to 30°C for 5 to 7 days. This means pharmacies with failed viable samples are not able to provide compounded sterile products to Missouri citizens for up to 10 or more days.
  - We are concerned about interruptions in the provision of CSPs from both the pharmacies within our own institutions as well as from our pharmacy partners (e.g., Centralized Admixture Pharmacy Services (CAPS)). If CAPS were required to cease compounding under this rule, we would expect a major shortage of TPNs and other CSPs affecting multiple hospitals and outpatient institutions in the Kansas City Area.
- When viable sampling is not performed correctly, accurate results are not obtained, and public safety is undermined. Current language imposes unnecessarily severe consequences for failed viable sampling in ISO 7 areas, and the unintended consequence may be that the following sup-optimal techniques are employed in order to avoid dangerous interruptions to patient care. Below are examples of techniques which have been discussed amongst Class H hospital pharmacy infusion centers to meet the current rule.
  - Shortening the incubation time of viable samples
  - Decreasing the number of samples drawn
  - Not performing CFU identification to the genus level for below action level CFU counts
  - Not performing viable sampling in segregated compounding areas
COMMENT #2

Current Language:
Section (1):
“(I) Controlled area: For purposes of these regulations, a controlled area is 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.”

(E) Buffer area: An ISO Class 7 or better area where the primary engineering control is physically located that is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

“(R) ISO Class 7: An area with less than three hundred fifty-two thousand (352,000) particles (0.5 μm and larger in size) per cubic meter.”

Section (5):
“(A) Risk Level 1: Risk Level 1 preparations must be prepared in a PEC located in a controlled area that meets the requirements of this rule.

“(B) Risk Level 2: In addition to all Risk Level 1 requirements, Risk Level 2 preparations must be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled area. Applicable environmental monitoring of air and surfaces must be conducted.”

Suggested Language: Section (1): “(I) Controlled area: For purposes of these regulations, a controlled area is 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. A Controlled area does not have to meet all ISO 7 requirements but may have facility features designed to reduce contamination to the area (i.e. HEPA filtration).”

Priority: Medium

Patient Safety Impact:
Board of Pharmacy inspectors have interpreted the current rule to mean that there are two facility options for sterile compounding: a controlled area or an ISO-7 buffer room. In order to provide a higher level of safety, some pharmacies have elected to prepare Risk Level 1 CSPs in a controlled area that meets some, but not all, ISO-7 room requirements. When Board inspectors have identified room certification reports for these controlled areas with viable sample results that are outside of USP 797 action levels, they have interpreted these reports as being a failed ISO-7 room requiring the cessation of compounding. Board of Pharmacy inspectors have suggested that the facility stop testing the room so that there is no report indicating ISO-7 features (i.e. Air Changes per Hour, Non-viable / Viable Samples).

Patient safety is enhanced when Risk Level 1 products are prepared in a controlled area that has facility features like HEPA filtration and reduced non-viable counts. Pharmacies should not be discouraged from testing and improving the air quality in these areas. The suggestions from Board of Pharmacy inspectors to remove HEPA filtration from the room so it is not misinterpreted as a buffer room would result in a room that has fewer safety precautions protecting the public.

Additional Comments: Alternatively, in lieu of amending the rule, inspectors should be made aware that when a Pharmacy compounds only Risk Level 1 products in a controlled area that has some ISO-7 room features, patient safety is enhanced and the intent of the rule as it is currently written is not to prohibit this practice.
COMMENT #3

Current Language: Section (8) “(B) Risk Level 2 and Risk Level 3: In addition to Risk Level 1 requirements, shoe covers and sterile gloves must be worn while compounding and cleaning, including, over RABS gloves. All personnel in the controlled or buffer area must garb as required by this section”

Suggested Language: Section (8) “(B) Risk Level 2 and Risk Level 3: In addition to Risk Level 1 requirements, shoe covers and sterile gloves must be worn while compounding and cleaning, including, over RABS gloves. All personnel in the controlled or buffer area must garb as required by this section. To ensure sterility, sterile gloves will be donned immediately prior to compounding in the buffer area”

Additional Comments: Alternatively, in lieu of amending the rule, inspectors could be notified that this advice is not consistent with USP 797 and is not what the board intended when drafting this section of the rule.

References:
USP 797 states:
- “Adequate provision for performing antiseptic hand cleansing using an alcohol-based surgical hand scrub with persistent activity followed by the donning of sterile gloves should be provided after entry into the buffer area.”
- “Once inside the buffer area or segregated compounding, and prior to donning sterile powder-free gloves, antiseptic hand cleansing shall be performed using a waterless alcohol-based surgical hand scrub with persistent activity following manufacturers’ recommendations. Hands are allowed to dry thoroughly before donning sterile gloves. Sterile gloves shall be the last item donned before compounding begins. Gloves become contaminated when they contact nonsterile surfaces during compounding activities.”

Priority: Medium

Patient Safety Impact:
- Donning sterile gloves in the ante room defeats the purpose of wearing sterile gloves as the gloves become contaminated when moving from the ante room to the buffer room for compounding.
COMMENT #4

**Current Language:** Section (8) “(A) Risk Level 1: Low-particulate and nonshedding gowns, hair covers, gloves, face masks, and, if applicable, beard covers must be worn during compounding and cleaning. All head and facial hair must be covered. During sterile preparation, gloves shall be disinfected before use and frequently thereafter with a suitable agent and changed when integrity is compromised. **All personnel in the controlled area must be appropriately garbed as required by this section.**”

**Suggested Language:** Section (8) “(A) Risk Level 1: Low-particulate and nonshedding gowns, hair covers, gloves, face masks, and, if applicable, beard covers must be worn during compounding and cleaning. All head and facial hair must be covered. During sterile preparation, gloves shall be disinfected before use and frequently thereafter with a suitable agent and changed when integrity is compromised. **All personnel in the controlled area must be appropriately garbed as required by this section. Pharmacies utilizing a RABS as the source of the ISO-5 environment may omit PPE not deemed necessary by the manufacturer if manufacturer documentation of validated environmental testing in the absence of PPE is maintained by the Pharmacy.**”

**References:**

USP 797 states “When CAIs and CACIs are the source of the ISO Class 5 environment, the garbing and gloving requirements for compounding personnel should be as described above, unless the isolator manufacturer can provide written documentation based on validated environmental testing that any component(s) of PPE or personnel cleansing are not required.”

**Priority: Medium**

**Patient Safety Impact:**
- A RABS is designed to protect the product from the sterile compounding employee, so garbing is an unnecessary step.
- The burden of unnecessary requirements on compounding personnel can have the unintended consequence of decreased compliance with other practices that impact public safety.
**COMMENT #5**

**Current Language:**  Section (10) B “A minimum of three (3) media-fill tests must be completed during initial media-fill testing and one (1) media-fill test completed for ongoing testing.”

Section (10) D “Individuals who fail media fill testing must pass three (3) successive media-fill tests prior to resuming sterile compounding”

**Suggested Language:**  Section (10) B “One media-fill test must be completed during initial media-fill testing and annually thereafter for ongoing testing.”

Section (10) D “Individuals who fail media fill testing must pass one media-fill test prior to resuming sterile compounding”

**References:**

- USP 797 does not require 3 media-fill tests during initial media-fill testing or when media-fill tests fail. It states:
- “Media-fill testing of aseptic work skills shall be performed initially before beginning to prepare CSPs and at least annually thereafter for low- and medium-risk level compounding and semiannually for high-risk level compounding.
- Compounding personnel who fail written tests or observational audits or whose media-fill test vials have one or more units showing visible microbial contamination shall be re-instructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic work practice deficiencies. Compounding personnel shall pass all evaluations prior to resuming compounding of sterile preparations.”

**Priority:** Medium
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
http://www.regulations.gov

February 22, 2017


To Whom It May Concern:

Cardinal Health Nuclear Pharmacy Services (NPS) is pleased to submit comments to the Food and Drug Administration (FDA) on the Draft Guidance – Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities, Guidance for Industry, Docket No. FDA-2016-D-4318.

Cardinal Health is a leader in nuclear pharmacy, with 132 specialized nuclear pharmacies operating in 45 states, employing over 550 nuclear pharmacists and more than 1,000 nuclear pharmacy technicians. With our national footprint, we prepare and dispense FDA approved, commercially manufactured, time critical, rapidly decaying radiopharmaceuticals with the ability to serve over 90% of the U.S. population.

Cardinal Health continues to actively participate with industry trade associations and constituency groups such as the National Association of Nuclear Pharmacies (NANP), the American Pharmacists Association (APhA), the Council on Radionuclides and Radiopharmaceuticals (CORAR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) to address industry-wide issues.

The multiple “listening sessions” the FDA has held since 2014 with organizations representing the radiopharmacy community (NANP, CORAR, SNMMI, and APhA) have proven to be of benefit. The draft guidance incorporates feedback from these listening sessions and the Compounding Policy Guidelines (CPG) developed by CORAR. We are supportive of the draft guidance as released and want to reinforce some key messages and seek further clarification on one point:

- Minor Deviations

We support the stance taken in the draft guidance with respect to minor deviations from a drug product’s approved labeling, including the amount of radioactivity, a change in volume and changes in the step-by-step procedures. Nuclear pharmacy practice has long standing rationale for minor deviations to the FDA approved labeling of commercially available products to increase safety and quality, and improve patient care. These minor deviations are necessary to incorporate new technologies, to accommodate extra time needed to serve patients in distant areas or after hours, or to reduce radiation exposure to those individuals preparing radiopharmaceuticals. In today’s current USP <797> terminology, the preparation of sterile radiopharmaceuticals using commercially manufactured FDA approved products is classified as a “low risk” compounded sterile preparation (CSP).
• Beyond Use Date (BUD)

We request clarification regarding beyond use dates. Please reference lines 322-327 (emphasis added), which state:

"The radiopharmaceutical is compounded or repackaged in compliance with the following USP Chapters:
- If it is a non-sterile radiopharmaceutical, it is compounded or repackaged in accordance with USP Chapter <795> (except for the BUD); or
- If it is sterile radiopharmaceutical, it is compounded or repackaged in accordance with USP <797> (except for the BUD)."

Similar text appears in lines 230-234.

Our interpretation of the FDA's draft guidance document is that, when supported by data, pharmacies are allowed to compound radiopharmaceuticals and assign BUDs up to and beyond the USP <797> BUD limits. Is that the FDA's intent and interpretation as well?

If it is not, we request that FDA adopt such a position and include such BUD extensions as minor deviations and treat them in a similar manner to how the addition of a supplemental quantity of Tc-99m sodium pertechnetate is handled and described on lines 130-133. An extended BUD can also facilitate providing a radiopharmaceutical to a geographically distant patient, with a later use time. Additionally, in nuclear medicine, radiopharmaceuticals are routinely used in emergency situations after hours to diagnose critical life-threatening conditions. A BUD that has been validated and that exceeds the drug product manufacturer's BUD would enable pharmacists to prepare and deliver radiopharmaceuticals to be used in emergency, after-hours situations. The availability of nuclear pharmacists to prepare radiopharmaceuticals for administration to patients is significantly limited with only approximately 400 nuclear pharmacies throughout the U.S.

• We support the stance taken in the draft guidance with respect to the prohibition on compounded radiopharmaceuticals that are essentially copies of marketed FDA-approved radiopharmaceuticals. Furthermore, pharmacists will appreciate the clarity provided regarding the conditions necessary to compound radiopharmaceuticals that involve manipulations other than minor deviations, and how to document a prescribing practitioner's request to have a compounded radiopharmaceutical prepared for an identified individual patient.

We would like to reiterate the value of nuclear medicine procedures in patient care. The unique practice of nuclear pharmacy was the first pharmacy specialty practice recognized in 1978 by the Board of Pharmaceutical Specialties, and for a decade it remained the only recognized specialty practice setting. The unique nature of nuclear pharmaceuticals necessitates minor deviations from product labeling, which, when performed by licensed nuclear pharmacists in licensed nuclear pharmacies, can improve safety and patient care with no negative effect on the safety or effectiveness of the drugs.

Thank you for the opportunity to comment on the draft regulatory guidance.

Sincerely,

David W. Pellicianini, CHP
Vice President, Pharmacy Safety, Practice & Technical Operations
Cardinal Health NPS

Tiffany Olson
President
Cardinal Health NPS
May 30, 2017

Tom Glenski, RPh
Chief Inspector
Missouri Board of Pharmacy
3605 Missouri Blvd.
Jefferson City, MO 65109
(660) 535-4374
Tom.glenski@pr.mo.gov

RE: 20CSR 2220-2.200 Sterile Compounding applicable to radiopharmaceuticals

Dear Mr. Glenski:

Thank you for taking the time to address the unique challenges faced by nuclear pharmacies. Currently, the FDA and USP are formulating specific regulations and standards for radiopharmaceuticals. The FDA will have their second radiopharmaceutical listening session June 5th, and a new guidance is expected to be published which will replace the last radiopharmaceutical FDA guidance published in 1984. The USP Compounding Expert Committee formed a roundtable February 2017 to discuss the compounding standards for radiopharmaceuticals. As a result, the USP has decided to develop a new chapter that will be specific for the compounding of radiopharmaceuticals.

The ability to prepare radioactive drugs with short half-lives became available, in part, through the use of the Molybdenum Mo-99/ Technetium Tc-99m generator (Tc-99m generator). The Tc-99m generator serves as a source of the short lived radiopharmaceutical Tc-99m pertechnetate which decays with a physical half-life of six hours. Today, 85% of radiopharmaceuticals used in nuclear medicine are Tc-99m radiopharmaceuticals. These Tc-99m radiopharmaceuticals are prepared with Tc-99m pertechnetate and various non-radioactive manufacturers’ kits. These prepared Tc-99m radiopharmaceuticals have suggested expiration times ranging from 4 hours to 18 hours after preparation. Using the manufacturer’s product labeling (i.e., package insert) is not always the best practice as they have been shown to have deficiencies. Because of these deficiencies, the industry has a standard of performing quality control on the Tc-99m radiopharmaceutical to ensure that stability is retained throughout the beyond use date (BUD).
A study by Weatherman examined and confirmed sterility of these products while in the manufacturer's vial (as would be the case with Missouri's In-Use Times) and when stored in the syringe.\textsuperscript{6,7} It is worth noting that in comparison to other pharmaceuticals, all Tc-99m radiopharmaceuticals have a short BUD and are used within 24 hours of preparation.

The Authorized Nuclear Pharmacist has the specialized training and knowledge to address the challenges of preparing and dispensing sterile radiopharmaceuticals. Current quality control testing ensures that BUDs established for Tc-99m radiopharmaceuticals are appropriate and safe.

The consequences from shortening the BUD from standard practice would result in a decrease in efficiency in the use of radiopharmaceuticals and no increase in the purity or safety of the radiopharmaceuticals. This would ultimately result in an increase in cost for the radiopharmaceutical with no benefit to the patient.

Although I no longer practice in Missouri I was the nuclear pharmacist at St. John's Mercy Medical Center in Creve Coeur, MO for fourteen years. Through the years I've been active with the American Pharmacist Association. Our Nuclear Pharmacy SIG has a regulatory affairs committee that has been following this issue in Missouri and other States. Through this SIG I've worked closely with Fred Gattas of Triad Isotopes in St. Charles and Sally Schwarz of Washington University in St. Louis. They are very knowledgeable and helpful individuals. I encourage the Board to continue to examine the unique practice of nuclear pharmacy and to work with nuclear pharmacists such as Fred and Sally to ensure the safe and consistent supply of these valuable radiopharmaceuticals.

Sincerely,

Steve Mattmuller MS, RPh, BCNP
Chief Nuclear Pharmacist
MO 030040

Kettering Medical Center
3535 Southern Blvd.
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References


Fred Gattas, RPh
fgattas@triadisotopes.com

Sally Schwarz
SchwarzS@mir.wustl.edu
June 1, 2017

Tom Glenski, RPh.
Chief Inspector
Missouri Board of Pharmacy
3605 Missouri Blvd.
Jefferson City, MO  65109

Dear Mr. Glenski,

Thank you for taking the time to review our concerns in regard to in-use-time (IUT) for radiopharmaceuticals. From what has been discussed, once a radiopharmaceutical has been prepared all doses drawn from that vial must be injected into the patients within the IUT specified by the package insert. It is my opinion, and the opinion of other nuclear pharmacists, that we have professional discretion to determine the expiration (IUT) of the radiopharmaceuticals as long as there is documentation to support the stability and sterility of the drugs.

Centralized nuclear pharmacies prepare the radiopharmaceuticals for that days use as early as 1:30AM. These compounds have finite shelf lives before the bound complex begins to deteriorate and fail quality control. Most of the compounds begin to deteriorate at 12 hours or even sooner. In addition, the locations of some of our customers are 1.5-2 hours away. Typically, hospitals start injecting patients around 7:30AM. If we were strictly held to following the package insert on some of the radiopharmaceuticals, they would expire before they could even be injected. This being the case, nuclear pharmacies would have difficulty adequately servicing rural customers. Instead of one to two shipments being sent per day, three to four would have to be sent. The costs of goods would increase which would in turn be passed on to the hospital which would ultimately be passed onto the patient, increasing the cost of health care. The Mo-99 generators we use that produce the Tc-99m cannot be eluted an infinite number of times and consistently receive the same activity of Tc-99m. The generators need time to recharge to get the concentration that is needed to prepare the radiopharmaceuticals. This means that a nuclear pharmacy would have to ship out the drugs at certain intervals during the day, especially to the more rural hospitals. This would in turn create downtime in the nuclear medicine department; frustrating doctors, nuclear medicine technologists, and patients. The end result is a hindrance in patient care.

The following example is one of many ways patient care would be hindered if nuclear pharmacists could not have professional discretion on IUT. A vial of Sestamibi (used for heart imaging) was prepared at
3:00AM and is set to expire at 9:00AM according to the package inserts 6 hour IUT. A hospital calls at 9:30 AM and wants to do a heart scan immediately on a patient that just came into the ER. Instead of being able to send out the dose using the IUT we currently use of 12-14 hours, the Mo-99 generator has to be eluted, the kit prepared, boiled for 25 minutes, do a quality control test on the finished product, dispense the dose and ship it to the hospital. Because of this, the patient and doctor will have to wait an extra 40 minutes, including travel time before the dose arrives. The unwanted outcomes could possibly be hospitals no longer using the centralized nuclear pharmacy and having nuclear medicine technologists in the hospitals compound the radiopharmaceuticals or doctors would order fewer doses because they could not always receive them when they need them.

Nuclear pharmacies have been around since the 1970’s. From that time until the late 1990’s to the early 2000’s most nuclear pharmacies did not have clean rooms or even a semi-sterile environment when compounding radiopharmaceuticals. Aseptic technique was utilized however. Over the past three decades, there have not been incidences of rampant infection in patients or any type of infection caused by a lapse of aseptic technique or improper dose drawing techniques by nuclear pharmacists. If infections from radiopharmaceutical preparations were occurring, nuclear pharmacies would have been investigated and shuttered decades ago, however this has not been the case. In addition, one-third of our preparations are boiled to complete the binding process. The length of the boil varies, but the end result is either denatured or destroyed pathogens, if there were any; which by the previous argument, has not been the case.

I thank the Missouri Board of Pharmacy for their time in addressing the IUT of radiopharmaceuticals. I, and many other nuclear pharmacists in the state of Missouri hopes the board continues to allow us to use our professional discretion in establishing the IUT of radiopharmaceuticals based upon stability and sterility of the preparations. In addition, I have attached peer reviewed articles on stability and sterility of radiopharmaceuticals and our in house stability tests on some of the preparations. Please feel free to contact me if you have any questions.

Sincerely,

Brent McHugh PharmD.
Manager- Mid America Isotopes
May 18, 2017

Brent McHugh
Mid-America Isotopes
706 E. Liberty Lane
Ashland, MO 65010

Dear Mr. McHugh,

Here is my opinion about the stability of radiopharmaceutical kits such as Tc-99m sestamibi. First, I have worked as a physician in a Nuclear Medicine clinic for 39 years and 9 months. Most of that time my clinic had a Mo99/Tc99m generator and we formulated our radiopharmaceuticals from kits. From 1977 to 1992 my clinic formulated its own kits under a federal IND by our radiopharmacist.

In my experience, Tc-99m sestamibi, and most radiopharmaceuticals, are stable for more than 8 hours [from time of formulation to the time of injection into the patient]. I have not observed imaging artifacts due to degradation from radiopharmaceutical purity. Attached are two articles that indicate that Tc-99m sestamibi is stable for 8-24 hours.

The statements in this letter are mine and do not represent those of the federal government or the University of Missouri.

Sincerely,

Thomas Dresser PhD, MD
Captain, Medical Corps, United States Navy (Retired)
Diplomate, American Board of Nuclear Medicine (1981, 2016)
Chief, Nuclear Medicine, Harry S Truman Memorial Veterans Hospital, Columbia, MO
Clinical Professor of Radiology, University of Missouri, Columbia, MO
Assessing the Stability of Common Radiopharmaceuticals Compounded and Utilized Outside Package Insert Guidelines

Kara D. Weatherman  
PharmD, BCNP, FAPhA
Samuel Augustine  
PharmD, FAPhA
Jeffrey Christoff  
PhD
Wendy Galbraith  
PharmD, BCNP

INTRODUCTION

The act of compounding radiopharmaceutical imaging agents is carried out by a licensed pharmacist, licensed medical physician, or by designees of either, working under the supervision of the licensed professionals. However, there is a significant amount of flexibility in how compounding is carried out. Over time, it has become common practice for radiopharmaceuticals to be compounded using amounts of activity that exceed manufacturers’ recommendations. To assure that compounded sterile preparations (CSPs) can be delivered and utilized in a timely yet economical fashion, it is often required that manufacturers’ defined-use times are extended as well. With the recent release of United States Pharmacopeia (USP) Chapter <797>, the practice of compounding any CSP, including radiopharmaceuticals, has required practitioners to review their policies and procedures when it comes to the preparation of these agents. While alteration of manufacturing guidelines may be necessary in an attempt to provide patients with the highest quality CSP in a timely fashion, at the best possible prices, while maximizing the resources, a major tenet of the new USP Chapter <797> standards requires that practitioners must be able to prove that if the manufacturer’s compounding instructions are altered, the preparation of the radiopharmaceutical will be carried out in a manner that assures the quality and safety of the end CSP. The intent of this study is to evaluate the stability of radiopharmaceutical kits compounded using various activity levels outside of those recommended by the manufacturer. In addition, we also evaluated how the changes in compounding activity impacted the stability of the CSP over extended periods of time in which the radiopharmaceutical could potentially be administered to patients for imaging, up to the time point

ABSTRACT

The objective of this study was to evaluate the stability of radiopharmaceuticals compounded using activities and expiration times in excess of manufacturers’ recommendations. Proof of the compounded sterile preparation quality when compounding outside of manufacturers’ recommendations has become a key component of maintaining compliance with the guidelines set forth in United States Pharmacopeia General Chapter <797> Pharmaceutical Compounding—Sterile Preparations, guidelines of which were released in 2008. Seven commercial nuclear pharmacies compounded various radiopharmaceuticals for patient use as part of daily pharmacy protocol. Samples of radiopharmaceuticals were tested using instant thin-layer chromatography testing to determine the radiochemical purity of the final compounded sterile preparation at t=0, t=6, t=12, and t=24 hours post compounding. Data submitted was summarized and divided into activity ranges allowing for calculation of average radiochemical purity for various activity levels at each of the four time points. Data was presented in graph form showing the average radiochemical purity values versus time, as well as in supplemental table form showing average radiochemical purity and standard deviation data. The stability of each kit at different activity levels and at different time points post compounding showed that many of the radiopharmaceutical kits prepared today may have an unacceptable decrease in radiochemical purity at higher activity levels and at extended times post compounding. The data submitted provides a general guideline for the stability of radiopharmaceuticals compounded outside of manufacturer guidelines and can be used as a tool to support the practices that are being carried out at individual institutions. However, this data should be used in conjunction with in-house data review to assure that the preparations being compounded and dispensed are of the highest quality for administration to the patient.
24 hours after compounding. To assess stability, we looked at the radiochemical purity of the compounds—the percent of the radioactivity that was bound to the desired ligand. This data was compiled from various nuclear pharmacies throughout the country to get a better review of the wide variation of compounding practices that are currently used. While individual users will still need to verify their own specific practice standards, this document is intended to give some guidance to compounding personnel, as well as to stimulate discussion between nuclear medicine departments and their radiopharmaceutical suppliers to assure that the highest quality CSPs are being administered to patients.

MATERIALS AND METHODS

Samples of radiopharmaceutical kits that were compounded and dispensed as part of normal, daily nuclear pharmacy activities were obtained from seven different commercial nuclear pharmacies between November 2006 and June 2010. The data for this study was collected concurrently with data that was utilized for a parallel study that looked at the sterility and pyrogenicity of radiopharmaceuticals. The data for the sterility/pyrogenicity arm of the study is presented elsewhere. The original study had a target goal of 175 samples for each of the various radiopharmaceutical kits being tested. Due to the Mo-99/technetium-99m (Tc-99m) generator availability issues over the last several months, data collection took significantly longer than anticipated and, in some cases, required a decrease in the number of samples that were submitted for final evaluation. Most of the commonly used radiopharmaceutical kits were able to reach our 175 sample goal, but this became increasingly difficult with some of the less-often used radiopharmaceutical kits.

Nuclear pharmacies that participated in the study were asked to use their site-specific compounding guidelines that allowed for a much greater range of compounding activities for evaluation purposes. After compounding each radiopharmaceutical kit, patient-specific unit doses were removed and dispensed per the nuclear pharmacy’s specific protocol. Kits that had sufficient residual material after dispensing the required unit doses were eligible for inclusion in this study, and each nuclear pharmacy was able to determine what preparations were used for sample submission. Since all radiopharmaceutical kits are tested for radiochemical purity prior to dispensing for human use, the initial radiochemical purity result was included as the t=0 time point for our study. In addition to this data point, pharmacies also were instructed to retain a sufficient quantity of the radiopharmaceutical kit for radiochemical testing at 6, 12, and 24 hours post compounding. Each nuclear pharmacy was permitted to utilize their site-specific radiochemical quality control method to provide data for radiochemical purity at each of the time points. All sites utilized thin-layer paper chromatography for testing, although the solvent/solid support combination may have been different from pharmacy to pharmacy. Data for each radiopharmaceutical kit was submitted for independent review and data summation. Results from each kit were entered into a spreadsheet upon submission to the review site for easy data manipulation and evaluation. Data for each radiopharmaceutical kit was separated into sub-groups based on the amount of activity used for compounding of the kits. For each activity sub-group, the average radiochemical purity was calculated at each of the four identified time points: 0, 6, 12, and 24 hours post compounding. In addition, standard deviation for the group was also calculated. Data is presented as a graphic representation of the radiochemical purity at each time point, providing a visual representation of the changes in radiochemical purity over time.

RESULTS

Data for each radiopharmaceutical is summarized in graph form showing the average radiochemical purity with error bars at each time point (0, 6, 12, and 24 hours) for each of the activity ranges. The number of activity ranges varied by CSP, depending on the overall range of activities used to compound.

Sodium Pertechnetate

Tc-99m sodium pertechnetate plays an essential role in the compounding process of the radiopharmaceuticals evaluated in this study, as a bulk-compounding agent for distribution to hospital nuclear medicine departments and as a stand-alone imaging agent. Our study evaluated the radiochemical purity of generator eluates from Mo-99/Tc-99m generators obtained from both

FIGURE 1. Tc-99m sodium pertechnetate.
manufacturers (TechneLite; Lantheus Medical, North Billerica, Massachusetts and Ultra-TechneKow; Covidien, Hazelwood, Missouri). There were 166 samples submitted from generator elutions, ranging from 4.44 GBq to 470.455 GBq (120 mCi to 12,715 mCi); a graphic distribution is presented in Figure 1.

Cardiac Imaging Agents

The three currently available radiopharmaceuticals for myocardial perfusion imaging are: (1) Tc-99m Cardiolite (Lantheus Medical); (2) Tc-99m sestamibi (various manufacturers); and (3) Tc-99m Myoview (GE Healthcare, Arlington Heights, Illinois). A total of 168 samples were evaluated in the Tc-99m Cardiolite group. Preparation activities for kits submitted ranged from 12.025 GBq to 123.58 GBq (325 mCi to 3340 mCi). A total of 180 Tc-99m sestamibi samples were evaluated, ranging from 11.211 GBq to 196.47 GBq (303 mCi to 5310 mCi). A total of 166 Tc-99m Myoview samples were evaluated with activities between 4.255 GBq and 55.685 GBq (115 mCi and 1505 mCi). Data for the myocardial imaging agents is presented in Figure 2.

Bone Imaging Agents

A total of 167 Tc-99m MDP samples were evaluated. This total was a summary of data from three different manufacturers: (1) DraxImage (Kirkland Quebec, Canada); (2) Bracco Diagnostics (Spokane, Washington); and (3) GE Healthcare. Preparation activities ranged from 9.731 GBq to 44.4 GBq (263 mCi to 1200 mCi). Samples from Tc-99m HDP (Covidien, Hazelwood, Missouri) included in this study numbered 171. Activity used for compounding ranged from 6.438 GBq to 46.25 GBq (174 mCi to 1250 mCi). Figure 3 shows the results for the bone imaging agents.

Particulate Agents

There are two particulate agents that were evaluated in this study: (1) Tc-99m MAA (DraxImage) and Tc-99m sulfur colloid (Pharmalucence, Bedford, Massachusetts). A total of 179 Tc-99m MAA
samples were evaluated ranging from 1.998 GBq to 17.834 GBq (54 mCi to 482 mCi). Assessment of 164 Tc-99m sulfur colloid samples from kits compounded with activities between 0.888 GBq and 18.019 GBq (24 mCi and 487 mCi) was performed. The results of the particulate imaging agents are presented in Figure 4.

Hepatobiliary Imaging Agents

Three preparations were tested for the hepatobiliary group: (1) Tc-99m Choletec (Bracco Diagnostics); (2) generic Tc-99m mebrofenin (Pharmalucence); and (3) Tc-99m Hepatolite (Pharmalucence).13-15 Over the course of the study, 213 samples of Tc-99m Choletec were submitted, ranging from 3.737 GBq to 12.21 GBq (101 mCi to 330 mCi). The generic mebrofenin product group includes 159 samples with activities between 2.109 GBq and 24.124 GBq (57 mCi and 652 mCi). Tc-99m Hepatolite had the smallest number of samples submitted (38); this was not unexpected since Tc-99m Hepatolite is used much less frequently than the other hepatobiliary imaging agents. For the samples submitted, activities ranged between 3.7 GBq to 5.809 GBq (100 mCi to 157 mCi). While this number of samples is small and most likely does not provide sufficient data to determine the true effect of increased activities and BUD times, data is included for comparison purposes with the other two agents. Figure 5 shows the data distribution for the three hepatobiliary agents.

Renal Imaging Agents

There were 176 Tc-99m DTPA (Drax-Image) data points used for evaluation purposes. Kits were compounded with activities ranging from 1.739 GBq to 30.192 GBq (47 mCi to 816 mCi).16 In addition, 174 Tc-99m MAG-3 (Mallinckrodt, St. Louis, Missouri) samples were submitted with activities between 1.332 GBq to 10.36 GBq (36 mCi to 280 mCi).17 The renal imaging agent data is shown in Figure 6.

Other Radiopharmaceuticals

Several radiopharmaceuticals were tested during the course of the study, but due to relative lack of clinical use did not generate a sufficient number of data points to provide any meaningful insight into the stability of these preparations and are not presented in this report. Since most of these products are used infrequently, it is a reasonable assumption that when compounding these preparations, utilizing manufacturer guidelines would provide the highest quality preparation. The products that fall into this category include Tc-99m Neurolite (Lantheus), Tc-99m Ceretec (GE Healthcare), and Tc-99m DMSA (GE Healthcare).18-20

DISCUSSION

There are obvious issues that can arise when exceeding manufacturer recommended activity and expiration time. In general, most radiopharmaceutical kits are formulated with an excess of both reducing agent (stannous ion) and ligand. This disparity serves to enhance the likelihood that the labeling reaction will progress to completion. In addition, the presence of excess ligand is essential to maintain solu-
bility of the metal ion (Tc-99m) once it is reduced to the proper oxidation state. Of greatest concern when altering the amount of Tc-99m that is introduced in the system, is that at some point the relative excess of stannous ion or ligand may not be sufficient to push the reaction to completion, which has the potential for negatively impacting the labeling yield. There is no publicly available reference source that identifies where the “cutoff point” would be located, and the scope of this study was not sufficient or extensive enough to determine precise data to provide this type of information, although some of the declining radiochemical purity values for some of the products may indicate that the increased amount of radioactivity may be approaching this critical point. Further evaluation to determine this more accurately would be a logical follow-up to this initial assessment of radiopharmaceutical stability.

Quality-control tests were performed at time of compounding (t=0), as well as 6, 12, and 24 hours post compounding. Radiopharmaceuticals are routinely used for up to 12 hours post compounding, and USP <797> provides a category for low-risk CSPs with a beyond-use date (BUD) of 12 hours or less. But, in some instances, expiration times for radiopharmaceuticals are extended even beyond the 12-hour point. In our study, we chose to look at a 24-hour time point, knowing that there are very few instances in which any preparation would be used this far beyond compounding. An 18-hour time point may have been a better representation of a time point where radiopharmaceutical kits might be used, but from a logistics standpoint, most nuclear pharmacies are closed at the time of the 18-hour assessment point. Data was divided into activity levels to try and maximize the number of samples that fell within each group. Unfortunately, for some preparations, this resulted in some activity levels with a very low number of samples, especially at the very high and very low ends of the compounded activity ranges. The number of samples included in each activity group is noted on the corresponding graph for reference purposes.

There are a few general observations about the data. The desired number of samples for each radiopharmaceutical was 175; however, several samples from each group were omitted, most often due to incomplete data. Obvious erroneous data points were also removed from evaluation while the remaining data for that sample were included in the final assessment. An example of an erroneous data point would be an unusually low radiochemical purity result reported at either 6 or 12 hours compared to the other data points in that series. If the radiochemical purity rebounded for the subsequent time points, that low data point was considered to be incorrect and was excluded. However, data points at 24 hours were included regardless of how significantly they deviated from the other data points in the series, due to the increased possibility of kit breakdown at that delayed time point. An added factor in the variation within the 24-hour time point is related to the concentration of the sample being tested at that time point. Given that only 6.25% of the activity remains at 24 hours post compounding, the single drop of sample used in quality-control testing would be of fairly low activity. The low-counting statistics of the samples at that
point could result in a falsely low-calculated radiochemical purity value. Finally, as with any quality-control test, operator error can never be excluded as a possible explanation for an inaccurate test result.

**Sodium Pertechnetate**

Given the importance of Tc-99m sodium pertechnetate, samples from generator eluates used to compound radiopharmaceutical kits in each pharmacy were tested as part of this study. The activity eluted from a generator is a function of the size of the generator (amount of Mo-99 on the column) at time of elution as well as the time elapsed since the last time the generator was eluted. In our evaluation, we did not track the time of elution, the amount of Mo-99 on the generator column, or the elapsed time since the last elution. At the time of elution, Tc-99m sodium pertechnetate can have no more than 5% of the radioactivity present in the hydrolyzed-reduced form. The radiochemical purity of all of the generator eluate samples at all time points, including the 24-hour point, was well above the 95% acceptable range.

**Cardiac Imaging Agents**

The package insert for Tc-99m Cardiolite states a maximum compounding activity of 5.55 GBq (150 mCi) and an expiration time of 6 hours. The data presented for the Tc-99m Cardiolite kits showed that this kit was extremely stable with a radiochemical purity of >90% at all activity levels at the 0- and 6-hour time points, with the exception of the 18.5 GBq to 37 GBq (500 mCi to 1000 mCi) samples. By 12 and 24 hours, several of the midpoint activity ranges fall at or below the 90% level and show significant variation. However, the higher activity levels (>74 GBq [2000 mCi]) continue to maintain a sufficient radiochemical purity level. It should be noted that for most of the kits compounded at these higher activity levels, a practice commonly referred to as “batching” was employed. In this practice, the non-radioactive contents of between two and four Cardiolite cold kits were reconstituted and combined into a single, large-vol-
ume vial and then radioactivity was added in relation to the number of vials used. When total activity added is divided by the total number of kits used in the compounding process, most “batched kits” use less than 37 GBq (1000 mCi) total activity per kit. This may explain the “rebound effect” observed in radiochemical purity at higher activity levels. The consistently low values for the 18.5 GBq to 37 GBq (500 mCi to 1000 mCi) group across all time points from 6 hours on were unexpected, especially when compared to the other higher activity kits at these time points. In reviewing the data individually for this data set, there were a total of 13 data points, eight of which came from a single nuclear pharmacy and were consistently lower than the other five data points. These low values decreased the average radiochemical purity values for this group and contributed to the substantially large error bars for these data points. This strongly points to the possibility that these low radiochemical purity values were most likely due to issues specific to that particular pharmacy.

The generic product sestamibi was released for commercial use in late 2008 and was added to the data collection for this study after this point. Although several manufacturers currently sell a generic sestamibi product, data for the generic kit formulation was collected and combined, regardless of what manufacturer’s product was used. As with Cardiolite, sestamibi has a package insert recommendation of 5.55 GBq (150 mCi) and an expiration time of 6 hours.5 The data submitted for this study showed excellent stability of this product at all activity levels and time points with the exception of the 24-hour time point for the 18.5 GBq to 37 GBq (501 mCi to 1000 mCi) group, which is slightly below the 90% radiochemical purity limit. As with the Cardiolite data, the 24-hour data could be falsely skewed due to poor counting statistics of the sample. An interesting finding when comparing the results from the Cardiolite and generic sestamibi products is that the radiochemical purity was consistently higher, and the standard deviation values were consistently lower for the generic sestamibi at all time points and for all activities. In theory, the generic version of a product should not have substantial differences as compared to the trade name product, so there is nothing in the data or in the kit formulation parameters that fully explains this finding.

According to manufacturer’s recommendations, Tc-99m Myoview should be compounded with a maximum of 8.88 GBq (240 mCi) with an expiration time of 12 hours post compounding.6 In our study, the only kits compounded at an activity that consistently exceeded the 90% radiochemical purity requirement at all time points were kits compounded with activities less than 11.1 GBq (300 mCi). Kits prepared at all activity levels had radiochemical purity values greater than 90% at 6 hours post compounding, while kits with activities less than 33.3 GBq (900 mCi) had average radiochemical purity values above 90% for up to 12 hours post compounding. The average radiochemical purity of higher activity level kits >33.3 GBq (901 mCi)) was significantly lower than the 90% acceptable limit at the 12-hour time point and beyond. This indicates that these groups most likely cross the 90% radiochemical purity limit somewhere between 6 and 12 hours. Given

**FIGURE 6.** Renal imaging agents.
that most users probably utilize these kits routinely up to the 12-hour expiration time point, it appears that the quality of the CSP at 12 hours could be significantly less than acceptable. For facilities that choose to compound at these increased activity levels, additional evaluation should be performed to determine the most consistent acceptable BUD time point for this kit.

**Bone Imaging Agents**

Tc-99m-labeled bone-imaging agents are extremely sensitive to oxidation by air. To counteract this effect, all of the commercial bone imaging agents contain an antioxidant as part of the standard formulation of the products. The Tc-99m MDP bone agents contain ascorbic acid, gentisic acid, or paraaminobenzoic acid to increase stability of the compounded preparation. The recommended maximum activity for compounding MDP is 18.5 GBq (500 mCi) with an expiration time of 6 hours post compounding. In our study, Tc-99m MDP data supports acceptable radiochemical purity standards for all activity levels up to and including the 12-hour time point. However, the 24-hour time point appears to be unacceptable for most of the kits compounded.

Tc-99m HDP contains the antioxidant gentisic acid and should be compounded with a maximum activity of 11.1 GBq (300 mCi) with an expiration of 8 hours post compounding. For the Tc-99m HDP kits in our study, the CSP was extremely stable at all time points, with only a slight degradation of most kits at the 24-hour time point. This is most likely due to the common practice of adding additional ascorbic acid to the kits during the compounding process. The addition of more antioxidant is a common process in many nuclear pharmacies to assure the stability of this CSP. In surveying the participating sites, all of the pharmacies utilized additional ascorbic acid when compounding HDP kits, and added approximately 2 mg of ascorbic acid to the kits after the radiolabeling reaction had been completed, but before dispensing any unit doses.

**Particulate Agents**

The particulate agents include Tc-99m MAA and Tc-99m sulfur colloid, both of which are radiolabeled insoluble particulates. While several manufacturers make a MAA product, the only one used in our study was the MAA kit from DraxImage. Per this package insert, the maximum amount of activity to be added to the kit is 3.7 GBq (100 mCi) with an expiration time of 6 hours post compounding. The data for Tc-99m MAA shows that this CSP is very stable up to the 12-hour time point, even at activities up to 18.5 GBq (500 mCi). There appeared to be a significant decrease in radiochemical purity at the 24-hour time point at most activity levels, most likely indicating that the CSP does not maintain stability for this length of time post compounding. For Tc-99m sulfur colloid, the manufacturer recommends compounding with a maximum of 18.5 GBq (500 mCi) with an expiration of 6 hours post compounding. Tc-99m sulfur colloid is a unique CSP in that the Tc-99m does not actually “bind” to the ligand. In the formation process, the Tc-99m is surrounded by a sulfur coat, which would make CSP breakdown and liberation of the free pertechnetate molecule less likely to occur. Based on our data, this CSP is very stable at all data points up to 12 hours, with a slight decrease at all activity levels at the 24-hour time point. Interestingly, the lower activity levels (<5.55 GBq [150 mCi]) showed consistently lower radiochemical purity values as well as greater standard deviations than compared to the higher activity level kits. This apparent decrease in radiochemical purity would most likely be due to poor counting statistics of the sample as the radioactive concentration decreased with time.

**Hepatobiliary Agents**

The hepatobiliary agents were the group that showed the greatest impact in stability over time. There are three commercially available hepatobiliary agents, one of which is a generic version that was released in 2008. According to package insert guidelines, Tc-99m Choletec should be compounded with a maximum of 3.7 GBq (100 mCi) of activity with an expiration time of 18 hours post compounding. This extended expiration time is due to the presence of the preservatives methylparaben and propylparaben in the kit formulation. Based on the data submitted for this study, the radiochemical purity of this CSP at all activity levels is acceptable at t=0 and, in general, at t=6 hours post compounding. However, by 12 hours post compounding, the average radiochemical purity at most activity levels fell below the 90% acceptable range. Based on this data, pharmacies should use caution in setting the BUD time for this CSP, as it appears that it is stable for less than 12 hours after compounding.

It should be anticipated that the generic mebrofenin kit should behave similarly to the trade name Choletec product, as it shares the same composition and recommendations for compounding activities and expiration times. Based on the data obtained in this study, the generic product appears to behave in a manner similar to the trade name product. Stability at t=0 and t=6 appear to be acceptable, while the 12-hour values are highly variable and the 24-hour values are significantly below acceptable levels. As with Tc-99m Choletec, the use of Tc-99m mebrofenin should be further evaluated to determine acceptable BUD times, depending on the compounding parameters used.

As stated earlier, data for the Tc-99m Hepatolite kit only consisted of 38 samples, and, while this small number may not give significant weight to the results in terms of true representation of the average radiochemical purity, the strong difference between this CSP and the other two more commonly used agents is highlighted by the data that was obtained. Tc-99m Hepatolite carries a manufacturer recommended maximum compounding activity of 3.7 GBq (100 mCi) and an expiration time of 6 hours. Interestingly, with the data that was submitted for this CSP, in most cases, the average radiochemical purity of the CSP even at t=0 fell below the 90% acceptable level. The CSP also showed a consistent decrease in radiochemical purity at all time points.
and all activity levels. As a result, the limited data appears to support following the manufacturer recommendations for both activity and BUD time when compounding. Since no data was submitted with kits compounded at activities <3.7 GBq (100 mCi), further studies of kits compounded using manufacturer guidelines should be performed to confirm this recommendation.

Renal Agents

The two renal agents evaluated in this work are Tc-99m DTPA and Tc-99m MAG-3. Manufacturer recommendations for compounding Tc-99m DTPA indicate a maximum activity of 18.5 GBq (500 mCi) with an expiration time of 12 hours. This product showed radiochemical purity values that consistently exceeded the 90% limit at 0, 6, and 12 hours. Only at the 24-hour time point was there significant variation in the purity levels.

Recommendations for Tc-99m MAG-3 preparation include a maximum compounding activity of 3.7 GBq (100 mCi) and an expiration of 6 hours. The data submitted for this kit show consistently greater than 90% radiochemical purity at all activity levels at the t=0 time point. By 6 and 12 hours post compounding, stability for kits compounded with less than 9.25 GBq (250 mCi) still maintain acceptable radiochemical purity values, but kits compounded in excess of this activity show an average radiochemical purity of 90%. However, the >9.25 GBq (250 mCi) data only included two data points, one consistently above 90% and one significantly less than 90% at all time points. This discrepancy should be further evaluated by studying more kits compounded at this increased activity level. All of the data at all activity levels show a continual decrease in radiochemical purity as time progresses, indicating that the preparation may be degrading with time. By the 24-hour time point, most of the data fell below the 90% acceptable radiochemical purity value.

CONCLUSION

In this submission, we attempted to get a picture of the range of compounding activities that are used to compound the most common radiopharmaceutical CSPs and to show how these widely variable compounding processes impact the quality of the final preparation. In many cases, the radiopharmaceuticals used today are very stable and can easily be used for 12 hours or more post compounding even when compounded using activities in excess of manufacturer recommendations. It is important to note, however, that while this data was compiled to show the general trend of radiopharmaceutical stability when CSPs are compounded outside of manufacturer recommendations, it was collected to supplement in-house verification of compounding procedures, not replace it. Nuclear pharmacies and nuclear medicine departments that compound radiopharmaceuticals should confirm these results by carrying out similar testing on CSPs that are compounded using their own site-specific preparation parameters, as these may provide slightly different results than what are presented in our study. These in-house studies can be used to prove to regulatory agencies and accreditation bodies that the procedures used for compounding provide an end preparation that is safe and effective for the patients who ultimately will receive them.

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Establishing Benchmark Rates of Microbial and Bacterial Endotoxin Contamination for Radiopharmaceuticals Compounded in Commercial Nuclear Pharmacy Settings

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BACKGROUND

The recent release of United States Pharmacopeia (USP) Chapter <797> has increased the focus on the safety of compounded sterile preparations (CSP), including radiopharmaceuticals. Until the most recent revision of USP <797>, radiopharmaceuticals were not specifically mentioned as a CSP even though they have always fallen under that designation. Due to the short half-life of most radiopharmaceuticals, the inherent risk of microbial contamination is mitigated by the fact that administration must occur in fairly short order after preparation. Since many nuclear medicine departments receive their radiopharmaceuticals in unit-dose form, there exists the general assumption that the doses received are of acceptable quality, but there has not been a publicly available large scale evaluation of the sterility and asepticity of radiopharmaceuticals compounded in a commercial nuclear pharmacy. The purpose of this study was to evaluate both microbial and aseptic contamination rates for radiopharmaceutical preparations compounded in a commercial nuclear pharmacy environment to provide benchmark contamination rates for compounded radiopharmaceutical sterile preparations.

USP <797> was released in 20041 with little fanfare. The original document had several issues that were in direct conflict with standards required for the safe handling of radioactive materials, but as part of the standard revision process, many of these issues were identified and revised due to input from practitioners and members of the public. The “final form” revision went into effect in 2008,2 and, at this point, pushed USP <797> to the forefront of concern for

ABSTRACT

The objective of this study was to establish benchmark rates for microbial and bacterial endotoxin contamination rates for radiopharmaceutical preparations compounded in commercial nuclear pharmacies. Radiopharmaceutical samples were obtained between November 2006 and June 2010 from seven commercial nuclear pharmacies. Preparations were compounded per the compounding protocols of each radiopharmacy, and each kit was used for unit-dose dispensing of patient-specific doses. Samples for testing were withdrawn after unit doses were dispensed. Sterility testing was performed on each radiopharmaceutical sample and incubated at appropriate temperatures for 14 days. A sample of the radiopharmaceutical was also used to complete limulus amebocyte lysate-based bacterial endotoxin testing. Over the course of the study, 1516 radiopharmaceutical samples from 16 different radiopharmaceutical preparations, including eluates from radionuclide generators, were tested for sterility and bacterial endotoxicity. For the sterility testing, 13 of the 1516 samples (0.86%) showed evidence of growth in the testing media, indicating the presence of microbes in the tested sample. For bacterial endotoxin testing, 4 of 1492 samples (0.27%) showed formation of gel clots, indicating the presence of bacterial endotoxins in the sample. The microbial and bacterial endotoxin contamination rates of aseptically compounded radiopharmaceuticals compounded in a commercial nuclear pharmacy environment are extremely low. The results of this study show the high level of safety and quality that is provided when obtaining radiopharmaceutical doses that are compounded and dispensed from a commercial nuclear pharmacy.

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nuclear pharmacies and nuclear medicine departments alike. Per USP <797>, most radiopharmaceuticals are considered “low-risk” compounded preparations. For the radiopharmaceuticals being evaluated in this study, the term “compounded” indicates the reconstitution of an FDA-approved reagent kit, using radioactivity obtained from an FDA-approved radionuclide generator as well as commercially available sterile normal saline as a diluent. As low-risk compounded preparations, radiopharmaceuticals should be prepared in an International Organization for Standardization (ISO) Class 5 or better compounding environment to minimize the potential for particulate and, most importantly, microbial contamination. ISO Class 5 designation is given to work areas in which there are less than 3,520 particles sized 0.5 micron or larger per cubic meter. Radiopharmaceuticals are unique as CSPs since they are technically multi-use vials with extremely short beyond-use dates (BUD) due to the radioactive component of each product. Radiopharmaceuticals can be compounded under other risk designations, (immediate use, 12 hour or less BUD with segregated compounding areas), but these are generally not the scope of practice that is seen in a commercial nuclear pharmacy. Following the release of USP <797>, with the increased focus of creating a cleanroom-compliant compounding environment regardless of the location where the compounding is being carried out, many nuclear medicine departments that previously compounded radiopharmaceuticals “in-house” are converting back to commercial nuclear pharmacy operations as a source for radiopharmaceuticals. One of the primary goals of this work is to provide a picture of the quality of radiopharmaceuticals prepared in a typical commercial nuclear pharmacy to give confidence to the end users—the nuclear medicine physician, nuclear medicine technologist, and ultimately the patient.

METHODS

Samples were obtained from seven commercial nuclear pharmacies between November 2006 and June 2010. This sterility/bacterial endotoxin study was in combination with a stability study (results presented elsewhere), which examined the radio-chemical purity of same radiopharmaceuticals. The CSPs were compounded with Tc-99m sodium pertechnetate obtained from a generator system, and each kit was prepared using various amounts of activity and pharmacy-specific BUDs which

Rapid Endotoxin Testing of Compounded Sterile Products

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were in some cases in excess of the manufacturers’ recommendations.[AUTHOR:NOTE]

The participating nuclear pharmacies were asked to prepare radiopharmaceuticals using their site-specific compounding protocols and quality-control methods. All of the sites participating in the study utilized ISO 5 laminar airflow hoods for compounding, although adherence to other USP <797> requirements varied from pharmacy to pharmacy, and in some cases changed as the pharmacies implemented new procedures during the sample collection process. Samples were taken from preparations after unit-dose dispensing if the preparations had sufficient residual material to perform sterility, bacterial endotoxicity, and stability testing. Sterility testing was performed on each sample, by inoculating both BBL Trypticase Soy Broth (TSB) and BBL Fluid Thioglycolate Medium (FTM) sterility testing media (BD BBL prepared culture media, Lots 221715 and 221195, respectively, Becton and Dickinson, Sparks, Maryland). The culture tubes were shielded and incubated (FTM at 32.5°C ± 2.5°C and TSB at 22.5°C ± 2.5°C) for 14 days as specified by USP Chapter <71> Sterility Tests. Each tube was evaluated for growth at 3, 7, and 14 days post inoculation. Results were reported as positive (turbidity noted) or negative (no turbidity noted). For bacterial endotoxin testing, samples were performed and processed per the instructions of the specific Limulus Amoebocyte Lysate (LAL) gel-clot bacterial endotoxin testing method used by the pharmacy with the use of either Endosafe LAL reagent (Lot R15012C; Charles River, Charleston, South Carolina with λ-labeled sensitivity 0.125 EU/mL or geometric mean used for 1:1000 maximum volume dilution) or Pyrosate LAL reagent (Lot PSD25; Cape Cod Associates, East Falmouth, Massachusetts with 0.250 EU/mL λ-labeled sensitivity used for 1:700 maximum volume dilution), and as described in USP Chapter <85> Bacterial Endotoxins Test.3

RESULTS

A total of 1516 sterility samples and 1492 bacterial endotoxin samples were collected over the course of the study. The number of samples collected per radiopharmaceutical preparation is listed in Table 1. [T2]

The original goal of the study was to obtain 175 data points for each preparation; however, given that usually more than two milliliters of the preparation were needed to complete all required sterility and bacterial endotoxin tests, there was a significant supply chain issue during the data collection period in which the availability of ⁹⁰Mo / ⁹⁹mTc generators was critically low. To assure continuity of supply to the customer, the need for careful utilization of preparations to meet clinical needs limited the collection of some samples for various preparations in the latter stages of the study. In addition, some preparations were utilized fairly infrequently, and the 175-sample goal was not achieved in our study period. The generic kits of sestamibi and mebrofenin were released during the data collection process and were added to the list of radiopharmaceutical samples upon their release. Given the shortened collection time, these preparations also did not reach the 175-sample goal. During the collection process, with the increasing concern regarding the generator supply issues, the desired number of samples was revised, with a new goal of at least 1500 samples, spread as evenly as possible over the different radiopharmaceuticals being tested.

Table 2 lists the results of the sterility-testing portion of the study. There were 1516 samples that were included in the data analysis. No sterility testing results were excluded from sample analysis, although as stated above, for several of the kits, we were unable to reach our 175-sample goal due to generator supply issues. [T2]

Of the 1516 samples submitted, 13 samples had evidence of growth at some point during the 14-day observation period, resulting in a 0.86% microbial contamination rate (13 positive samples/1516 total samples). While by USP definition, all compounded radiopharmaceuticals are categorized under the low-risk compounding level, many of the Cardiolite kits were prepared by “batching” in which several cold kits are reconstituted and combined into a larger evacuated vial, then radiolabeled with large amounts of radioactivity. This process can increase the number

| TABLE 1. Sterility/Bacterial Endotoxin Submitted Sample Distribution. |
|-------------------------------------------------|-----------------|-----------------|
| **RADIOPHARMACEUTICAL** | **NUMBER OF STERILITY SAMPLES** | **NUMBER OF BACTERIAL ENDOXIN SAMPLES** |
| Myoview | 106 | 105* |
| Cardiolite | 171 | 168* |
| Sestamibi (generic) | 14 | 14 |
| MDP (all brands) | 168 | 163** |
| HDP | 67 | 67 |
| MAA | 172 | 170** |
| Sulfur Colloid (SC) | 147 | 141** |
| NaTcO₄ (Lanth/Covid) | 166 | 165* |
| Choletect | 204 | 199xx |
| Mebrofenin (generic) | 59 | 59 |
| Hepatolite | 38 | 38 |
| DTPA | 93 | 93 |
| MAG-3 | 83 | 83 |
| Neurolite | 8 | 8 |
| Filtered SC | 18 | 17x |
| DMSA | 2 | 2 |
| **TOTALS:** | **1516** | **1492** |

Note: The total number of sterility/stability samples differ because several of the bacterial endotoxin test results were excluded. Preparations marked with (*) had at least one kit that failed positive control testing for the bacterial endotoxin kit. Preparations marked with (x) had sterility results submitted, but bacterial endotoxin tests for that sample were omitted.
of punctures required in the compounding process to ten or more, depending on the number of kits that are combined in the process. In this case, the preparation of Cardiolite no longer falls into the low-risk category since it does not meet the two-puncture limit and most likely represents a medium-risk compounding situation. In our study, if the Cardiolite data are considered a medium-risk category preparation and the entire group (6 positive samples out of 171 samples submitted) is removed from consideration when calculating the contamination rate for true, low-risk compounding activities, the level of contamination for the low-risk level category becomes 0.52% (7 positive samples/1345 total samples). Though limited by a small sample size, if the Cardiolite data is considered to fall under medium-risk compounding and assessed as an individual group, the positive sterility test result rate for medium-risk compounding processes would be 3.51% (6 positive samples/171 total samples). Table 3 provides greater detail regarding the radiopharmaceuticals with a positive sterility result. [T3]

The results of the bacterial endotoxin tests are provided in Table 4. A total of 1492 samples were submitted for analysis. There were 4 samples that showed gel formation during the bacterial endotoxin testing, indicative of the presence of bacterial endotoxins in the kit formulation. This results in a 0.27% bacterial endotoxin contamination rate. [T4]

**DISCUSSION**

The preparation and dispensing of radiopharmaceuticals in a centralized nuclear pharmacy setting may differ from what is traditionally observed in other areas of sterile preparation compounding. In a nuclear pharmacy, almost every radiopharmaceutical is treated as a multi-use kit, allowing for removal of multiple patient doses from a single radiopharmaceutical kit formulation. In addition, most nuclear pharmacies utilize substantially greater activities of Tc-99m sodium pertechnetate when compounding...
the kit. This allows for removal of increasingly greater numbers of doses per kit, requiring more punctures of the septum, a process that could potentially increase the risk of microbial contamination in the final preparation being dispensed.

To date, no study has looked at microbial contamination rates of commercially prepared unit-dose radiopharmaceuticals, and this, along with the recent release of USP <797> and a heightened focus on sterile preparation compounding, provided the impetus for this study. Although commercial nuclear pharmacy operations differ to some extent from typical hospital pharmacy practices, the most relevant comparison of achievable contamination rates can be drawn from works published by Trissel et al in 2003 and 2005. In these works, Trissel established benchmark microbial contamination rates for low-risk (<0.1%) and medium-risk (5.2%) compounding practices in a hospital setting. Since most Tc-99m sodium pertechnetate CSP-radiopharmaceuticals are considered to be “low-risk” compounding procedures per USP <797>, Trissel’s work evaluating low-risk compounding procedures would initially be the first choice for comparison. Per USP <797>, low-risk compounding requires that a preparation has no more than two punctures in the vial during the compounding process. While most radiopharmaceuticals are compounded within the two-puncture rule, unlike most traditional pharmaceuticals, there will be multiple doses dispensed out of the vial, requiring multiple additional punctures in the dispensing process, which potentially increases the chance for microbial contamination. In addition, some radiopharmaceuticals require more complex preparation steps, such as boiling and filtering; neither of which is addressed in Trissel’s low-risk evaluation. Therefore, it is also reasonable to compare radiopharmaceutical preparation to Trissel’s medium-risk compounding evaluation, in which multiple punctures are made into compounding vessels and multiple manipulations of material are carried out. Again, it is important to reiterate that radiopharmaceuticals are considered “low-risk” due to many factors, including the small volume administered but, most importantly, the BUD, due to the radioactive component of the preparations. Therefore, it is reasonable to accept that the risk of microbial contamination for radiopharmaceutical preparations would most likely fall within the values put forth by Trissel in these two works.

In evaluating the rate of microbial contamination in the radiopharmaceuticals compounded for this study, 13 of the 1516 samples showed some evidence of microbial growth during the 14-day evaluation period. This resulted in a microbial contamination rate of 0.86%. If the results from the “batched” Tc-99m Cardiolite group are removed from the analysis, the contamination rate is lowered to 0.52%. While both are higher than the low-risk compounding rate set forth by Trissel, both also are considerably lower than the medium-risk benchmark rate for medium-risk compounding. Even if the Tc-99m Cardiolite group is considered to be in the medium-risk category of USP <797> because of the multiple-entries to the septum and is evaluated independently of all other data, its positive sterility test result rate is 3.51%, which is lower than that reported in the second Trissel work on medium-risk compounding.4,5

In evaluating the actual distribution of kits with positive microbial contamination, some of the results were anticipated, based on an understanding of kit components and compounding processes, while some results were not initially anticipated. The following sections discuss the sterility and bacterial endotoxin results for each of the radiopharmaceutical kits that showed either positive growth in one or more sterility test samples or positive bacterial endotoxin testing.

**Sterility - MAA/Sulfur Colloid**

The positive results for MAA and Sulfur (SC) (four positive results in 319 kit preparations or 1.25% aggregate for both) were not unexpected, since both of these agents contain material (albumin and gelatin) that can support microbial growth. In observing the distribution of positive results in these preparations, the MAA had growth in the FTM media at all time points in two of the samples and a single positive in the day 14 sample of the TSB media. The SC kit showed growth in both day 7 and 14 of the TSB sample. Given the distribution, it is reasonable to assume that these results are accurate.

**Sterility - HDP**

The positive result (one in 67 preparations or 1.5%) for the HDP kit occurred in the day-7 evaluation of the FTM testing media. However, the 14-day evaluation of the same tube showed no evidence of growth, strongly indicating that the day-7 result is questionable because of evaluator interpretation or error. Either the 7-day reading was “misread” as being turbid, thus the positive evaluation, or the day-14 reading was not read correctly and was truly turbid, but not reported correctly. Although the results most likely indicate that some type of error may have occurred, the sample was included in the total results.

**Sterility - Sodium Pertechnetate**

Both of the positive samples (two in 166 test results or 1.2%) of Tc-99m sodium pertechnetate (from generator elutions that were used to compound radiopharmaceutical kits) showed growth at more than one time point—one elution had positive growth in all three evaluation points for the FTM media, while the other had growth in the 7- and 14-day FTM evaluations. Tc-99m sodium pertechnetate generator elutions are sterile upon removal of the eluate from the generator but have increased risk of potential contamination due to the multiple punctures required when removing the radioactivity for the compounding process. It is feasible to assume that these results are accurate.

**Sterility - Cardiolite**

The most surprising result was found in the analysis of the Cardiolite samples. Six of the 171 samples (3.51%) showed evidence
of microbial growth. Two of the six samples showed growth in two time points (7 and 14 day) for both of the media. One of the samples showed growth in two time points (7 and 14 day) for the FTM media only, and three of the samples showed growth on the 14-day FTM evaluation. It is highly likely that these results are accurate.

The unexpectedly high rate of microbial contamination in this group introduces one of the greatest concerns with the data obtained in this study since myocardial perfusion studies make up a significant percentage of dispensed doses from any nuclear pharmacy. Preparation of Tc-99m Cardiolite requires a boiling step, which could contribute to the risk of contamination, depending on the heat source used for the boiling step. If a water bath is used as a heating source, formation of a thin film over the septum of the vial occurs that, if not cleaned correctly, could be introduced into the kit formulation when puncturing the vial with a syringe. In addition, in many pharmacies, the heat sources (water bath or heating block) is usually housed in a separated, controlled-negative pressure environment to prevent widespread contamination issues if the vial would happen to break during the heating process. This most likely introduces transient exposure to non-ISO 5 air during the transfer process that could potentially increase the risk of inadvertent microbial contamination. However, in discussions with the various compounding sites, the increased risk of growth in this study appears to be related to a practice called “batching” in which several cold radiopharmaceutical kits are reconstituted using 0.9% normal saline, and the contents of each kit are transferred to a larger-size vial. The mixed sample is compounded using a single, very high amount of radioactivity equivalent to the total amount of activity that would be added to each of the vials independently.

As reported by the study participants, the rationales behind the practice of batching include:

- Increased speed of compounding
- Decreased number of quality-control tests required to be completed after compounding
- Decreased number of kits available (which may minimize the risk for potential medication errors)

However, the more significant consideration is the inherent risk associated with this practice due to the increasing number of punctures required in the entire compounding process. If four individual kits were combined to make a “batch,” it would require more than 10 punctures in the compounding process alone, well over the two-puncture limit for low-risk compounding and changing the practice to the medium-risk compounding category. It is reasonable to expect that the greater the number of punctures into the vial, the greater the risk for inadvertent microbial contamination. All six of the Tc-99m Cardiolite kits with a positive sterility test were “batched,” making it likely that the results are accurate.

### Bacterial Endotoxins

When evaluating the bacterial endotoxin results, there were four positive results in a total of 1492 samples. It is interesting to note that the positive bacterial endotoxin tests were found in samples that did not have a positive sterility test result at any evaluation point during the 14-day evaluation period. The most likely explanation for positive bacterial endotoxin testing is related to inexperience of the operators performing the test. Bacterial endotoxin testing is not a common quality-control test carried out in a centralized nuclear pharmacy, so many of the participants had never performed a bacterial endotoxin test prior to the start of the study. The decreased number of bacterial endotoxin samples (1492 as compared to the 1516 sterility samples) is an indication of the difficulties that occurred early in the testing process with several sites that had not performed this type of test before this study. Several of the samples submitted did not have the expected gel formation in the positive control that was included in the testing procedure, indicating that the test results were invalid, so these samples were not included in the data analysis. The failure of the positive control was most likely due to inhibition caused by the ligand or other kit components, but several of the nuclear pharmacy sites struggled with identification of this early in the data-collection period due to operator inexperience.

The reasons for the four positive results found during the study are difficult to identify, and unfortunately may be due to operator inexperience as stated earlier. However, it is not possible to exclude the possibility that the positive results were in fact valid results. The absence of a positive sterility test does not rule out the presence of bacterial endotoxins in a sample. Repeat testing of the radiopharmaceutical kit with a positive bacterial endotoxin result should have been undertaken to confirm the initial results of any failed test.

### STUDY LIMITATIONS

Concerns with consistency of inter- and intra-operator performances are always among study limitations when multi-center experimentation is undertaken. In this case, the use of end-of-day kit preparations allowed the analysis of preparations that were not treated in any special way since all were used in clinical studies prior to sterility and bacterial endotoxin testing. This also provided for several compounders’ aseptic compounding techniques to be assessed throughout the study interval.

Sterility testing is not a routine component of commercial nuclear pharmacy operations. Variables from site to site that potentially could have impacted the data obtained during the study and should be considered when evaluating the data include such things as:

- Operator training
- Size of inoculums
- Sample incubation times
- Operator observation of samples for turbidity
An attempt was made to standardize both the sterility and the bacterial endotoxin testing for all sites, but consistency in performing the testing may have been compromised due to site familiarity with the sterility and LAL gel-clot testing procedures and with any equipment that might be used in the testing procedures.

Another limitation that could not be accounted for in this study was the potential for improvement in the aseptic compounding processes simply because of the presence of the study itself. Most of the testing failures (both sterility and bacterial endotoxin testing) occurred within the first year of data collection in which many of the data collection sites were performing these tests for the first time. Early failures could be a result of poor operator technique, not due to the true contamination of the radiopharmaceutical kits. As operators became more familiar with the collection process, the number of failures decreased.

Finally, the implementation of USP <797> standards was not consistent across all pharmacies for the entire duration of the study period. All compounding and dispensing activities in all of the participating pharmacies were carried out in USP <797>-compliant laminar airflow hoods, providing fairly consistent and uniform ISO 5-compounding environments for all samples. However, with the 2008 USP <797>-compliance date falling in the middle of our study, participating pharmacies were constantly making changes to operating procedures and protocols to move towards greater compliance over the course of the study period. The participants in our study were geographically distributed over several states, and since oversight for implementation and compliance of USP <797> falls under the responsibility of the Board of Pharmacy for each individual state, it was impossible to assure that the compounding processes at each of the participating pharmacies were exactly the same. The lack of uniformity between pharmacies makes it difficult to prove that any improvements in microbial and bacterial endotoxin contamination rates over the course of the study were directly related to any particular aspect of USP <797>.

CONCLUSIONS

The results of this study indicate that radiopharmaceuticals compounded in a centralized nuclear pharmacy have a very low incidence of microbial and bacterial endotoxin contamination. However, radiopharmaceutical kit preparation and dispensing of patient-specific, unit-dose radiopharmaceuticals are processes that require multiple manipulations and septal punctures, which increase the chance for inadvertent contamination of the final compounded preparations. Based on the data presented in this work, the incidence of microbial contamination in compounded radiopharmaceuticals approaches the benchmark sterility rates established for compounding of low-risk and medium-risk level CSPs in a hospital setting. The current practice standards for compounding sterile radiopharmaceutical preparations in a centralized nuclear pharmacy setting provides radiopharmaceuticals with acceptable levels of both microbial and bacterial endotoxin contamination, providing safe and effective preparations to the end user.

REFERENCES


Address correspondence to Kara D. Weatherman, PharmD, BCNP, FAPhA, Clinical Assistant Professor of Pharmacy Practice, Purdue University College of Pharmacy, 575 Stadium Mall Drive, RHPH 502B, West Lafayette, IN 47907. E-mail: kdwman@purdue.edu
Kim, comment for the sterile subcommittee

Tom

-----Original Message-----
From: Scott C. Brower R.Ph., BCNP [mailto:scbrph@aol.com]
Sent: Thursday, May 18, 2017 5:04 PM
To: Glenski, Tom
Subject: Practice of Nuclear Pharmacy

Dear Mr. Glenski:

It is my understanding that the sterile compounding committee is reconvening to discuss proposed policies that could have a negative impact on the practice of nuclear pharmacy. This would directly affect patient care in a negative way. As a Board Certified Nuclear Pharmacist I believe it is my obligation to request that you include nuclear pharmacists in your decision process as they relate to the practice of radiopharmacy (nuclear pharmacy).

Having practiced nuclear pharmacy for 37 years (Purdue 1980) it has always been my attitude and professional approach to put the patient first. When we all practice that goal everything else will fall into place. This applies to one of the most simplest tools we have as a pharmacist, "the drug package insert".

Many of the drugs for nuclear pharmacy have been on the market since the late 1970's with little or absolutely no major changes made to them as described in their package insert. This could be a result of many reasons. Some being, costs to the manufacturer for PI (package insert) changes, nuclear pharmacy is a small niche, quality control in the nuclear pharmacy is the truest predictor of product quality or too many regulatory hurdles in changing a PI.

All that being said, nuclear pharmacists over the years have been forced to learn what formulation procedures and changes must be performed to prepare the best radiopharmaceutical product. During this time we have shared these procedures with our nuclear pharmacist colleagues as well as the manufacturers.

For one example, I will use the brand name drug Cardiolite (generic sestamibi).

PI says to boil drug for 10 minutes. We determined that the optimum boil time is 15-18 minutes. You actually need more time to hold the boil temp at 100 degrees Celsius to sufficiently displace the copper which results in a tagging efficiency of greater than 95%. Ten minute boiling times result in lower tagging efficiencies of 90% and lower. This fact was confirmed with the manufacturer and they recommended longer boiling times as described since it produces a better product. For this reason how could you benefit by following the PI?

Package insert says "should be used within 6 hours". The key word here is "should". By performing proper quality control on this drug throughout the day we determined that sestamibi was tagged greater than 95% at 12 hours under properly modified preparation circumstances. However, if you make up a vial with older Tc99m as allowed by the PI, that same product will break down much earlier than 6 hours and has even been found to fail QC (not meet product specifications). For this reason We will always follow the modified procedure that assures a product good for 12 hours and not a PI procedure that sometimes would not even meet the stated 6 hours of quality.

For the reasons listed above I strongly urge and request that the Missouri Board of Pharmacy not implement any regulations that would severely affect a nuclear pharmacist's ability to prepare the best Radiopharmaceutical possible. I am currently licensed in six other states as a registered pharmacist and am not aware of any similar actions being considered by these Boards of Pharmacies. Please each out to the other nuclear pharmacy businesses.
in Missouri and you will discover that what I describe applies to many drug products used in nuclear medicine.

I look forward to hearing from you and ask that you make my comments available to the Missouri Board so they are well known. Thank you!

Sincerely,

Scott

Scott C. Brower R.Ph., BCNP
Board Certified Nuclear Pharmacist
President / CEO
Essential Isotopes, LLC
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Columbia, MO. 65211
Mobile Phone: 573-864-7358
May 19, 2017

Tom Glenski, RPh.
Chief Inspector
Missouri Board of Pharmacy
3605 Missouri Blvd.
Jefferson City, MO 65109

Dear Mr. Glenski,

I am writing this letter to you as both the Program Director of Nuclear Medicine Training Program at the University of Missouri, and as a former Director of Radiology at a small rural hospital in Marshall, Missouri.

As you are aware, there has been extensive discussions regarding interpretations of in-use-times (IUT) for radiopharmaceuticals produced by commercial radiopharmacies when the package insert contains suggested expiration times that are interpreted as required expiration times. With the understanding that traditionally, these “kits” were being prepared by nuclear medicine technologists with limited resources for ensuring sterility and quality assurance, as opposed to Board Certified Pharmacists, those suggested expiration times made practical sense. On the other hand, when one considers that commercial pharmacies are able to provide a higher level of control and technical expertise, as long as the prepared compounds have been documentation to support both stability and sterility, the preparing pharmacists should be allowed professional discretion as to expiration times.

By disallowing pharmacist’s discretion on expiration times, and by adopting more stringent guidelines, there will be significant negative repercussions in the nuclear medicine community which will be magnified in rural communities.

The problem is that most rural hospital have neither the resources to maintain their own radiopharmacy nor are they close to centrally located radiopharmacies. The only way these hospitals can continue to provide nuclear services is if they both have access to radiopharmaceuticals, and they have the ability to share costs for the drugs with other hospitals in the area via using a central pharmacy. Should the time widow for using these drugs be shortened as a result of the Board’s guidance regarding IUT, the Board of Pharmacy will have effectively eliminated access to nuclear medicine procedures for thousands of rural Missourians.

The argument that central pharmacies can accommodate these shorter time windows by simply producing more kits throughout the day and doing more deliveries is flawed because the end result will be a dramatic increase in costs of manufacturing that gets pushed on to both the clinics and ultimately the patients.

The other argument that rural institutions can just start making their own radiopharmaceutical kits in-house is also not a viable approach. Aside from the fact that this would cause the costs of pharmaceuticals to skyrocket, this would also force institutions who have far less adequate
compounding capabilities to start making their own drugs. I really don’t think that this is what the Pharmacy Board would want since there would be far less oversight in these small clinics than there would be at the commercial facilities.

To illustrate this point, given a small rural hospital that sees 3-4 patients a day (2 cardiac patients and 2-3 other patients), they typically share the costs of their radiopharmaceutical kits among 2 to 3 other hospitals so that each vial maximizes the number of patients that it can be used for. Should they be forced to make the drugs in house, the kit which would normally take care of 6-9 patients now has its cost spread over 1 to 2 patients. Further, this hospital must buy its own individual $^{99}$Mo-$^{99m}$Tc generator, which would normally supply isotopes for 5-9 hospitals. This quickly becomes cost prohibitive for both the institution (with capped reimbursement) and the patients. In short, nuclear medicine would no longer be provided.

I appreciate your time and thank you for considering my concerns regarding in-use-time (IUT) for radiopharmaceuticals. Should you have any questions for me please feel free to contact me at your earliest convenience.

Sincerely,

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12 May 2017

Kim Grinston, JD
Executive Director
Missouri Board of Pharmacy
3605 Missouri Boulevard
P.O. Box 625
Jefferson Cit, MO 65102-0625

Dear Ms.Kimberly Grinston,

There are several concerns that I have with the new Sterile Compounding Regulations that have been established for the State of Missouri. My concern specifically is that the rules for sterile compounding, when they are applied to the practice of nuclear pharmacy, create significant problems for the practice, due to the fact that the same rules cannot be applied across the board for radiopharmaceuticals and therapeutic drugs.

One issue is the use of In Use Time (IUT), which is a term that has been adopted only by the State of Missouri. This is not a term that is generally used, and the definition is not clear to me. I feel that it is important to use terms that are well understood. The term that is more commonly used is the Beyond Use Date (BUD) which means expiration time for a preparation. This terminology was popularized since at the time the USP wrote Chapter <797>

Pharmaceutical Compounding—Sterile Preparations.

In regard to radiopharmaceuticals, if a package insert states that the expiration time is 6 hours, and you want to use the product to 12 hours, you would be required to add the maximum amount of radioactivity that you intend to use on a routine basis, and then wait until 12 hours, and perform the appropriate radiochemical purity analysis and sterility testing for 3 batches. These tests can be easily performed in a nuclear pharmacy. In other words, you would need to validate the process. If the test results are acceptable, you could extend the expiration time or BUD to 12 hours from 6 hours. Additionally you should repeat that 12 hour analysis of stability on a yearly basis. This is not something that would be done for a therapeutic drug, since there would be no in-house way that a therapeutic drug could be reconstituted and held for say 12 hours instead of 6 hours, and tested in-house for the stability of the drug. You would need to send it to an analytic laboratory that was equipped to test the drug, to analyze that the drug had not decomposed, and was still therapeutically active. This is not the case for radiopharmaceuticals.

Unfortunately USP Chapter 797 is difficult to interpret for nuclear pharmacy. I know that there is a proposed revision out there, but it is currently on hold. It is not likely that the revised version as it currently exists will be published. I know that the USP has been petitioned to write a Chapter on Radiopharmaceuticals, and I do think that they will decide to do this, but unfortunately it will take time. Additionally I do know that the FDA is in favor of having the USP write this new Chapter on Radioactivity. Radiopharmaceuticals are a different type of
“drug,” and the regulations for their use and handling require different considerations than for therapeutic drugs.

I do think that it is important to develop regulations for radiopharmaceuticals, but I think that to strictly apply the Sterile Compounding Rule to the practice of nuclear pharmacy it not appropriate, and will negatively impact the practice. Radiopharmaceuticals are in a unique category, and shouldn’t be regulated in the same way as therapeutic drugs.

Some of these unique characteristics are: 1) the radiation emitted by these radiopharmaceuticals which require the use of shielding, and is not a property of traditional therapeutic drugs. 2) the mass of the radiopharmaceuticals is in the ng to μg levels, compared to the mg or gram quantities that are present in therapeutic drugs 3) every vial of radiopharmaceutical that is prepared for human use is tested for radiochemical purity, which is not the case for every vial of therapeutic drug that is reconstituted for iv injection.

I feel that the State Board of Pharmacy is interpreting compounding of radiopharmaceuticals according to therapeutic drug compounding, and there is no consideration being given to the issues that need to be addressed in nuclear pharmacy.

Sincerely,

Sally W. Schwarz, RPh, MS, BCNP
Professor of Radiology
Mallinckrodt Institute of Radiology
Co-director Cyclotron Facility
Washington University School of Medicine
St. Louis, MO 63110

Cc Sam Leveritt Pharm.D., BCNP
May 15, 2017

Tom Glenski, RPh.
Chief Inspector
Missouri Board of Pharmacy
3605 Missouri Blvd.
Jefferson City, MO 65109

Re: End use time for nuclear kits

Dear Mr. Glenski,

Nuclear pharmacy is a well-established discipline with standard operating procedures developed over the last 40 years of the practice’s existence. Approximately 10 million doses are dispensed in the United States annually and over its history there has not been a documented incidence of adverse events to patients relating to compounded product sterility. This exceptional track record is a testament to the efficacy of the industries procedures coupled with the chemistry of radiopharmaceutical drugs used and the relatively short time period from drug preparation to patient injection.

USP 797 has recognized that the practice of nuclear pharmacy, by its nature, should be considered separately from traditional sterile compounding and has characterized its practices as primarily Low Risk compounding with a small percentage potentially qualified as Medium Risk, such as manipulations of patient blood which are used within a 4-5 hour time period. Generally, USP 797 has established guidance when compounding in a ISO 5 area within an ISO 7 room suggests Low Risk compounded products stored for up to 48 hours at room temperature and medium risk for 30 hours. These storage times are based on the absence of sterility testing. (See USP 797 page 8 item #4). In addition, 503A of the Food, Drug and Cosmetic Act allows for anticipatory compounding for prescription-based drugs to facilitate ongoing patient needs with a history of regular occurring volume demand. We further know from years of experience, and testing, our products are stable and safe well beyond six hours. While sterility testing is a manufacturers responsibility, we as a compounding nuclear pharmacy use aseptic technique and qualify each of our dispensers in the process. We have also done stability studies of each of our products. These studies show stability well beyond six hours.
While it is not required under USP 797, we have begun sterility testing of all of our products. I will get these results to you as soon as complete.

We respectfully request the board not expire our kits compounded with saline at six hours, and allow us to continue the long-standing practice which currently is in place.

I plan to attend the board meeting in July.

Kind Regards,

Richard L. Van Sant, PharmD
Director Regulatory Affairs
Establishing Benchmark Rates of Microbial and Bacterial Endotoxin Contamination for Radiopharmaceuticals Compounded in Commercial Nuclear Pharmacy Settings

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ACKNOWLEDGMENT
The authors disclose that financial support for this project was provided through a grant from United Pharmacy Partners, Incorporated.

BACKGROUND
The recent release of United States Pharmacopeia (USP) Chapter <797> has increased the focus on the safety of compounded sterile preparations (CSP), including radiopharmaceuticals. Until the most recent revision of USP <797>, radiopharmaceuticals were not specifically mentioned as a CSP even though they have always fallen under that designation. Due to the short half-life of most radiopharmaceuticals, the inherent risk of microbial contamination is mitigated by the fact that administration must occur in fairly short order after preparation. Since many nuclear medicine departments receive their radiopharmaceuticals in unit-dose form, there exists the general assumption that the doses received are of acceptable quality, but there has not been a publicly available large-scale evaluation of the sterility and pyrogenicity of radiopharmaceuticals compounded in a commercial nuclear pharmacy. The purpose of this study was to evaluate both microbial and bacterial endotoxin contamination rates for radiopharmaceuticals compounded in a commercial nuclear pharmacy environment to provide benchmark contamination rates for compounded radiopharmaceutical sterile preparations.

USP <797> was released in 20041 with little fanfare. The original document had several issues that were in direct conflict with standards required for the safe handling of radioactive materials, but as part of the standard revision process, many of these issues were identified and revised due to input from practitioners and members of the public. The “final form” revision went into effect in 2008,2 and, at this point, pushed USP <797> to the forefront of concern for

ABSTRACT
The objective of this study was to establish benchmark rates for microbial and bacterial endotoxin contamination rates for radiopharmaceutical preparations compounded in commercial nuclear pharmacies. Radiopharmaceutical samples were obtained between November 2006 and June 2010 from seven commercial nuclear pharmacies. Preparations were compounded per the compounding protocols of each radiopharmacy, and each kit was used for unit-dose dispensing of patient-specific doses. Samples for testing were withdrawn after unit doses were dispensed. Sterility testing was performed on each radiopharmaceutical sample and incubated at appropriate temperatures for 14 days. A sample of the radiopharmaceutical was also used to complete limulus amebocyte lysate-based bacterial endotoxin testing. Over the course of the study, 1516 radiopharmaceutical samples from 16 different radiopharmaceutical preparations, including eluates from radionuclide generators, were tested for sterility and bacterial endotoxinicity. For the sterility testing, 13 of the 1516 samples (0.86%) showed evidence of growth in the testing media, indicating the presence of microbes in the tested sample. For bacterial endotoxin testing, 4 of 1492 samples (0.27%) showed formation of gel clots, indicating the presence of bacterial endotoxins in the sample. The microbial and bacterial endotoxin contamination rates of aseptically compounded radiopharmaceuticals compounded in a commercial nuclear pharmacy environment are extremely low. The results of this study show the high level of safety and quality that is provided when obtaining radiopharmaceutical doses that are compounded and dispensed from a commercial nuclear pharmacy.

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nuclear pharmacies and nuclear medicine departments alike. Per USP <797>, most radiopharmaceuticals are considered “low-risk” compounded preparations. For the radiopharmaceuticals being evaluated in this study, the term “compounded” indicates the reconstitution of an FDA-approved reagent kit, using radioactivity obtained from an FDA-approved radionuclide generator as well as commercially available sterile normal saline as a diluent. As low-risk compounded preparations, radiopharmaceuticals should be prepared in an International Organization for Standardization (ISO) Class 5 or better compounding environment to minimize the potential for particulate and, most importantly, microbial contamination. ISO Class 5 designation is given to work areas in which there are less than 3,520 particles sized 0.5 micron or larger per cubic meter. Radiopharmaceuticals are unique as CSPs since they are technically multi-use vials with extremely short beyond-use dates (BUD) due to the radioactive component of each product. Radiopharmaceuticals can be compounded under other risk designations, (immediate use, 12 hour or less BUD with segregated compounding areas), but these are generally not the scope of practice that is seen in a commercial nuclear pharmacy. Following the release of USP <797>, with the increased focus of creating a cleanroom-compliant compounding environment regardless of the location where the compounding is being carried out, many nuclear medicine departments that previously compounded radiopharmaceuticals “in-house” are converting back to commercial nuclear pharmacy operations as a source for radiopharmaceuticals. One of the primary goals of this work is to provide a picture of the quality of radiopharmaceuticals prepared in a typical commercial nuclear pharmacy to give confidence to the end users—the nuclear medicine physician, nuclear medicine technologist, and ultimately the patient.

METHODS

Samples were obtained from seven commercial nuclear pharmacies between November 2006 and June 2010. This sterility/bacterial endotoxin study was in combination with a stability study (results presented elsewhere), which examined the radiochemical purity of same radiopharmaceuticals. The CSPs were compounded with Tc-99m sodium pertechnetate obtained from a generator system, and each kit was prepared using various amounts of activity and pharmacy-specific BUDs which

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were in some cases in excess of the manufacturers' recommendations.

The participating nuclear pharmacies were asked to prepare radiopharmaceuticals using their site-specific compounding protocols and quality-control methods. All of the sites participating in the study utilized ISO 5 laminar airflow hoods for compounding, although adherence to other USP <797> requirements varied from pharmacy to pharmacy, and in some cases changed as the pharmacies implemented new procedures during the sample collection process. Samples were taken from preparations after unit-dose dispensing if the preparations had sufficient residual material to perform sterility, bacterial endotoxicity, and stability testing. Sterility testing was performed on each sample, by inoculating both BBL Trypticase Soy Broth (TSB) and BBL Fluid Thioglycollate Medium (FTM) sterility testing media (BD BBL prepared culture media, Lots 221715 and 221196, respectfully; Becton and Dickinson, Sparks, Maryland). The culture tubes were shielded and incubated (FTM at 32.5°C ± 2.5°C and TSB at 22.5°C ± 2.5°C) for 14 days as specified by USP Chapter <71> Sterility Tests. Each tube was evaluated for growth at 3, 7, and 14 days post inoculation. Results were reported as positive (turbidity noted) or negative (no turbidity noted). For bacterial endotoxin testing, samples were performed per the instructions of the specific Linth-Amebro Lysate (LAL) gel-clot bacterial endotoxin testing method used by the pharmacy with the use of either Endosafe LAL reagent (Lot R15012C; Charles River, Charleston, South Carolina with L-labeled sensitivity 0.125 EU/mL or geometric mean used for 1:1000 maximum volume dilution) or Pyrosate LAL reagent (Lot P3525; Cape Cod Associates, East Falmouth, Massachusetts with 0.250 EU/mL L-labeled sensitivity used for 1:700 maximum volume dilution) or Pyrosate LAL reagent (Lot R15012C; Charles River, Charleston, South Carolina with L-labeled sensitivity 0.125 EU/mL or geometric mean used for 1:1000 maximum volume dilution) or Pyrosate LAL reagent (Lot P3525; Cape Cod Associates, East Falmouth, Massachusetts with 0.250 EU/mL L-labeled sensitivity used for 1:700 maximum volume dilution), and as described in USP Chapter <85> Bacterial Endotoxins Test.

RESULTS

A total of 1516 sterility samples and 1492 bacterial endotoxin samples were collected over the course of the study. The number of samples collected per radiopharmaceutical preparation is listed in Table 1. [T2]

The original goal of the study was to obtain 175 data points for each preparation; however, given that usually more than two milliliters of the preparation were needed to complete all required sterility and bacterial endotoxin tests, there was a significant supply chain issue during the data collection period in which the availability of 99mTc/99mRe generators was critically low. To assure continuity of supply to the customer, the need for careful utilization of preparations to meet clinical needs limited the collection of some samples for various preparations in the latter stages of the study. In addition, some preparations were utilized fairly infrequently, and the 175-sample goal was not achieved in our study period. The generic kits of sestamibi and mebrofenin were released during the data collection process and were added to the list of radiopharmaceutical samples upon their release. Given the shortened collection time, these preparations also did not reach the 175-sample goal. During the collection process, with the increasing concern regarding the generator supply issues, the desired number of samples was revised, with a new goal of at least 1500 samples, spread as evenly as possible over the different radiopharmaceuticals being tested.

Table 2 lists the results of the sterility-testing portion of the study. There were 1516 samples that were included in the data analysis. No sterility testing results were excluded from sample analysis, although as stated above, for several of the kits, we were unable to reach our 175-sample goal due to generator supply issues. [T2]

Of the 1516 samples submitted, 13 samples had evidence of growth at some point during the 14-day observation period, resulting in a 0.86% microbial contamination rate (13 positive samples/1516 total samples). While by USP definition, all compounded radiopharmaceuticals are categorized under the low-risk compounding level, many of the Cardiolite kits were prepared by "batching" in which several gold kits are reconstituted and combined into a larger evacuated vial, then radio labeled with larger amounts of radioactivity. This process can increase the number

| TABLE 1. Sterility/Bacterial Endotoxin Submitted Sample Distribution. |
|-----------------|------------------|------------------|
| SAMPLES              | STERILITY SAMPLES | BACTERIAL ENDOTOXIN SAMPLES |
| RADIOPHARMACEUTICALS | NUMBER OF        | NUMBER OF         |
|                     | STERILITY        | BACTERIAL         |
|                     | SAMPLES          | ENDOTOXIN         |
| Myoview             | 106              | 105              |
| Cardiolite          | 171              | 169              |
| Sestamibi (generic) | 14               | 14               |
| MDP (all brands)    | 168              | 163              |
| HDP                 | 67               | 67               |
| MAA                 | 172              | 170              |
| Sulfur Collid (SC)  | 147              | 141              |
| NaTeO4 (Lanth/Covid)| 166              | 156              |
| Choletec            | 204              | 199              |
| Mebrofenin (generic)| 59               | 59               |
| Hupetolene          | 38               | 38               |
| DTPA                | 93               | 93               |
| MAG-3               | 83               | 83               |
| Neurulite           | 8                | 8                |
| Filtered SC         | 18               | 17               |
| DMUSA               | 2                | 2                |
| TOTALS:             | 1516             | 1452             |

Note: The total number of sterility/stability samples differ because several of the bacterial endotoxin test results were excluded. Preparations marked with an * had at least one kit that failed positive control testing for the bacterial endotoxin kit. Preparations marked with (x) had sterility results submitted, but bacterial endotoxin tests for that sample were omitted.
of punctures required in the compounding process to ten or more, depending on the number of kits that are combined in the process. In this case, the preparation of Cardiolite no longer falls into the low-risk category since it does not meet the two-puncture limit and most likely represents a medium-risk compounding situation. In our study, if the Cardiolite data are considered a medium-risk category preparation and the entire group (6 positive samples out of 171 samples submitted) is removed from consideration when calculating the contamination rate for true, low-risk compounding activities, the level of contamination for the low-risk level category becomes 0.52% (7 positive samples/1345 total samples). Though limited by a small sample size, if the Cardiolite data is considered to fall under medium-risk compounding and assessed as an individual group, the positive sterility test result rate for medium-risk compounding processes would be 3.53% (6 positive samples/171 total samples). Table 3 provides greater detail regarding the radiopharmaceuticals with a positive sterility result.[T3.4]

The results of the bacterial endotoxin tests are provided in Table 4. A total of 1492 samples were submitted for analysis. There were 4 samples that showed gel formation during the bacterial endotoxin testing, indicative of the presence of bacterial endotoxins in the kit formulation. This results in a 0.27% bacterial endotoxin contamination rate. [T4]

DISCUSSION

The preparation and dispensing of radiopharmaceuticals in a centralized nuclear pharmacy setting may differ from what is traditionally observed in other areas of sterile preparation compounding. In a nuclear pharmacy, almost every radiopharmaceutical is treated as a multi-use kit, allowing for removal of multiple patient doses from a single radiopharmaceutical kit formulation. In addition, most nuclear pharmacies utilize substantially greater activities of Tc-99m sodium pertechnetate when compounding.

<table>
<thead>
<tr>
<th>TABLE 2. Sterility Testing Results.</th>
<th>NUMBER OF STERILITY SAMPLES</th>
<th>+ GROWTH STERILITY TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>RADIOPHARMACEUTICAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoview</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Cardiolite</td>
<td>171</td>
<td>6</td>
</tr>
<tr>
<td>Sestamibi (generic)</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>MDP (all brands)</td>
<td>168</td>
<td>0</td>
</tr>
<tr>
<td>HDP</td>
<td>67</td>
<td>1</td>
</tr>
<tr>
<td>MAA</td>
<td>172</td>
<td>3</td>
</tr>
<tr>
<td>Sulfur Colloid (SC)</td>
<td>147</td>
<td>1</td>
</tr>
<tr>
<td>TcO4 (Lanth/Covid)</td>
<td>166</td>
<td>2</td>
</tr>
<tr>
<td>Choletec</td>
<td>204</td>
<td>0</td>
</tr>
<tr>
<td>Mebrofenin (generic)</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Hepatolite</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>DTPA</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>MAG-3</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>Neurollie</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Filtered SC</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>DMSA</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TOTALS:</td>
<td>1516</td>
<td>13 (0.86%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3. Distribution of Positive Sterility Tests.</th>
<th>TSB DAY 3</th>
<th>FTM DAY 3</th>
<th>TSB DAY 7</th>
<th>FTM DAY 7</th>
<th>TSB DAY 14</th>
<th>FTM DAY 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP KIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiolite</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>HDP</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MAA</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sulfur Colloid (SC)</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NaTcO4 (Lanth/Covid)</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 4. Bacterial Endotoxin Testing Results.</th>
<th>NUMBER OF BACTERIAL ENDOTOXIN SAMPLES</th>
<th>+ GEL BACTERIAL ENDOTOXIN TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>RADIOPHARMACEUTICAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoview</td>
<td>105</td>
<td>0</td>
</tr>
<tr>
<td>Cardiolite</td>
<td>168</td>
<td>0</td>
</tr>
<tr>
<td>Sestamibi (generic)</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>MDP (all brands)</td>
<td>163</td>
<td>0</td>
</tr>
<tr>
<td>HDP</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>MAA</td>
<td>170</td>
<td>0</td>
</tr>
<tr>
<td>Sulfur Colloid (SC)</td>
<td>141</td>
<td>2</td>
</tr>
<tr>
<td>NaTcO4 (Lanth/Covid)</td>
<td>165</td>
<td>0</td>
</tr>
<tr>
<td>Choletec</td>
<td>199</td>
<td>1</td>
</tr>
<tr>
<td>Mebrofenin (generic)</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Hepatolite</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>DTPA</td>
<td>93</td>
<td>1</td>
</tr>
<tr>
<td>MAG-3</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>Neurollie</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Filtered SC</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>DMSA</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TOTALS:</td>
<td>1402</td>
<td>4 (0.27%)</td>
</tr>
</tbody>
</table>
the kit. This allows for removal of increasingly greater numbers of doses per kit, requiring more punctures of the septum, a process that could potentially increase the risk of microbial contamination in the final preparation being dispensed.

To date, no study has looked at microbial contamination rates of commercially prepared unit-dose radiopharmaceuticals, and this, along with the recent release of USP <797> and a heightened focus on sterile preparation compounding, provided the impetus for this study. Although commercial nuclear pharmacy operations differ to some extent from typical hospital pharmacy practices, the most relevant comparison of achievable contamination rates can be drawn from works published by Trissel et al in 2003 and 2005. In these works, Trissel established benchmark microbial contamination rates for low-risk (<0.1%) and medium-risk (5.2%) compounding practices in a hospital setting. Since most Tc-99m sodium pertechnetate CSP-radiopharmaceuticals are considered to be "low-risk" compounding procedures per USP <797>, Trissel's work evaluating low-risk compounding procedures would initially be the first choice for comparison. Per USP <797>, low-risk compounding requires that a preparation has no more than two punctures in the vial during the compounding process. While most radiopharmaceuticals are compounded within the two-puncture rule, unlike most traditional pharmaceuticals, there will be multiple doses dispensed out of the vial, requiring additional punctures in the dispensing process, which potentially increases the chance for microbial contamination. In addition, some radiopharmaceuticals require more complex preparation steps, such as boiling and filtering; neither of which is addressed in Trissel's low-risk evaluation. Therefore, it is also reasonable to compare radiopharmaceutical preparation to Trissel's medium-risk compounding evaluation, in which multiple punctures are made into compounding vessels and multiple manipulations of material are carried out. Again, it is important to reiterate that radiopharmaceuticals are considered "low-risk" due to many factors, including the small volume administered but, most importantly, the BUD, due to the radioactive component of the preparations. Therefore, it is reasonable to accept that the risk of microbial contamination for radiopharmaceutical preparations would most likely fall within the values put forth by Trissel in these two works.

In evaluating the rate of microbial contamination in the radiopharmaceuticals compounded for this study, 13 of the 1516 samples showed some evidence of microbial growth during the 14-day evaluation period. This resulted in a microbial contamination rate of 0.86%. If the results from the "batched" Tc-99m Cardiolite group are removed from the analysis, the contamination rate is lowered to 0.52%. While both are higher than the low-risk compounding rate set forth by Trissel, both also are considerably lower than the medium-risk benchmark rate for medium-risk compounding. Even if the Tc-99m Cardiolite group is considered to be in the medium-risk category of USP <797> because of the multiple-entries to the septum and is evaluated independently of all other data, its positive sterility test result rate is 3.51%, which is lower than that reported in the second Trissel work on medium-risk compounding.

In evaluating the actual distribution of kits with positive microbial contamination, some of the results were anticipated, based on an understanding of kit components and compounding processes, while some results were not initially anticipated. The following sections discuss the sterility and bacterial endotoxin results for each of the radiopharmaceutical kits that showed either positive growth in one or more sterility test samples or positive bacterial endotoxin testing.

Sterility - MAA/Sulfur Colloid

The positive results for MAA and Sulfur (SC) (four positive results in 319 kit preparations or 1.25% aggregate for both) were not unexpected, since both of these agents contain material (albumin and gelatin) that can support microbial growth. In observing the distribution of positive results in these preparations, the MAA had growth in the FTM media at all time points in two of the samples and a single positive in the day 14 sample of the TSB media. The SC kit showed growth in both day 7 and 14 of the TSB sample. Given the distribution, it is reasonable to assume that these results are accurate.

Sterility - HDP

The positive result (one in 67 preparations or 1.5%) for the HDP kit occurred in the day-7 evaluation of the FTM testing media. However, the 14-day evaluation of the same tube showed no evidence of growth, strongly indicating that the day-7 result is questionable because of evaluator interpretation or error. Either the 7-day reading was "misread" as being turbid, thus the positive evaluation, or the day-14 reading was not read correctly and was truly turbid, but not reported correctly. Although the results most likely indicate that some type of error may have occurred, the sample was included in the total results.

Sterility - Sodium Pertechnetate

Both of the positive samples (two in 166 test results or 1.2%) of Tc-99m sodium pertechnetate (from generator elutions that were used to compound radiopharmaceutical kits) showed growth at more than one time point—one elution had positive growth in all three evaluation points for the FTM media, while the other had growth in the 7- and 14-day FTM evaluations. Tc-99m sodium pertechnetate generator elutions are sterile upon removal of the eluate from the generator but have increased risk of potential contamination due to the multiple punctures required when removing the radioactivity for the compounding process. It is feasible to assume that these results are accurate.

Sterility - Cardiolite

The most surprising result was found in the analysis of the Cardiolite samples. Six of the 171 samples (3.51%) showed evidence...
of microbial growth. Two of the six samples showed growth in two
time points (7 and 14 day) for both of the media. One of the
samples showed growth in two time points (7 and 14 day) for the FTM
media only, and three of the samples showed growth on the 14-day
FTM evaluation. It is highly likely that these results are accurate.

The unexpectedly high rate of microbial contamination in
this group introduces one of the greatest concerns with the data
obtained in this study since myocardial perfusion studies make up
a significant percentage of dispensed doses from any nuclear phar-
my. Preparation of the Cardiolite requires a boiling step, which
could contribute to the risk of contamination, depending on
the heat source used for the boiling step. If a water bath is used as a
heating source, formation of a thin film over the septum of the vial
occurs that, if not cleaned correctly, could be introduced into the
kit formulation when puncturing the vial with a syringe. In addi-
tion, in many pharmacies, the heat sources (water bath or heating
block) is usually housed in a separated, controlled-negative pres-
sure environment to prevent widespread contamination issues if
the vial would happen to break during the heating process. This
most likely introduces transient exposure to non-ISO 5 air dur-
ing the transfer process that could potentially increase the risk
of inadvertent microbial contamination. However, in discussions
with the various compounding sites, the increased risk of growth
in this study appears to be related to a practice called “batching”
in which several cold radiopharmaceutical kits are reconstituted
using 0.9% normal saline, and the contents of each kit are trans-
ferred to a larger-size vial. The mixed sample is compounded using
a single, very high amount of radioactivity equivalent to the total
amount of activity that would be added to each of the vials inde-
pendently.

As reported by the study participants, the rationales behind the
practice of batching include:

- Increased speed of compounding
- Decreased number of quality-control tests required to be
  completed after compounding
- Decreased number of kits available (which may minimize the
  risk for potential medication errors)

However, the more significant consideration is the inherent
risk associated with this practice due to the increasing number
of punctures required in the entire compounding process. If four
individual kits were combined to make a “batch,” it would require
more than 10 punctures in the compounding process alone, well
over the two-puncture limit for low-risk compounding and chang-
ing the practice to the medium-risk compounding category. It is
reasonable to expect that the greater the number of punctures into
the vial, the greater the risk for inadvertent microbial contamination.
All six of the Tc-99m Cardiolite kits with a positive sterility
were “batched,” making it likely that the results are accurate.

Bacterial Endotoxins

When evaluating the bacterial endotoxin results, there were
four positive results in a total of 1462 samples. It is interesting
to note that the positive bacterial endotoxin tests were found in
samples that did not have a positive sterility test result at any evalu-
ation point during the 14-day evaluation period. The most likely
explanation for positive bacterial endotoxin testing is related to
inexperience of the operators performing the test. Bacterial endo-
toxin testing is not a common quality-control test carried out in
a centralized nuclear pharmacy, so many of the participants had
never performed a bacterial endotoxin test prior to the start of
the study. The decreased number of bacterial endotoxin samples
(1462 as compared to the 1516 sterility samples) is an indication
of the difficulties that occurred early in the testing process with
several sites that had not performed this type of test before this
study. Several of the samples submitted did not have the expected
gel formation in the positive control that was included in the test-
ing procedure, indicating that the test results were invalid, so
these samples were not included in the data analysis. The failure
of the positive control was most likely due to inhibition caused
by the ligand or other kit components, but several of the nuclear
pharmacy sites struggled with identification of this early in the
data-collection period due to operator inexperience.

The reasons for the four positive results found during the study
are difficult to identify, and unfortunately may be due to opera-
tor inexperience as stated earlier. However, it is not possible to
exclude the possibility that the positive results were in fact valid
results. The absence of a positive sterility test does not rule out the
presence of bacterial endotoxins in a sample. Repeat testing of the
radiopharmaceutical kit with a positive bacterial endotoxin result
should have been undertaken to confirm the initial results of any
failed test.

STUDY LIMITATIONS

Concerns with consistency of inter- and intra-operator perfor-
mances are always among study limitations when multi-center
experimentation is undertaken. In this case, the use of end-of-day
kit preparations allowed the analysis of preparations that were not
treated in any special way since all were used in clinical studies
prior to sterility and bacterial endotoxin testing. This also pro-
vided for several compounders’ aseptic compounding techniques
to be assessed throughout the study interval.

Sterility testing is not a routine component of commercial
nuclear pharmacy operations. Variables from site to site that
potentially could have impacted the data obtained during the
study and should be considered when evaluating the data include
such things as:

- Operator training
- Size of inoculums
- Sample incubation times
- Operator observation of samples for turbidity
An attempt was made to standardize both the sterility and the bacterial endotoxin testing for all sites, but consistency in performing the testing may have been compromised due to site familiarity with the sterility and LAL gel-clot testing procedures and with any equipment that might be used in the testing procedures. Another limitation that could not be accounted for in this study was the potential for improvement in the aseptic compounding processes simply because of the presence of the study itself. Most of the testing failures (both sterility and bacterial endotoxin testing) occurred within the first year of data collection in which many of the data collection sites were performing these tests for the first time. Early failures could be a result of poor operator technique, not due to the true contamination of the radiopharmaceutical kits. As operators became more familiar with the collection process, the number of failures decreased.

Finally, the implementation of USP <797> standards was not consistent across all pharmacies for the entire duration of the study period. All compounding and dispensing activities in all of the participating pharmacies were carried out in USP <797>-compliant laminar airflow hoods, providing fairly consistent and uniform ISO 5-compounding environments for all samples. However, with the 2008 USP <797>-compliance date falling in the middle of our study, participating pharmacies were constantly making changes to operating procedures and protocols to move towards greater compliance over the course of the study period. The participants in our study were geographically distributed over several states, and since oversight for implementation and compliance of USP <797> falls under the responsibility of the Board of Pharmacy for each individual state, it was impossible to assure that the compounding processes at each of the participating pharmacies were exactly the same. The lack of uniformity between pharmacies makes it difficult to prove that any improvements in microbial and bacterial endotoxin contamination rates over the course of the study were directly related to any particular aspect of USP <797>.

CONCLUSIONS

The results of this study indicate that radiopharmaceuticals compounded in a centralized nuclear pharmacy have a very low incidence of microbial and bacterial endotoxin contamination. However, radiopharmaceutical kit preparation and dispensing of patient-specific, unit-dose radiopharmaceuticals are processes that require multiple manipulations and septal punctures, which increase the chance for inadvertent contamination of the final compounded preparations. Based on the data presented in this work, the incidence of microbial contamination in compounded radiopharmaceuticals approaches the benchmark sterility rates established for compounding of low-risk and medium-risk level CSPs in a hospital setting. The current practice standards for compounding sterile radiopharmaceutical preparations in a centralized nuclear pharmacy setting provides radiopharmaceuticals with acceptable levels of both microbial and bacterial endotoxin contamination, providing safe and effective preparations to the end user.

REFERENCES


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May 19, 2017

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RE: Comments on 20 CSR 2220-2.200 Sterile Compounding rules

Executive Director Grinston and Chief Inspector Glenski,

Thank you for allowing us the opportunity to comment on the Missouri Board of Pharmacy rules regarding sterile compounding and we are happy to do so. By way of background, Triad Isotopes, Inc. is a nationwide nuclear pharmacy company headquartered in Orlando, Fl. The company’s national network of over 50 locations serves 4 million patients each year, making Triad Isotopes the nation’s second-largest radiopharmaceutical provider in the US, and the largest dedicated solely to preparing and dispensing radiopharmaceuticals. These specialized facilities provide the products used by hospitals and nuclear medicine operators to help diagnose and treat patients, primarily those with cardiac and cancer concerns.

Triad Isotopes, Inc. Pharmacies works collaboratively with several professional organizations including the National Association of Nuclear Pharmacies, the American Pharmacists Association (APhA), the Council on Radionuclides and Radiopharmaceuticals (CORAR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) to communicate the best practices in nuclear pharmacy. These efforts have greatly harmonized the practice of nuclear pharmacy to ensure patients receive safe and effective radiopharmaceuticals along with the inherent lack of risk associated with compounding radiopharmaceuticals due to a short BUD, small volume, lack of growth medium and radiation exposure. These efforts have resulted in an outstanding record of quality and safety, as evidenced by the near zero incidence of adverse events following nuclear pharmacies’ preparation of over 30,000 99mTc-drugs each day that are administered to patients in the US over the past multiple decades. It is hard to argue the fact that no other area of pharmacy is even close to nuclear pharmacy’s safety record and that the risk of any infection due to our compounded preparations is statistically zero based on the above evidence.

It is difficult to write rules to apply to all aspects of pharmacy, but nuclear pharmacy has always been that one exception that typically is treated as a one off to all others and generally has its
own set of rules applicable to them. Nuclear Pharmacy was the first BPS specialty because of this uniqueness, most boards of pharmacy including Missouri’s has a separate nuclear pharmacy section, nuclear is a partitioned section from USP 797, it was excluded from the FDA 503A compounding rules and in fact now has a draft guidance for Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities, Guidance for Industry, nuclear pharmacy was one of two special roundtables held by USP in 2017 to discussion having its own chapter, and further, FDA has specifically called out radiopharmaceutical organizations as a topic of their listening sessions for 2017. It would be best to either exclude nuclear pharmacy from the traditional sterile compounding rules from the Missouri Board of Pharmacy, have specific ones for nuclear in these rules, or include specific rules for compounding in the nuclear pharmacy section of the rules.

One item we wanted to comment on was the definition and enforcement or the “In Use Time”. Per the current MO BOP rules, it is defined as:

(P) In-use time/date: The time/date before which a conventionally manufactured product or a CSP must be used after it has been opened or needle-punctured.

Further, it states:

(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. 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.

This wording of “in use time” is not used by any other regulatory or active guidance and we can only assume that it was pulled from the current draft revision of USP 797. This draft received over 8700 comments and in a rare move, the USP Sterile Compounding Committee will send out another revision for comment once it revises the draft based on those comments. I would encourage not using this term until it is fully vetted, understood, and used appropriately by regulatory agencies, manufacturers, and compounders. There were many comments that address the confusion of using this term and its appropriateness.

The above language also does not address multi dose vials that do not include a preservative. Having a preservative is not the only quality that makes a kit labeled as multi use, but the MO BOP rules have done just that. I would just use the words multi or single use and leave out any reference to the wording of preservatives and leave that up to the FDA and the approved drugs from the manufacturers.

Also, this wording seems to be inspired or taken from USP 797. It is stated in the chapter that:
The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.

As such, nuclear pharmacies for years have been deviating from the package inserts from the suggested use by times from the manufacturer for many reasons. Testing data above USP BUD limits (12hrs for radiopharmaceuticals, or 48hrs for room temperature low risk compounded preparations) should be on hand for any excursions and that wording should be included in the rule. Our need to an extended BUD is necessary to prepare radiopharmaceuticals to serve a geographically distant patient with a later use time. Additionally, in nuclear medicine, radiopharmaceuticals are routinely used in emergency situations after hours to diagnose critical life-threatening conditions. A BUD that has been validated and that exceeds the drug product manufacturer’s BUD would enable pharmacists to prepare and deliver radiopharmaceuticals to be used in emergency, after-hours situations. The availability of nuclear pharmacists to prepare radiopharmaceuticals for administration to patients is significantly limited with only approximately 400 nuclear pharmacies throughout the US. As long as the preparation meets the USP monographic guideline for purity and is within the USP limits for BUD (which is almost always the case since 24hrs is usually the limit of use), that is what is important to keep the patient safe.

As referenced above, the Draft FDA guidance for state licensed nuclear pharmacies came from multiple listening sessions with the FDA. During the USP radiopharmaceutical roundtable, this was also discussed with the FDA representative in attendance. They do not consider most of what we do with our FDA approved kits as “compounding” and that includes minor deviation, and even excluded nuclear preparations from the USP 797 BUDs. Many letters were written back to the FDA as comments and are available on their website for viewing and most of them were in complete agreement with the draft with the exception of some minor grammatical and technical understanding mistypes. This was a great example of a regulatory agency communicating with their stakeholders and getting guidance out that helps protect the patients and keeps access to the compounded preparations. I would encourage the Missouri Board of Pharmacy to create a nuclear pharmacy committee to draft and edit our existing rules and include the sterile compounding language in it as well.

The second rule that we would like reviewed is based on the below rule:

If a highly pathogenic microorganism is detected, or if the CFU count exceeds USP 797 action levels in any ISO-5 or ISO-7 classified area, no further compounding shall be performed until resampling shows a suitable state of microbial control. The pharmacy shall ensure that no misbranded, contaminated, or adulterated CSP is administered or dispensed for patient use.

(B) 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 use of the term “highly pathogenic” is academic at best and all microbiologists we have discussed with do not understand this term. There is no standard reference for it outside of USP 797 and is not included in any microbiologic or medical references that can be found. It is an unfortunate term that will hopefully be removed in the new version. Despite this, these
guidelines of action limits are just that from USP 797 and are suggested. It could be entirely acceptable and appropriate for a state of control to have one fungal CFU in the door way that joins the ante area to the buffer area in a cleanroom. That would have no effect on the preparation and safety to the patient. What this rules does is introduce some unintended consequences that are more dangerous for the patients of Missouri. USP 797 doesn’t mandate an immediate shut down of operations and just states immediate remediation needs to occur. What the Missouri Board of Pharmacy rule does is incentivize keeping sterile preparations being prepared in an ISO 8 SCA so the immediate shut down is not a risk to business or access to medications. While having a clean room is generally preferable to a SCA for compounding preparations, the risk of having to shut down operations is too great to have pharmacies invest a lot of capital just to risk a shut down from a variant CFU that has no bearing on the safety of our Missouri patients. It also creates a limit of testing so while a pharmacy would normally want to test in many areas to obtain their state of control and how to engineer their areas better, this rules incentivizes limited testing sites to reduce the opportunity for a rogue CFU of a “highly pathogenic” organism. Even the state of Massachusetts doesn’t go this far with shutting down operations upon first testing and that is of course where the tragic events of NECC occurred. There are also times when there is self-contamination from a tester, so having to shut down a pharmacy from compounding due to potentially the tester not being careful with the samples is not what is in the best interest of the patient.

Thank you again for giving Triad Isotopes, Inc. the opportunity to comment on the current sterile compounding rule and we look forward to working with you in whatever capacity you need to help draft purposeful and responsible rules that help protect the patients of Missouri in all aspects.

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RE: 20CSR 2220-2.200 Sterile Compounding applicable to radiopharmaceuticals

Dear Mr. Glenski:

Thank you for taking the time to address the unique challenges faced by nuclear pharmacies. As the Chair of the APhA-APPM Nuclear Pharmacy SIG, I know nuclear pharmacists are committed to providing a high level of professional care for our patients. Currently, the FDA and USP are considering unique regulations and standards for radiopharmaceuticals. The FDA will have their second radiopharmaceutical listening session June 5th, and a new guidance is expected to be published, which will replace the last radiopharmaceutical FDA guidance published in 1984.¹ ² The USP Compounding Expert Committee formed a roundtable February 1, 2017 to discuss the unique compounding standards for radiopharmaceuticals. As a result, the Senior Director of Science-HQS and the Vice Chair of the USP Compounding Expert Committee expect there to be significant changes to the revised USP <797> concerning radiopharmaceuticals.

The ability to prepare radioactive drugs with short half-lives became available, in part, through the use of the technetium 99m generator, which must be shielded by approximately 300 pounds of lead. 85% of radiopharmaceuticals used in nuclear medicine departments, rely on the radioactive technetium 99m combined with a non-radioactive manufacturer kit. The non-radioactive manufacturer kits have suggested expiration times ranging from 4 hours to 18 hours after radiolabeling with technetium 99m. Using the manufacturer’s product labeling (not to be confused with radiolabeling) is not the best practice as these instructions have been shown to have deficiencies.³ Because of these deficiencies, the industry has a standard of performing quality control on the radiolabeled preparation to ensure that stability is retained throughout the beyond use date.⁴ ⁵ A study by Weatherman reported sterility of these products while in the manufacturer’s vial (as would be the case with MO In-Use Times) and when stored in the syringe.⁶ Currently, all technetium 99m radiolabeled drugs are used within 24 hours of
preparation. The short beyond use date of these drugs is half of the current USP 797 respective standard.

Radiopharmaceutical radiolabeling must take into account unique properties such as specific activity and radiolysis. It also has unique handling parameters which require protection of the user such as interruption of first air from vial and syringe shielding and use of a vertical flow PEC for contamination containment. The Authorized Nuclear Pharmacist and Authorized Physician have the specialized training and knowledge for the challenges dispensing sterile radiopharmaceuticals.

Lastly, the Molybdenum 99 (Mo-99)/technetium 99m generator is our daily source for technetium 99m and our supply of technetium 99m depends on a robust supply chain for Mo-99. Currently that supply chain is fragile as no Mo-99 is produced in the United States. In a report by the National Academies of Science, the efforts of the industry were included in the overall supply chain equation. Inadvertent consequences from shortening the BUD from standard practice would result in a decrease of important resources and an increase of waste.

In the next few years, with the revision of the current USP <797>, we should see a public standard for the preparation, compounding, and dispensing of sterile radiopharmaceuticals within the practice of nuclear pharmacy. I encourage the Board to continue to examine the unique practice of nuclear pharmacy and to work with pharmacists and physicians to ensure the safe and consistent supply of these drugs.

If you have any questions or require additional information, please do not hesitate to contact me.

Sincerely,

[Signature]

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References


Radiopharmaceuticals that come from the manufacturer with radioactivity already added (may be sent directly to the end user or to the pharmacy. Pharmacy may draw doses directly or use it to radiolabel a cold kit)

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Manufacturer’s In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon-11 choline</td>
<td>Zevacor</td>
<td>Mayo Clinic Wash U</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Fluorine-18 florbetaben</td>
<td>Neuraceq</td>
<td>Piramal Imaging</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Fluorine-18 florbetapir</td>
<td>Amyvid</td>
<td>Eli Lilly</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Fluorine-18 sodium fluoride</td>
<td>(various)</td>
<td>Cardinal Health Triad Isotopes Zevacor</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Fluorine-18 fludeoxyglucose</td>
<td>Various</td>
<td></td>
<td>No in-use time</td>
</tr>
<tr>
<td>Fluorine-18 flutemetamol</td>
<td>Vizamyl</td>
<td>GE Healthcare</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Gallium-67 citrate</td>
<td></td>
<td>Mallinckrodt Lantheus</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Indium-111 chloride (used to radiolabel Prostascint &amp; Zevalin)</td>
<td>Indiclor</td>
<td>Mallinckrodt GE Healthcare (Indiclor)</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Indium-111 pentetate (intrathecal product)</td>
<td>GE Healthcare</td>
<td>No in-use time. Discard vial after single use</td>
<td></td>
</tr>
<tr>
<td>Indium-111 oxyquinolone (used for radiolabeling leukocytes)</td>
<td>GE Healthcare</td>
<td>No in-use time (Single use product used to label WBCs)</td>
<td></td>
</tr>
<tr>
<td>Iodine-123 iobenguane</td>
<td>Adreview</td>
<td>GE Healthcare</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Iodine-123 ioflupane</td>
<td>DatScan</td>
<td>GE Healthcare</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Iodine-125 human serum albumin</td>
<td>Jeanatope</td>
<td>IsoTex Diagnostics</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Iodine-125 iothalamate</td>
<td>Glofil-125</td>
<td>IsoTex Diagnostics</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Iodine-131 human serum albumin</td>
<td>Megatope</td>
<td>IsoTex Diagnostics</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Nitrogen-13 ammonia</td>
<td></td>
<td>Various</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Radium-223 dichloride</td>
<td>Xifigo</td>
<td>Bayer Healthcare</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Samarium-153 lexidronam</td>
<td>Quadramet</td>
<td>Lantheus</td>
<td>Use within 8 hours of thawing</td>
</tr>
<tr>
<td>Strontium-89 chloride</td>
<td>Metastron</td>
<td>GE Healthcare</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Thallous chloride-201</td>
<td></td>
<td>Mallinckrodt Lantheus</td>
<td>No in-use time</td>
</tr>
<tr>
<td>Yttrium-90 chloride</td>
<td></td>
<td>Eckert &amp; Ziegler</td>
<td>No in-use time</td>
</tr>
</tbody>
</table>
Radiopharmaceuticals that are compounded by the pharmacy (begin with a cold kit and add radioactivity via a generator or other manufactured radiopharmaceutical)

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Manufacturer’s In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indium-111 capromab pendetide</td>
<td>ProstaScint</td>
<td>AYTU Bioscience</td>
<td>8 hours</td>
</tr>
<tr>
<td>Indium-111 pentetreotide</td>
<td>Octreoscan</td>
<td>Mallinckrodt</td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m bicisate</td>
<td>Neurolite</td>
<td>Lantheus</td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m disofenin</td>
<td>Hepatolite</td>
<td>Pharmalucence</td>
<td>6 hours (Aseptically withdraw material for use within six (6) hours)</td>
</tr>
<tr>
<td>Technetium-99m exametazine</td>
<td>Ceretec</td>
<td>GE Healthcare</td>
<td>Depends upon method of preparation. If prepped with stabilizer = 4 hours. If prepped without stabilizer = 30 minutes. Can also be used to tag WBC.</td>
</tr>
<tr>
<td>Technetium-99m macroaggregated albumin (MAA)</td>
<td>Draximage</td>
<td></td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m mebrofenin</td>
<td>Choletec</td>
<td>Pharmalucence Bracco Diagnostics</td>
<td>Pharmalucence- 6 hours Bracco – 18 hours</td>
</tr>
<tr>
<td>Technetium-99m medronate</td>
<td>Draximage MDP-25 MDP-Bracco</td>
<td>Draximage Pharmalucence Bracco Diagnostics</td>
<td>6 hours Draximage-12 hours</td>
</tr>
<tr>
<td>Technetium-99m mertiatide</td>
<td>Technescan MAG3</td>
<td>Mallinckrodt</td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m oxidronate</td>
<td>Technescan HDP</td>
<td>Mallinckrodt</td>
<td>8 hours</td>
</tr>
<tr>
<td>Technetium-99m pentetate</td>
<td>DTPA</td>
<td>Draximage</td>
<td>12 hours</td>
</tr>
<tr>
<td>Technetium-99m pyrophosphate</td>
<td>Technescan PYP</td>
<td>Mallinckrodt Pharmalucence</td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m red blood cells</td>
<td>Ultratag</td>
<td>Mallinckrodt</td>
<td>No in-use time (Kit used to label RBC)</td>
</tr>
<tr>
<td>Technetium-99m sestamibi</td>
<td>Cardiolite</td>
<td>Lantheus Cardinal Draximage Pharmalucence Mallinckrodt</td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m sulfur colloid</td>
<td></td>
<td>Pharmalucence</td>
<td>6 hours</td>
</tr>
<tr>
<td>Technetium-99m tetrofosmin</td>
<td>Myoview</td>
<td>GE Healthcare</td>
<td>12 hours</td>
</tr>
<tr>
<td>Technetium-99m tilmanocept</td>
<td>Lymphoseek</td>
<td>Navidea Biopharmaceuticals</td>
<td>6 hours</td>
</tr>
<tr>
<td>Yttrium-90 ibritumomab tiuxetan</td>
<td>Zevalin</td>
<td>Spectrum</td>
<td>No in-use time</td>
</tr>
</tbody>
</table>
Generators (In-use times for the radioactive solution that comes off the generator)

<table>
<thead>
<tr>
<th>Generator</th>
<th>Manufacturer</th>
<th>Manufacturer's In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technetium-99m sodium pertechnetate</td>
<td>GE Healthcare</td>
<td>The sodium pertechnetate Tc99m injection eluate should be used within twelve (12) hours of the generator elution time. If the eluate is used to reconstitute a kit, the radio-labeled kit should not be used after twelve (12) hours from the time of generator elution or six (6) hours after reconstitution of the kit, whichever is earlier.</td>
</tr>
<tr>
<td>Technetium-99m sodium pertechnetate (Technelite)</td>
<td>Lantheus</td>
<td>Since the eluate does not contain an antimicrobial agent, it should not be used later than one (1) working day after the elution (12 hours). If the eluate is to be used to reconstitute a kit for the preparation of a Technetium Tc99m radiopharmaceutical, the kit should not be used after 12 hours from time of Generator elution or after the expiration time stated on the labeling for the prepared drug, whichever is earlier.</td>
</tr>
<tr>
<td>Technetium-99m sodium pertechnetate (Ultra-TechneKow)</td>
<td>Mallinckrodt</td>
<td>Since the eluate does not contain an anti-microbial agent, it should not be used after 12 hours from the time of generator elution. If the eluate is used to reconstitute a kit, the radiolabeled kit should not be used after 12 hours from the time of generator elution or after the expiration time stated on the labeling for the prepared drug, whichever is earlier.</td>
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</table>
May 11 2017

Missouri Board of Pharmacy
ATT: Ms. Kimberly Grinston, Executive Director
3605 Missouri Blvd, Jefferson City,
MO 65102-0625


Dear Ms. Grinston,

My name is Hank Rahe and I am the technology director for Containment Technologies Group, Inc. (CTC). My responsibilities at CTG include reviewing standards, rules and regulations both state and federal. Certifications performed in compliance with your state’s rules and regulations, as well as, USP <797> is critical. However, CTG has identified a conflict between your state’s rules, USP <797> and the ISO 14644-1:2015(E) standard-classification of air particulate concentration certification.

Specifically, your rules and regulations as well as USP <797> are in direct conflict with the Controlled Environment Testing Association (CETA), CETA CAG-002-2006 guide, to certify CAI/CACI’s. The Guide’s testing conditions not acceptable to the ISO 14644-1:2015(E) standard-classification of air particulate concentration certification.


The CETA Guide’s failure to comply with the testing conditions (see attached details) of the ISO Standard negates any certification using the CETA guide. All pharmacies that employ CAI/CACI’s as their Primary Engineering Control devices (PEC) and are certified to the CETA Guide are out of compliance with ISO 14644-1:2015(E) classification of air cleanliness by particle concentration required by your board’s rules as well as USP <797>.

5460 Victory Drive, Suite 300 • Indianapolis, Indiana 46203
317.713.8200 phone • 317.713.8201 fax
www.mic4.com
Non-compliance is a very serious problem and many pharmacies are not aware of the issue. Informing sterile compounding pharmacies through communications and your inspector's visits that any reports stating "certified to the CETA guide CAG-002-2006" is non-compliant will allow them to contact their certification company for correct testing procedures to those described in the ISO standard.

As part of our goal of patient safety awareness, we will be sending out this information to pharmacy directors across the county. This letter is intended to prepare your board for questions you may receive.

Please let me know if you need additional information.

Sincerely,

Hank Rahe, BSIM, MSE
Director Technology CTG
hrahe@mic4.com
317 713-8203

Attachments:
March 31, 2017

Carmen A. Catizone, Executive Director NABP
1600 Fechanville Drive
Mount Prospect, IL 60056

RE: Non-compliance of CETA guide to ISO Standards

Dear Ms. Catizone,

I am writing to seek your help in communicating with members of your association.

On August 26, 2016 you were copied on a letter (attached) to Dr. Sun, United States Pharmacopeia concerning the noncompliance of the Controlled Environment Testing Association CETA CAG-002-2006 to ISO 14644-1: 2015(E). The testing conditions required by the ISO Standard are not followed by the CETA guide.

I understand how my letter could be overlooked thus the follow up.

CETA guide failure to comply with the testing conditions (see attached details) of the ISO Standard negates any certification using the CETA guide. All pharmacies that employ CAI/CACI’s as their Primary Engineering Control devices (PEC) and are certified to the CETA guide are out of compliance with ISO 14644-1:2015(E). All state boards of pharmacy, USP <797>, USP <800> and FDA guidance require this ISO Standard for classification of air cleanliness by particle concentration. As you are also aware, pharmacy boards and federal agencies, such as the FDA, depend upon the certification as part of their inspection process.

Communications will be going out to state pharmacy boards presidents, USP, federal agencies and individual pharmacy directors making them aware of the problem of being certified to the CETA guide. This is likely to create questions and concerns that will reach your association members.

I look forward to working with you and NABP to communicate this important information. Let me know if you have any questions.

Sincerely,

Hank Rahe, Director Technology CTG
hrahe@mic4.com
317 713-8203

CC: NABP Executive Committee

Attachments:
August 23, 2016

United States Pharmacopeia
Dr. Jeanne Sun, Scientific Liaison to the Compounding Expert Committee
12601 Twinbrook Parkway
Rockville, MD 20852-1790

RE: ISO 14644-1:2015 (E)

Dear Dr. Sun,

As you may be aware that the International Standards Organization has issued a second addition of IS0 14644-1:2015(E) in December 2015.

ISO 14644-1: 2015(E) Classification of air cleanliness by particle concentration is sited in both USP <797>, and USP <800> as a requirement for levels of air cleanliness. The language of ISO 14644-1: 2015 (E) addresses the required test conditions “occupancy states” for testing cleanliness levels by particle concentrations to comply with the ISO standard. The USP standards are inconsistent with the language of the ISO standards and causes confusion, when comparing the required testing conditions.

The ISO 14644-1:2015 (E) require occupancy states 1 during testing be “as built, at rest, and operational” while USP <797> and USP <800> use the term “dynamic conditions”. Though the terms dynamic conditions and operational would seem to mean the same thing dynamic conditions cannot be cross referenced with ISO 14644-1:2015(E). For consistency USP should change the wording in USP <797> and USP <800> to properly identify the state in which the standard air cleanliness particle concentration is to be measured.

Also, USP <797> currently references the Controlled Environment Testing Association (CETA) as an example (per Susan deMars your chief legal counsel) of testing and certification of Compounding Aseptic Isolators (CAI) and Containment Compounding Aseptic Isolator (CACI). A number of state pharmacy boards have wrongly interpreted this to mean the CETA guide is the required testing standard for USP <797>, while USP sites it only as an example of testing and certification. USP should clarify that the CETA reference is an example to state pharmacy boards.
In addition, the CETA guide has compliance issues with the ISO 14644-1:2015(E) standard in that the CETA guide CAG-002-2006 requires "particle elevation" for tests 2.06, 2.07, and 2.09 which conflicts with ISO 14644-1:2015(E) requirements for an operational state while performing testing. The CETA guide also has additional conflicting testing requirements such as only testing for vertical airflow (2.08) and stating in the overview of the document that it is not intended to set specific acceptance criteria and yet follows with a series of subjective test acceptance criteria.

In summary I am requesting USP to align the wording for levels of air cleanliness with the ISO standard 14644-1: 2015(E) and inform your customers, the state pharmacy boards, that the CETA referenced in the current USP <797> is only an example.

Thank you for your attention to this important matter and I look forward to the changes.

Sincerely,

Hank Rahe, BSIM, MSE
Director Technology CTG
317 713-8203
hrahe@mic4.com

CC: Ms. Susan deMars, Chief Legal Counsel USP
    Mr. Dan King, Frost, Brown, Todd LLC
    Ms. Carmen Catizone, Executive Director NABP
    Mr. Dale Atkinson, Atkinson & Atkinson LLC legal Counsel NABP
    Executive Directors all state Boards of Pharmacy
    Legal Counsels all state Boards of Pharmacy

1. ISO 14644-1:2015 (E): Cleanrooms and associated controlled environment – Part 1: Classification of air cleanliness by particle concentration, p3 3.3 Occupancy states; Ch -1223 Vernier; Geneva Switzerland
Specific wording ISO 14644-1(E); 2015

ISO 14644-1:2015 (E): Cleanrooms and associated controlled environment – Part 1:
Classification of air cleanliness by particle concentration, p3 3.3 Occupancy states; Ch -1223
Vernier, Geneva Switzerland

The language of ISO 14644-1: 2015 (E) addresses the required test conditions “occupancy
states” for testing cleanliness levels by particle concentrations to comply with the ISO standard.
The required occupancy states are as built, at rest, and operational.

Specific wording CETA CAG-002-006

CETA Compounding Isolator Testing Guide CETA CAG-002-2006 Revised December 8, 2008,
P3 glossary of terms- particle elevation, Controlled Environment Testing Association,1500
Sunday Drive, Suite 102, Raleigh, NC 276

CETA guide CAG-002-2006 requires “particle elevation” for testing and has additional
conflicting testing requirements such as only testing for vertical airflow and stating in the
overview of the document that it is not intended to set specific acceptance criteria.

1. The CETA guides are not standards and contain tests to not meet ISO standard 14644-
   1:2015(E). Each of these tests require an adjustment to background particle levels
   (particulate elevation) that do not represent operational conditions. The specific tests
   that create the barrier for the MIC contained in CETA-CAG-002-2006:
   a. 2.06 Particle Containment Integrity and Enclosure Leak Test -Procedure 2- “If the
      count is too low, elevate the background levels”
      1. Increasing particle counts above operational levels overcomes the capabilities of
         the MIC which has been validated challenge levels of 400,000 particles of 0.5
         micron (ISO class 9). Documentation informs customer of the limit
   b. 2.07 Recovery Time Determination Test - Procedure 6- “fill the chamber with
      particulate”
      1. Elevates background inside the MIC to levels exceeding ISO Class 9 (1,000,000)
         exceeding any operational condition under which compounding would occur.
   c. 2.09 Preparation ingress and Egress Test- Procedure “If the count is too low elevate
      the background levels”
      1. Elevates background particulates in the anti-chamber (airlock) to a level
         exceeding ISO class 9. This exceeds any operation condition in a pharmacy
         compounding area.
   d. 2.08 Airflow Smoke Test- Specifics “Airflow in the Direct Compounding Area is
      downward”
      1. This does not allow for horizontal airflow such as the MIC’s unidirectional
         airflow and would fail the MIC based on the wording in the standard.
   e. General Responsibility Section “The engineering and design concept employed are up
      to the individual manufacturer’s discretion.
## RULE REVIEW REPORT

### CURRENT DRAFT RULE UNDER CONSIDERATION

<table>
<thead>
<tr>
<th>CURRENT DRAFT RULE UNDER CONSIDERATION</th>
<th>REVIEW DATE/NOTES</th>
</tr>
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</table>
| 1) 20 CSR 2220-2.010 (Pharmacy Standards of Operation) | • January Agenda  
• February Agenda  
• April Agenda: Changes made review in June |
| 2) 20 CSR 2220-2.012 (Pharmacy Supervision) | • April- Bd. voted to separate portions from 2.010 and return to Bd. for additional review.  
• Review in June |
| 3) 20 CSR 2220-2.025 (Non-Resident Pharmacies) | • January Agenda  
• February Agenda  
• April Agenda: Changes made review in June |
| 4) 20 CSR 2220-2.090 (Pharmacist-In-Charge Rule) | • January Agenda  
• February Agenda  
• April Agenda: Changes made review in June |
| 5) 20 CSR 2220-2.650 (Class J: Shared Services Pharmacy) | • February Agenda  
• April Agenda: Changes made review in June |
| 6) 20 CSR 2220-6.040 (Administration by Medical Prescription Order) | • October 2016 Agenda  
• April 2017 Agenda- Ask HAC to provide recommendations on RPh training programs.  
• Review in June |
| 7) 20 CSR 2220-6.050 (Immunization by Protocol) | • February Agenda  
• April agenda- Held pending possible changes that would not require BOHA approval.  
• June agenda- Returned to Bd. for additional review. |

### UNDER DISCUSSION (No Current Draft)

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<tbody>
<tr>
<td>1) 20 CSR 2220-2.085 (Electronic Transmission of Prescription Data)</td>
<td>• April 2017 Agenda: Vote to begin revision; Will be returned to Bd. in July</td>
</tr>
<tr>
<td>2) 20 CSR 2220-2.140 (Prescription Services by Pharmacists/Pharmacies for Residents in LTC Facilities)</td>
<td>• April 2017 Agenda: Forward to LTC task force to review</td>
</tr>
<tr>
<td>3) 20 CSR 2220-2.145 (Minimum Standards for Multi-Med Dispensing)</td>
<td>• April 2017 Agenda: Forward to LTC review task force</td>
</tr>
</tbody>
</table>
| 4) 20 CSR 2220-2.950 (Automated Filling Systems) | • February Agenda (By request)  
• April Agenda- Doug Lang will review statistician comments and return suggestions at the July meeting. |
| 5) 20 CSR 2220-6.055 (Non-Dispensing Activities) | • October 2016 Agenda: Further review requested  
• April 2007 Agenda- Hold pending recommendations from |
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| **6) Class-N Automated Dispensing Systems (Health Care Facilities)** | • January Agenda  
• February Agenda  
• Additional research/information requested by Bd. Companies will present to the Board in April.  
• April Agenda- Hold pending recs from the HAC and LTC Committee. |
| **7) Class-O Automated Dispensing Systems (Ambulatory Care)** | • April Agenda- Hold pending recs from the HAC and LTC Committee. |

**HOLD/ NO REVISION AT THIS TIME**

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<tr>
<td>20 CSR 2220-2.005 (Definitions)</td>
<td>• January Agenda</td>
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<tr>
<td>20 CSR 2220-2.015 (Termination of Business as a Pharmacy)</td>
<td>• January Agenda</td>
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<tr>
<td>20 CSR 2220-2.016 (Pharmacy Operating Procedures During Declared Disasters)</td>
<td>• January Agenda</td>
</tr>
<tr>
<td>20 CSR 2220-2.020 (Pharmacy Permits)</td>
<td>• January Agenda</td>
</tr>
<tr>
<td>20 CSR 2220-2.080 (Electronic Prescription Records)</td>
<td>• January Agenda</td>
</tr>
<tr>
<td>20 CSR 2220-2.083 (Electronic Record-Keeping Systems)</td>
<td>• January Agenda</td>
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</tbody>
</table>
| 20 CSR 2220-2.700 (Pharmacy Technician Registration) | • January Agenda  
• Held pending outcome of Pharmacy Technician Working Group |
| 20 CSR 2220-6.060 – 6.080 (MTS) | • April 2017: Hold pending recommendations from the HAC Committee  
• HAC reviewed 5/4/17- Recommended further review after consultation with industry partners. |
20 CSR 2220-2.010 Pharmacy Standards of Operation

PURPOSE: This rule defines terms used in the regulations of the State Board of Pharmacy and outlines the conditions necessary for the operation of a pharmacy.

(1) The word medicine or medicines is a word similar or of like import to the words pharmacist, pharmacy, apothecary shop, chemist shop, drug store, druggist and drugs, and no person shall carry on, conduct or transact a business under a name which contains, as part of the name, the word medicine or medicines, unless the place of business is supervised by a licensed pharmacist.

(A) At all times when prescriptions are compounded in a pharmacy or other establishments holding a Missouri pharmacy permit, there shall be on duty and present in that place of business a pharmacist licensed in Missouri as provided by law. In any Class J: Shared Service pharmacy where a permit is maintained at a location for the purpose of remote dispensing as defined in 20 CSR 2220-2.900 the pharmacist may be considered on duty and present as long as all required electronic connection requirements are maintained and the pharmacist is accessible at all times to respond to patient’s or other health professionals’ inquiries or requests pertaining to drugs dispensed through the use of the automated pharmacy system. When there is no pharmacist on duty, no prescription will be compounded, dispensed or otherwise provided and the public will be advised that no pharmacist is on duty by means of signs stating this fact. The signs will be displayed prominently on the doors of all entrances and the prescription counter of the pharmacy and the signs will be composed of letters of a minimum height of two inches (2”).

(B) Whenever, in a pharmacy or other establishment holding a Missouri pharmacy permit, a person other than a licensed pharmacist does compound, dispense or in any way provide any drug, medicine or poison pursuant to a lawful prescription, a licensed pharmacist must be physically present within the confines of the dispensing area, able to render immediate assistance and able to determine and correct any errors in the compounding, preparation or labeling of that drug, medicine or poison before the drug, medicine or poison is dispensed or sold. In any Class J: Shared Service pharmacy where a permit is maintained at a location for the purpose of remote dispensing as defined in 20 CSR 2220-2.900 the pharmacist may be considered on duty and present as long as all required electronic connection requirements are maintained and the pharmacist is accessible at all times to respond to patient’s or other health professionals’ inquiries or requests pertaining to drugs dispensed through the use of the automated pharmacy.
system. The pharmacist personally shall inspect and verify the accuracy of the contents of, and
the label after it is affixed to, any prescribed drug, medicine or poison compounded or dispensed
by a person other than a licensed pharmacist.

All licensed pharmacies by the Board shall comply with the rules of the Board and any
applicable state and federal law governing pharmacy practice or medication handling, including,
but not limited to, all applicable patient counseling, compounding, controlled substances and
medication dispensing, disposal and distribution laws and regulations.

(2) Pharmacist-In-Charge. All pharmacies must be under the supervision of a properly
designated pharmacist-in-charge who is responsible for managing the pharmacy and supervising
pharmacy staff. The pharmacist-in-charge must hold a current and active Missouri pharmacist
license or, for pharmacies located outside of Missouri, a current and active pharmacist license in
the state where the pharmacy is located. The pharmacist-in-charge shall comply with 20 CSR
2220-2.090.

(A) A pharmacist must immediately notify the Board electronically or in writing on a
form designated by the Board if he/she stops serving as the designated pharmacist-in-charge. The pharmacy may not continue pharmacy operations until a new pharmacist-in-charge is
designated. A change of pharmacist-in-charge application must be submitted to the Board with
the applicable fee within fifteen (15) calendar days after a new pharmacist-in-charge is
designated.

(B) An inventory of controlled substances must be taken at or immediately prior to a
pharmacist-in-charge change by both the outgoing pharmacist-in-charge and the incoming
pharmacist-in-charge. Schedule II controlled substances must be physically counted. Schedule
II – V drugs may be counted or estimated as allowed by federal law. The inventory must be
documented in writing and must include the inventory date and the signature of the outgoing and
incoming pharmacist-in-charge. If a joint inventory is not possible, the new or former
pharmacist-in-charge and an official designee of the permit holder must complete, sign and date
the inventory.
(3) Pharmacy Equipment and Reference Materials. No pharmacy shall be licensed under
the provisions of this chapter unless it is equipped with proper pharmaceutical equipment and
reference manuals for the pharmacy services performed. Requirements for proper
equipment and references may vary between pharmacies, and must insure accuracy and safety of
all pharmaceutical activity. Equipment must be maintained in good working order and capable of
accurately and properly functioning to ensure patient safety and proper pharmaceutical activity.

At a minimum, pharmacies must comply with the following:

1. (A) At least one (1) current edition of statutes and rules governing the pharmacy’s practice
must be manually maintained or electronically available at the pharmacy, including, but not
limited to, Chapter 338, RSMo, Chapter 195, RSMo, 20 CSR 2220 and, if applicable, 19 CSR 30
governing the Missouri Bureau of Narcotics and Dangerous Drugs;

(B) Basic equipment recognized by the latest edition of the United States Pharmacopoeia
(USP), the United States Pharmacopoeia/Drug Information (USP/DI) or Remington’s
Pharmaceutical Sciences shall be available for any procedures utilized in the dispensing,
compounding or admixture of drug medication and drug medical-related devices, and must
maintain conformance with these publications.

2. (C) A suitable mechanical or electronic data device or equipment must be
maintained for numbering or uniquely identifying prescriptions and medication orders, for the
numbering of all prescriptions must be maintained along with appropriate printing equipment for
the production of prescription/medication order drug labels.

(D) Reference materials may include any generally recognized or peer-reviewed
pharmaceutical publication other than periodicals or journals. At a minimum, the pharmacy
must maintain, at a minimum, or have electronically available the current or latest edition of a
reference manual(s) or other resource(s) which includes all Federal Drug Administration (FDA)-
approved drugs. The following topics must be included in the reference(s) selected Additionally,
the pharmacy must maintain or have electronically available reference materials that include the
following topics:

1. Pharmacology of drugs;
2. Dosages and clinical effects of drugs; and
3. Patient information and counseling; and
4. If applicable, sterile or non-sterile compounding.
(E) If reference materials/resources are electronically maintained, the electronic material must be immediately accessible by pharmacy staff on inspection or when requested by the Board or a Board authorized designee; general internet access alone shall not be sufficient.

(4) General Standards of Operation. Except as otherwise provided by law, all Board licensed pharmacies shall comply with the following:

(F)(A) Medication must be properly and accurately compounded, packaged, dispensed, distributed and labeled. Any excessive or suspicious prescriptions or medication orders must be verified prior to dispensing.

(B) All pharmacies The pharmacy shall be maintained in a clean and sanitary condition at all times. Any procedures used in the dispensing, compounding and admixture of drugs or drug-related devices must be completed under clean and, when required, aseptic conditions.

1. Waste and hazardous materials must be handled and disposed of in compliance with all applicable state and federal law. Except as otherwise authorized by the Board, appropriate sewage disposal and a hot and cold water supply within the pharmacy must be available within the pharmacy. The required water supply may not be located within a bathroom.

2. Appropriate housekeeping and sanitation, lighting, ventilation and humidity must be maintained in all areas where drugs are stored or dispensed must be maintained. All shelves, aisles, walkways and medication storage areas must be kept free and clean of debris, dirt or filth. Trash must be disposed of in a timely manner. Medication shall not be stored on the floor or near trash areas.

3. The pharmacy must be free from insects, rodents, birds or vermin of any kind. Animals, except for service animals as defined by the Americans with Disabilities Act (ADA), are not allowed in pharmacies.

(G)(C) The temperature of the facility where drugs are stored must be maintained thermostatically to ensure proper drug storage. Medication must be stored within temperature requirements as provided for by the manufacturer or the latest edition of the USP, or both. Adequate refrigeration must be available to ensure enough storage space for drugs requiring refrigeration or freezing and under temperatures adequate to maintain the drug products as recommended by the manufacturer, the latest edition of the USP, or both. Drugs and drug-
related devices must be stored separately from food and other items. Appropriate manual, electromechanical or electronic temperature recording equipment and devices must be used to document proper temperature storage in drug storage areas, including, refrigerators and freezers. Temperature recordings must be reviewed and documented each day the pharmacy is in operation. Alternatively, a continuous temperature monitoring system may be used if the system maintains ongoing documentation of temperature recordings that are reviewed daily.

Proof of compliance with this subsection must be maintained in the pharmacy’s records.

(D) Food and beverage items that are not in their original, sealed manufacturing packaging must be stored separately from medication and medication-related devices. Open food or beverage items used in compounding or intended for patient use with medication may be stored in the same area as drugs and drug-related devices as long as the items are separated from other inventory and sanitary conditions are maintained at all times.

(E) Pharmacies must maintain adequate security and locking mechanisms must be maintained in order to deter theft of drugs by personnel or the public and to prevent unauthorized access to the pharmacy. Sufficient alarm systems or locking mechanisms must be in place if the pharmacy is located in a facility into which the public has access that is accessible to the public and the pharmacy’s hours of operation are different from those of the remainder of the facility. Ceilings and walls must be constructed of plaster, drywall or other substantial substance so that the pharmacy permit area is separate and distinct from the remainder of the facility. Drop down ceilings that would allow unauthorized access into the pharmacy are not allowed;

(F) Pharmacies which maintain storage sites or warehouse facilities for the storage of pharmaceuticals—storing medication or confidential patient records at a separate address or premises from the main pharmacy that holds a pharmacy permit shall register those sites as storage facilities of the licensed pharmacy prior to use. Information required for proper registration of a storage facility—Registration notification must be submitted in writing in a form approved by the Board and shall include the address of the facility, hours of operation (if applicable), and the pharmacy permit numbers of the pharmacies that it services, and a certified statement that the facility is used for the sole purpose of distributing drugs only within its own pharmacy operations.

1. Records Adequate security and storage conditions must be maintained at these facilities to guarantee the security, storage and accountability—integrity and proper storage of all drugs and

Comment [GK1]: Should temp. recordings only be required for refrigerators/freezers?
medication, drug-related devices and records under proper conditions. At a minimum, a registered storage and warehouse location must maintain a functioning alarm system. Any breach in security must be documented and reported in writing via facsimile, email communication, or letter to the board within fifteen (15) days of the breach.

2. All storage and warehouse locations will be considered facilities of a pharmacy pursuant to section 338.240, RSMo and shall be subject to inspection by the board as defined in section 338.150, RSMo.

3. Storage and warehouse locations used to store controlled substances or controlled substance records must comply with state and federal controlled substance laws, including but not limited to, 19 CSR 30-1.

4. No record less than two (2) years old may be stored offsite. Confidential pharmacy records stored at an offsite location must be retrievable within two (2) business days of a request from the board or its authorized representatives and must be maintained in compliance with applicable federal and state confidentiality/privacy laws and regulations.

5. No fee will be charged by the board for registering a storage or warehouse facility as defined in subsection (1)(I) of this rule under this subsection.

(J) Pharmacies that maintain storage sites or warehouse facilities for the storage of confidential pharmacy records at a separate address or premises from the main pharmacy that holds a pharmacy permit shall register those sites as storage facilities of the licensed pharmacy. Information required for proper registration of a storage facility shall include the address of the facility, hours of operation (if applicable), pharmacy permit numbers of the pharmacies that it services, and a statement that the facility is used for the sole purpose of storing records within its own pharmacy operations.

1. All storage and warehouse locations must maintain adequate security including an alarm system. Any breach in security must be documented and reported in writing via facsimile, email communication, or letter to the board within fifteen (15) days of the breach of confidentiality.

2. All storage and warehouse locations will be considered facilities of a pharmacy pursuant to section 338.240, RSMo and shall be subject to inspection by the board as defined in section 338.150, RSMo.

3. No fee will be charged by the board for registering a facility as defined in subsection (1)(J) of this rule.
4. All storage and warehouse locations must comply with 19 CSR 30-1.

5. No records less than two (2) years old may be stored off-site.

6. All storage and warehouse locations storing confidential pharmacy records must make records retrievable within two (2) business days when requested by the board or its representatives.

(K) All pharmacists will be required to have a photo of themselves not smaller than two inches by two inches (2” x 2”) in the upper right hand corner of the current renewal licenses. This photo and license renewal shall be conspicuously exposed in the pharmacy or drug store or place of business in which the pharmacist is employed as required by law.

(G) All pharmacists shall conspicuously post their current Missouri pharmacist license in the pharmacy or other place of business in which the pharmacist is employed. Licenses must be posted in a manner that is easily viewable by the public and include a photo that is not smaller than two by two inches (2” x 2”). All pharmacy technicians and intern pharmacists shall have an identification badge or similar identifying article that clearly identifies them as a pharmacy technician.

(L) Pharmacists regularly working as relief persons for more than one (1) store shall have in their possession proper identification of their pharmacy licensure (e.g., Board issued license, wallet card or official online verification from the Board).

(M) Pharmacy operations must be conducted at all times under the supervision of a properly designated pharmacist in charge. When a licensed pharmacist leaves the employment of a pharmacy where she has been pharmacist-in-charge, she immediately shall notify the executive director of the board of the termination of his/her services in the pharmacy. Likewise, the holder of the permit shall notify the executive director of the board of the termination of the services and give the name of the new licensed pharmacist-in-charge.

(N) Pharmacists are responsible to inform the executive director of the board in the case of changed address. Any mail or communications returned to the executive director’s office marked Unknown, Incorrect Address, and the like, will not be sent out a second time until the correct address is sent in.

(I) Pharmacists shall notify the Board of a change of personal or employment address no later than thirty (30) days of the address change. Notification must be electronically submitted in a form provided by the Board.
When a pharmacy permit holder knows or should have known, within the usual and customary standards of conduct governing the operation of a pharmacy as defined in Chapter 338, RSMo, that an employee, licensed or unlicensed, has violated the pharmacy laws or rules, the permit holder shall be subject to discipline under Chapter 338, RSMo.

All pharmacy technician registrations must be maintained in a central location. Alternatively, the pharmacy may maintain a technician list of all current pharmacy technicians that includes the technician’s name, registration number or a copy of a completed registration application that has been submitted to the board. The technician list must be immediately available on inspection or at the request of the Board or the Board’s authorized designee. The pharmacist-in-charge and the permit holder are jointly responsible for determining which individuals must be registered as a technician.

When required by section 338.013(10), RSMo, to report technician disciplinary action, the pharmacy must notify the board in writing or electronically within fifteen (15) days of the action. The notification must include:

1. The name and permit number of pharmacy;
2. Name of person making the notification;
3. Name of technician;
4. Technician registration number;
5. Date of action; and

Pharmacists must inform the executive director of the board of any change in their employment address. The notification of an employment change must be provided in writing to the board no later than fifteen (15) days following any effective change.

Every pharmacy shall designate as its primary means of record keeping either a manual system which provides for the consecutive numbering, sequential numbering or unique identification of hard copy prescriptions and complies with the provisions of section (3)(6) of this rule or an electronic system which complies with the provisions of 20 CSR 2220-2.080. The designated record system shall be used to record the pharmacy’s dispensing of all drugs, medicines and poisons. Records maintained by a pharmacy that contain patient medical or drug information must be confidentially maintained as required by state and federal law.
(3) A pharmacy using a record keeping system other than an electronic system meeting the
requirements of 20 CSR 2220-2.080 to record its dispensing of drugs, medicines and poisons
shall provide a method of recording all of the following information concerning the refill of any
prescription medication on the back or reverse side of every prescription order:

(A) The date the drug, medicine or poison was dispensed;
(B) The dispensing pharmacist’s initials; and
(C) The amount of drug, medicine or poison dispensed to the patient if different from the
amount on the face of the prescription order.

(4)(6) Each licensed pharmacy shall maintain at least three (3) separate files of prescriptions and
medication orders they shall be as follows:

(A) All prescriptions and medication orders for controlled drugs listed in Schedules I and II
shall be maintained in a separate prescription file;
(B) All prescriptions and medication orders for controlled drugs listed in Schedules III, IV and
V shall be maintained in a separate prescription file; and
(C) All other prescriptions and medication orders for noncontrolled drugs shall be maintained
in a separate prescription file(s).

(5)(7) Pharmacies shall establish and maintain inventories and records of all transactions
regarding the receipt and distribution or other disposition of legend drugs. Said records shall be
Records must be manually or electronically maintained for two (2) years and must be readily
retrievable upon if requested by the board or its representatives. At a minimum, distribution
records must include:

(A) Date of the transaction/distribution;
(B) Product name, strength and quantity;
(C) The names of the parties; and
(D) The receiving entity’s address and, if a controlled substance, controlled substance
registration number.
(6) Drugs and devices that are maintained as part of the pharmacy inventory or are being processed for dispensing or other distribution purposes must be physically separated at all times from articles, supplies or other drugs that are for employee personal use or that are outdated, distressed, misbranded or adulterated. An area separate from drug storage must be used to store quarantined, nonusable substances. Areas used for this type of drug storage must be clearly identified. Any prescription drugs that are present in a licensed pharmacy but are for the personal use of pharmacy personnel must be labeled in accordance with section 338.059, RSMo.

(8) Medication that is outdated, distressed, misbranded, adulterated or for personal employee use must be quarantined in a designated area that is physically separate from medication maintained for dispensing, distribution or other pharmacy use. The quarantine area must be clearly identified. Medication for the personal use of pharmacy staff or personnel must be labeled in accordance with section 338.059, RSMo, or as otherwise required by law.

(7)(9) All records required by Chapters 195 and 338, RSMo or divisions 20 CSR 2220 and 19 CSR 30 shall be available for inspection, photocopying, photographing or electronic duplication by a board of pharmacy representative. All records required by Chapter 330 or 20 CSR 2220 that do not have a specified retention time shall be kept for two years.


(9)(11) A home health or hospice agency licensed or certified according to Chapter 197, RSMo, or any licensed nurses of such agency, may possess drugs in the usual course of business of such agency without being licensed as a pharmacist or a pharmacy.

(A) The list of drugs that may be possessed by a home health or hospice agency without a license or permit, as defined in section (9), is as follows:

1. Injectable dosage forms of sodium chloride and water;
2. Irrigation dosage forms of sodium chloride and water that carry a federal prescription only restriction.
3. Injectable dosage forms of heparin and alteplase in concentrations that are indicated for
maintenance of venous access devices;
4. Injectable dosage forms of diphenhydramine and epinephrine;
5. Vaccines indicated for public health needs, such as influenza, pneumonia, hepatitis A and
hepatitis B; and
6. Tuberculin test material.

(B) The agency shall have a policy and procedure that addresses at least the following:
1. Specific drugs authorized to be possessed by the agency and the nurse;
2. Indications for use of the drugs possessed;
3. Receiving physicians’ orders for administration of the drugs orders from an authorized
prescriber for administration of drugs;
4. Leaving drugs with the patient for routine care procedures;
5. Conditions for storage and transport of the drugs by the agency and the nurse; and
6. Quantity of drugs possessed by the agency and the nurse.

(C) The nurse must have a physician’s authorization from an authorized prescriber, such as an
individual patient order, protocol or standing order, to administer the drugs.

(D) When the patient or the patient’s representative has been instructed, verbally and in
writing, in the performance of routine care procedures, up to a two (2)-week supply of sodium
chloride, water, and heparin may be left with the patient for these procedures. Drugs left with the
patient shall be labeled with instructions for use. A record shall be made of all drugs left with the
patient in the patient’s medical record. Drugs left with the patient may not be returned to the
agency.

(E) Drugs may be stored at the agency or transported by the nurse, and shall be stored or
transported at all times in accordance with the manufacturer’s storage requirements. Refrigerator
units used by the agency for storing drugs shall not be used for storing non-drug items.

(F) All drugs must be received from a licensed pharmacy or drug distributor. The quantity of
drugs possessed by an agency shall be limited to that necessary to meet the needs of the agency’s
patient population for two (2) weeks.
Class I: Consultant Pharmacies as defined in 20 CSR 2220-2.020(9)(1) and approved by the board to be located within a residence shall be required to address and comply with the following minimum standards of practice:

(A) Location Requirements—

1. The pharmacy must be located in a separate room that provides for a door with suitable lock;
2. Sufficient storage for securing confidential documents and any hardware used in accessing a central pharmacy by electronic connection must be provided;
3. Ceiling and walls must be constructed of plaster, dry wall, brick or other substantial substance that affords a design that makes the room separate and distinct from the remainder of the domicile. Drop down ceilings that allow access into the room are not allowed;
4. All locations must be inspected and have approval by the board prior to the initiation of services; and
5. Patients are not allowed in the pharmacy.

(B) Documentation—

1. Maintain a current policy and procedure manual that is attested by the signature and date of review of the pharmacist-in-charge to its accuracy. All pharmacists working at the pharmacy shall be required to sign the manual attesting to their review and understanding of all policies and procedures in force;
2. Maintain documentation that the permit holder has provided training to all personnel on all operations associated with the pharmacy;
3. The permit holder must complete an audit to ensure compliance with pharmacy policy and procedures and this regulation at a minimum of twice per year, through physical visits by representatives of the permit holder. Audit results must be maintained by the permit holder for a period of three (3) years; and
4. If the pharmacist is working under a contract for the permit holder, a copy of the contract shall be available during an inspection.
(C) Security—Records and Internet—

1. All electronic data processing systems must meet all applicable state and federal confidentiality laws and regulations;

2. Data processing systems must utilize sufficient security software;

3. Any breach in the security of the system must be documented and reported to the board of pharmacy within seven (7) days of the breach of confidentiality. Such documentation shall be available during an inspection.

(D) Licensure and Inspection—

1. Each location must maintain and display a current Class I permit. The permit holder for this permit must be the pharmacy the individual pharmacist is employed by or contracted with;

2. Routine inspections for in-state pharmacies shall be arranged ahead of time. Notification by the inspector to the permit holder will be provided a minimum of seventy-two (72) hours ahead of the scheduled inspection. The permit holder must arrange for a designated representative to be present that is not a resident of the location under inspection;

3. A pharmacy located outside the state must maintain a pharmacist-in-charge with a current and active pharmacist license with the state of Missouri;

4. The audits required in paragraph (10)(B)3 shall be available for review during the inspection; and

5. The pharmacy shall provide copies of inspections completed by the state in which they are located if such inspections are required within seven (7) business days of the inspection date.

(12) A Class-I pharmacy within a residence must be located in a separate room that provides for a door with a suitable lock. Patients shall not be allowed in a Class-I pharmacy located within a residence. Other than a Class-I pharmacy, no pharmacy permit shall be issued to any location that is located in a residence regardless of zoning.
Exemptions. At its discretion, the Board may grant an exemption to the facility requirements of this rule if such exemption is not contrary to law and the exemption will provide equal or greater protection of the public safety, health or welfare [or would not adversely impact the public health, safety or welfare]. Exemption requests must be submitted in writing and must identify the specific exemption requested, the grounds for exemption, the requested exemption length and proposed procedures or safeguards for protecting the public safety, health or welfare if the exemption is approved.


20 CSR 2220-2.010 Pharmacy Standards of Operation

PURPOSE: This rule defines terms used in the regulations of the State Board of Pharmacy and outlines the conditions necessary for the operation of a pharmacy.

(1) All licensed pharmacies by the Board shall comply with the rules of the Board and any applicable state and federal law governing pharmacy practice or medication handling, including, but not limited to, all applicable patient counseling, compounding, controlled substances and medication dispensing, disposal and distribution laws and regulations.

(2) Pharmacist-In-Charge. All pharmacies must be under the supervision of a properly designated pharmacist-in-charge who is responsible for managing the pharmacy and supervising pharmacy staff. The pharmacist-in-charge must hold a current and active Missouri pharmacist license or, for pharmacies located outside of Missouri, a current and active pharmacist license in the state where the pharmacy is located. The pharmacist-in-charge shall comply with 20 CSR 2220-2.090.

(A) A pharmacist must immediately notify the Board electronically or in writing on a form designated by the Board if he/she stops serving as the designated pharmacist-in-charge. The pharmacy may not continue pharmacy operations until a new pharmacist-in-charge is designated. A change of pharmacist-in-charge application must be submitted to the Board with the applicable fee within fifteen (15) calendar days after a new pharmacist-in-charge is designated.

(B) An inventory of controlled substances must be taken at or immediately prior to a pharmacist-in-charge change by both the outgoing pharmacist-in-charge and the incoming pharmacist-in-charge. Schedule II controlled substances must be physically counted. Schedule II – V drugs may be counted or estimated as allowed by federal law. The inventory must be documented in writing and must include the inventory date and the signature of the outgoing and incoming pharmacist-in-charge. If a joint inventory is not possible, the new or former pharmacist-in-charge and an official designee of the permit holder must complete, sign and date the inventory.
(3) Pharmacy Equipment and Reference Materials. No pharmacy shall be licensed under the provisions of this chapter unless it is equipped with proper pharmaceutical equipment and reference materials for the pharmacy services performed. Requirements for proper equipment and references may vary between pharmacies. Equipment must be maintained in good working order and capable of accurately and properly functioning to ensure patient safety and proper pharmaceutical activity. At a minimum, pharmacies must comply with the following:

(A) At least one (1) current edition of statutes and rules governing the pharmacy’s practice must be manually maintained or electronically available at the pharmacy, including but not limited to, Chapter 338, RSMo, Chapter 195, RSMo, 20 CSR 2220 and, if applicable, 19 CSR 30 governing the Missouri Bureau of Narcotics and Dangerous Drugs;

(B) Basic equipment recognized by the latest edition of the United States Pharmacopoeia (USP), the United States Pharmacopoeia/Drug Information (USP/DI) or Remington’s Pharmaceutical Sciences must be available for any procedures utilized in the dispensing, compounding or admixture of medication and medical-related devices.

(C) A suitable mechanical or electronic device or equipment must be maintained for numbering or uniquely identifying prescriptions and medication orders along with appropriate printing equipment for producing prescription/medication order labels.

(D) Reference materials may include any generally recognized or peer-reviewed pharmaceutical publication. At a minimum, the pharmacy must maintain or have electronically available the current or latest edition of a reference manual(s) or other resource(s) which includes all Federal Drug Administration (FDA)-approved drugs. Additionally, the pharmacy must maintain or have electronically available reference materials that include the following topics:

1. Pharmacology of drugs;
2. Dosages and clinical effects of drugs;
3. Patient information and counseling; and
4. If applicable, sterile or non-sterile compounding.

(E) If reference materials/resources are electronically maintained, the electronic material must be immediately accessible by pharmacy staff on inspection or when requested by the Board or a Board authorized designee; general internet access alone shall not be sufficient.
(A) Medication must be properly and accurately compounded, packaged, dispensed, distributed and labeled. Any excessive or suspicious prescriptions or medication orders must be verified prior to dispensing.

(B) The pharmacy must be maintained in a clean and sanitary condition at all times. Any procedures used in the dispensing, compounding and admixture of drugs or drug-related devices must be completed under clean and, when required, aseptic conditions.

1. Waste and hazardous materials must be handled and disposed of in compliance with all applicable state and federal law. Except as otherwise authorized by the Board, appropriate sewage disposal and a hot and cold water supply must be available within the pharmacy. The required water supply may not be located within a bathroom.

2. Appropriate housekeeping, sanitation, lighting, ventilation and humidity must be maintained in all areas where drugs are stored or dispensed. All shelves, aisles, walkways and medication storage areas must be kept free and clear of debris, dirt or filth. Trash must be disposed of in a timely manner. Medication shall not be stored on the floor or near trash areas.

3. The pharmacy must be free from insects, rodents, birds or vermin of any kind. Animals, except for service animals as defined by the Americans with Disabilities Act (ADA), are not allowed in pharmacies.

(C) The temperature of the facility where drugs are stored must be maintained thermostatically to ensure proper drug storage. Medication must be stored within temperature requirements as provided for by the manufacturer or the latest edition of the USP, or both. Adequate refrigeration must be available to ensure enough storage space for drugs requiring refrigeration or freezing. Appropriate manual, electromechanical or electronic temperature recording equipment and devices must be used to document proper temperature storage in drug storage areas, including refrigerators and freezers. Temperature recordings must be reviewed and documented each day the pharmacy is in operation. Alternatively, a continuous temperature monitoring system may be used if the system maintains ongoing documentation of temperature recordings that are reviewed daily. Proof of compliance with this subsection must be maintained in the pharmacy’s records.
(D) Food and beverage items that are not in their original, sealed manufacturing packaging must be stored separately from medication and medication-related devices. Open food or beverage items used in compounding or intended for patient use with medication may be stored in the same area as drugs and drug-related devices as long as the items are separated from other inventory and sanitary conditions are maintained at all times.

(E) Adequate security and locking mechanisms must be maintained in order to deter theft of drugs by personnel or the public and to prevent unauthorized access to the pharmacy. If the pharmacy is located in a facility that is accessible to the public and the pharmacy’s hours of operation are different from those of the remainder of the facility, ceilings and walls must be constructed of plaster, drywall or other substantial substance so that the pharmacy permit area is separate and distinct from the remainder of the facility. Drop down ceilings that would allow unauthorized access into the pharmacy are not allowed;

(F) Pharmacies which maintain storage sites or warehouse facilities for storing medication or confidential patient records at a separate address or premises from the main pharmacy that holds a pharmacy permit shall register those sites as storage facilities of the licensed pharmacy prior to use. Registration notification must be submitted in writing in a form approved by the Board and shall include the address of the facility, hours of operation (if applicable) and the pharmacy permit numbers of the pharmacies that it services.

1. Adequate security and storage conditions must be maintained at these facilities to guarantee the security, integrity and proper storage of all medication, drug-related devices and records. At a minimum, a registered storage and warehouse location must maintain a functioning alarm system. Any breach in security must be documented and reported in writing via facsimile, email communication, or letter to the board within fifteen (15) days of the breach.

2. All storage and warehouse locations will be considered facilities of a pharmacy pursuant to section 338.240, RSMo and shall be subject to inspection by the board as defined in section 338.150, RSMo.

3. Storage and warehouse locations used to store controlled substances or controlled substance records must comply with state and federal controlled substance laws, including, but not limited to, 19 CSR 30-1.

4. No record less than two (2) years old may be stored offsite. Confidential pharmacy records stored at an offsite location must be retrievable within two (2) business days of a request.
from the board or its authorized representatives and must be maintained in compliance with
applicable federal and state confidentiality/privacy laws and regulations.

5. No fee will be charged by the board for registering a storage or warehouse facility under
this subsection.

(G) All pharmacists shall conspicuously post their current Missouri pharmacist license in the
pharmacy or other place of business in which the pharmacist is employed. Licenses must be
posted in a manner that is easily viewable by the public and include a photo that is not smaller
than two by two inches (2” x 2”). All pharmacy technicians and intern pharmacists shall have
an identification badge or similar identifying article that clearly identifies them as a pharmacy
technician.

(H) Pharmacists regularly working for more than one (1) store must have in their possession or
posted proper identification of their pharmacy licensure (e.g., Board issued license, wallet card
or official online verification from the Board).

(I) Pharmacists shall notify the Board of a change of personal or employment address no later
than thirty (30) days of the address change. Notification must be electronically submitted in a
form provided by the Board.

(J) When a pharmacy permit holder knows or should have known, within the usual and
customary standards of conduct governing the operation of a pharmacy as defined in Chapter
338, RSMo, that an employee, licensed or unlicensed, has violated the pharmacy laws or rules,
the permit holder shall be subject to discipline under Chapter 338, RSMo.

(K) All pharmacy technician registrations must be maintained in a central location.
Alternatively, the pharmacy may maintain a technician list of all current pharmacy technicians
that includes the technician’s name, registration number or a copy of a completed registration
application that has been submitted to the board. The technician list must be immediately
available on inspection or at the request of the Board or the Board’s authorized designee. The
pharmacist-in-charge and the permit holder are jointly responsible for determining which
individuals must be registered as a technician.

(L) When required by section 338.013(10), RSMo, to report technician disciplinary action, the
pharmacy must notify the board in writing or electronically within fifteen (15) days of the action.
The notification must include:

1. The name and permit number of pharmacy;
2. Name of person making the notification;
3. Name of technician;
4. Technician registration number;
5. Date of action; and

(5) Every pharmacy shall designate as its primary means of record keeping either a manual system which provides for the sequential numbering or unique identification of hard copy prescriptions and complies with the provisions of section (6) of this rule or an electronic system which complies with the provisions of 20 CSR 2220-2 (80). The designated record system shall be used to record the pharmacy’s dispensing of all drugs, medicines and poisons. Records maintained by a pharmacy that contain patient medical or drug information must be confidentially maintained as required by state and federal law.

(6) Each licensed pharmacy shall maintain at least three (3) separate files of prescriptions and medication orders as follows:

(A) All prescriptions and medication orders for controlled drugs listed in Schedules I and II shall be maintained in a separate prescription file;
(B) All prescriptions and medication orders for controlled drugs listed in Schedules III, IV and V shall be maintained in a separate prescription file; and
(C) All other prescriptions and medication orders for noncontrolled drugs shall be maintained in a separate prescription file(s).

(7) Pharmacies shall establish and maintain inventories and records of all transactions regarding the receipt and distribution or other disposition of legend drugs. Records must be manually or electronically maintained for two (2) years and must be readily retrievable if requested by the board or its representatives. At a minimum, distribution records must include:

(A) Date of the transaction/distribution;
(B) Product name, strength and quantity;
(C) The names of the parties; and
(D) The receiving entity’s address and, if a controlled substance, controlled substance registration number.

Comment [GK2]: Should we keep consecutive?
(8) Medication that is outdated, distressed, misbranded, adulterated or for personal employee use
must be quarantined in a designated area that is physically separate from medication maintained
for dispensing, distribution or other pharmacy use. The quarantine area must be clearly
identified. Medication for the personal use of pharmacy staff or personnel must be labeled in
accordance with section 338.059, RSMo, or as otherwise required by law.

(9) All records required by Chapters 195 and 338, RSMo or divisions 20 CSR 2220 and 19 CSR
30 shall be available for inspection, photocopying, photographing or electronic duplication by a
board of pharmacy representative. All records required by Chapter 330 or 20 CSR 2220 that do
not have a specified retention time shall be kept for two years.

(10) Drug samples shall not be maintained in pharmacies, except as otherwise authorized by state
and federal law, including, but not limited to, 21 U.S.C. section 353 and the federal Prescription

(11) A home health or hospice agency licensed or certified according to Chapter 197, RSMo, or
any licensed nurses of such agency, may possess drugs in the usual course of business of such
agency without being licensed as a pharmacist or a pharmacy.

(A) The list of drugs that may be possessed by a home health or hospice agency without a
license or permit, as defined in section (9), is as follows:

1. Injectable dosage forms of sodium chloride and water;
2. Irrigation dosage forms of sodium chloride and water that carry a federal prescription only
restriction;
3. Injectable dosage forms of heparin and alteplase in concentrations that are indicated for
maintenance of venous access devices;
4. Injectable dosage forms of diphenhydramine and epinephrine;
5. Vaccines indicated for public health needs, such as influenza, pneumonia, hepatitis A and
hepatitis B; and
6. Tuberculin test material.

(B) The agency shall have a policy and procedure that addresses at least the following:

1. Specific drugs authorized to be possessed by the agency and the nurse;
2. Indications for use of the drugs possessed;
3. Receiving orders from an authorized prescriber for administration of drugs;
4. Leaving drugs with the patient for routine care procedures;
5. Conditions for storage and transport of the drugs by the agency and the nurse; and
6. Quantity of drugs possessed by the agency and the nurse.

(C) The nurse must have authorization from an authorized prescriber, such as an individual patient order, protocol or standing order, to administer the drugs.

(D) When the patient or the patient’s representative has been instructed, verbally and in writing, in the performance of routine care procedures, up to a two (2)-week supply of sodium chloride, water, and heparin may be left with the patient for these procedures. Drugs left with the patient shall be labeled with instructions for use. A record shall be made of all drugs left with the patient in the patient’s medical record. Drugs left with the patient may not be returned to the agency.

(E) Drugs may be stored at the agency or transported by the nurse, and shall be stored or transported at all times in accordance with the manufacturer’s storage requirements. Refrigerator units used by the agency for storing drugs shall not be used for storing non-drug items.

(F) All drugs must be received from a licensed pharmacy or drug distributor. The quantity of drugs possessed by an agency shall be limited to that necessary to meet the needs of the agency’s patient population for two (2) weeks.

(12) A Class-I pharmacy within a residence must be located in a separate room that provides for a door with a suitable lock. Patients shall not be allowed in a Class-I pharmacy located within a residence. Other than a Class-I pharmacy, no pharmacy permit shall be issued to any location, that is located in a residence regardless of zoning.

(13) Exemptions. At its discretion, the Board may grant an exemption to the facility requirements of this rule if such exemption is not contrary to law and the exemption will provide equal or greater protection of the public safety, health or welfare [or would not adversely impact the public health, safety or welfare]. Exemption requests must be submitted in writing and must identify the specific exemption requested, the grounds for exemption, the requested exemption length and proposed procedures or safeguards for protecting the public safety, health or welfare if the exemption is approved.

20 CSR 2220-2.012 Pharmacy Supervision

PURPOSE: This rule establishes supervision requirements for Missouri licensed pharmacies.

(1) All pharmacies must be under the supervision of a properly designated pharmacist-in-charge who is responsible for managing the pharmacy and supervising pharmacy staff. The pharmacist-in-charge must hold a current and active Missouri pharmacist license or, for pharmacies located outside of Missouri, a current and active pharmacist license in the state where the pharmacy is located. The pharmacist-in-charge shall comply with 20 CSR 2220-2.090.

(2) Except as otherwise provided by section (3) or by other applicable law, all pharmacies must comply with the following:

(A) No prescription or medication order may be prepared, compounded, dispensed or otherwise provided without a pharmacist on duty. The pharmacist must be present within the confines of the dispensing area or pharmacy permit area and must be able to render immediate assistance and to determine and correct any compounding, preparation or labeling error. A technician or intern pharmacist may accept written prescriptions or medication orders from a patient when a pharmacist is absent. Except as otherwise authorized by section (3) of this rule, the prescription or medication order may not be prepared, compounded, dispensed, filled or entered into the pharmacy’s prescription/medication order system by a technician of intern pharmacist without a pharmacist present and supervising.

(B) A sign must be prominently displayed on the pharmacy counter advising the public when no pharmacist is on duty. The sign must be displayed in an area where medication is dispensed to patients in a manner that is easily viewable by the public; sign lettering must be a minimum height of two inches (2”).

(C) Except as otherwise provided by law or regulation, a pharmacist must verify the accuracy of prescription or medication order data prior to dispensing on each original prescription or medication order. Additionally, a pharmacist must personally inspect and verify the accuracy of the contents of any prescribed/ordered medication or poison, and the label after it is affixed thereto, prior to dispensing each original and refill prescription.

(D) Pharmacies must maintain written standards setting out the responsibilities of pharmacy technicians as well as current and accurate policies and procedures for supervising...

Comment [GT1]: Do we want to require OOS pharmacies controlling ADS located in MO to have a MO licensed PIC for the OOS permit??

Further question, should individual OOS pharmacist operating a ADS in MO hold a MO pharmacist license? May be a question for the ADS rule.

As we proceed towards remote supervision of techs, these same question would apply to OOS pharmacists supervision techs working remotely in MO.

Comment [GK2]: Should the rule reference and define the dispensing/pharmacy permit area? For example:

“Pharmacy Permit Area” - Any area used to store, compound or dispense medication or to provide pharmacy services and that is officially approved by the Board as part of the pharmacy permit.

Comment [GT3]: Should we also include handling drug stock to this list?
technicians in compliance with 20 CSR 2220-2.700(1). Policies and procedures must be maintained manually or electronically available at the pharmacy during an inspection.

(3) Temporary Pharmacist Absence. A pharmacist may authorize a properly registered/licensed pharmacy technician or intern pharmacist to continue assisting in the practice of pharmacy during a temporary absence of the pharmacist subject to the following:

(A) The pharmacist must be physically present on the premises and available to answer questions and provide assistance in the event of an emergency. The pharmacist must ensure adequate security is maintained over medication inventory in his or her absence.

(B) An authorized temporary absence shall not exceed thirty (30) minutes [and shall be limited to XX times per day.]. If the temporary absence exceeds the required time limits, the no pharmacist on duty sign must be posted and no pharmacy technician or intern pharmacist activities may be performed except as otherwise authorized by subsection (2)(A) of this rule.

(C) If authorized by the pharmacist, final and completed prescriptions or medication orders may be dispensed during an authorized temporary absence if the prescription/medication order and the required label have been previously checked and verified by a pharmacist. If patient counseling is requested, the medication may not be dispensed until the pharmacist returns or, at the recipient’s option, a contact telephone number for the patient must be collected for the pharmacist to call on return. Medication may not be dispensed during an authorized temporary absence if a pharmacist prohibits dispensing or indicates counseling is mandatory.

(D) Notwithstanding any other provision of this section, no compounding may be performed nor may any verbal prescription or medication order be taken without a pharmacist present.
20 CSR 2220-2.025 Nonresident Pharmacies

PURPOSE: This rule establishes licensure guidelines for nonresident pharmacies.

(1) Nonresident pharmacies shall not ship, mail or deliver prescription drugs into Missouri without first obtaining a pharmacy license from the Missouri Board of Pharmacy. An exemption to licensure is allowed when a nonresident pharmacy provides a prescription drug in an emergency situation or supplies lawful refills to a patient from a prescription that was originally filled and delivered to a patient within the state in which the nonresident pharmacy is located or provides medications upon receipt of a prescription or physician order for patients in institutional settings and the nonresident pharmacy is not recognized as a primary provider.

(2) To obtain a license as a pharmacy, a nonresident pharmacy must comply with each of the following:

(A) Maintain a pharmacy license in good standing from the state in which the nonresident pharmacy is located;

(B) Submit an application as provided by the Missouri Board of Pharmacy for licensure in compliance with 20 CSR 2220-2.020(2) and (3);

(C) Pay all appropriate licensing fees;

(D) Submit a copy of the state pharmacy license from the state in which the nonresident pharmacy is located;

(E) Submit a copy of the state and federal controlled substance registrations from the state in which it is located, if controlled substances are to be shipped into Missouri;

(F) If the designated pharmacist-in-charge does not have a current and active Missouri pharmacist license issued by the Board, submit an official verification from the state board of pharmacy or equivalent state pharmacist licensing agency verifying that the designated pharmacist-in-charge holds a current and active pharmacist license in the state in which the nonresident pharmacy is located; and
(G) Submit a copy of the applicant’s most recent pharmacy inspection by the applicant’s resident state board of pharmacy or its equivalent state regulatory body. Except as otherwise authorized by the Board for good cause, the inspection must have occurred within the last eighteen (18) months for sterile compounding pharmacy applicants or within the last twenty-four (24) months for all other pharmacy applicants. If a state inspection is unavailable, an inspection by the Missouri Board of Pharmacy or from the National Association of State Boards of Pharmacy may be accepted.

(3) When requested to do so by the Missouri Board of Pharmacy, if requested by the Board, each nonresident pharmacy shall supply any inspection reports, warning notices, notice of deficiency reports or any other related reports from the state in which it is located concerning the operation of a nonresident pharmacy for review of compliance with state and federal drug laws.

(4) The Missouri Board of Pharmacy will extend reciprocal cooperation to any state that licenses and regulates nonresident pharmacies for the purpose of investigating complaints against pharmacies located in Missouri or the sharing of information and investigative reports, as long as the other state will extend the same reciprocal cooperation to the Missouri Board of Pharmacy.


20 CSR 2220-2.090 Pharmacist-in-Charge

PURPOSE: This amendment updates and further defines the duties of the pharmacist-in-charge.

(1) Except as otherwise authorized by law, each pharmacy shall designate a pharmacist-in-charge who is responsible for managing pharmacy compliance and supervising pharmacy staff.

(2) At a minimum, the pharmacist-in-charge shall ensure:

(A) The pharmacy complies with the rules of the Board and all applicable state and federal law governing pharmacy practice, including, but not limited to, all applicable patient counseling, compounding, controlled substances and medication dispensing, disposal and distribution laws and regulations;

(B) The pharmacy is supervised by a Missouri-licensed pharmacist at all times when prescriptions are being prepared, compounded, dispensed or sold and whenever technicians are assisting in the practice of pharmacy, except as otherwise provided by law;

(C) All Missouri and federal pharmacy licenses, permits or registrations are current and accurate, including, the pharmacy’s permit classification(s);

(D) All individuals are appropriately licensed or registered with the Board and all required licenses/registrations are conspicuously displayed;

(E) The pharmacy maintains all current technician registrations or a technician listing as required by 20 CSR 2220-2.010. The pharmacist-in-charge and the permit holder are jointly responsible for determining which individuals must be registered as a technician. Except as otherwise provided by law, any person other than a pharmacist, intern pharmacist or permit holder who has independent access to legend drug stock on a routine basis in a pharmacy must be registered with the board as a pharmacy technician;

(F) Required pharmacy policies and procedures are current and accurate and comply with all applicable state and federal law;

(G) Pharmacy staff are appropriately trained for the duties performed;

(H) The pharmacy is maintained in a clean and sanitary condition. Waste and hazardous materials must be handled and disposed of in compliance with all applicable federal and state law;
(I) No outdated, misbranded or adulterated drugs are dispensed or maintained within the active inventory of the pharmacy, including prescription and related nonprescription items;

(J) Medication is properly and accurately stored within the temperature requirements recommended by the manufacturer or the United States Pharmacopeia (USP), or both;

(K) Medication is properly and accurately compounded, packaged, dispensed, distributed and labeled. Any excessive or suspicious prescriptions or medication orders must be verified prior to dispensing;

(L) Pharmacy records are accurately and properly maintained in compliance with applicable state and federal law. If exempt narcotics are sold, complete records must be kept of all exempt narcotics in a bound exempt narcotic register. If poisons are sold, the pharmacy must maintain a poison register;

(M) All required pharmacy equipment is available and in good working order;

(N) Adequate security is maintained at all times to ensure the safety and integrity of drugs and medication records, including any drugs/records stored at an authorized offsite facility registered with the Board. Traffic in the pharmacy must be restricted to authorized persons so that proper control over drugs and confidential records can be maintained at all times;

(O) Changes in the pharmacy’s name, address location or permit classification(s) are timely and accurately submitted to the Board; and

(P) Notification of pharmacy technician and pharmacist disciplinary actions or voluntary resignations are timely and accurately submitted to the Board as required by law, including, but not limited to, section 338.013 and 383.133, RSMo.

(3) Change of Pharmacist-In-Charge. The following requirements shall apply when the Board designated pharmacist-in-charge changes:

(A) A pharmacist must immediately notify the Board electronically or in writing on a form designated by the Board if he/she stops serving as the designated pharmacist-in-charge. The pharmacy may not continue pharmacy operations until a new pharmacist-in-charge is designated. A change of pharmacist-in-charge application must be submitted by the pharmacy to the Board with the applicable fee within fifteen (15) calendar days after a new pharmacist-in-charge is designated.
(B) An inventory of controlled substances must be taken at or immediately prior to the pharmacist-in-charge change by both the outgoing pharmacist-in-charge and the incoming pharmacist-in-charge. The inventory must be documented in writing and must include the inventory date and the signature of the outgoing and incoming pharmacist-in-charge. If a joint inventory is not possible, the new pharmacist-in-charge and an official designee of the permit holder must complete, sign and date the inventory.

(5) Failure to comply with this section shall constitute grounds for discipline against the pharmacist-in-charge, as authorized by Missouri law. However, this rule shall not be construed to exempt a permit holder from responsibility for compliance with Chapter 338, RSMo, the rules of the Board or any applicable state or federal law.


EMERGENCY AMENDMENT

20 CSR 2220-2.650 Standards of Operation for a Class J: Shared Services Pharmacy

PURPOSE: The purpose of this rule is to establish minimum standards of operation for Class J: Shared Services Pharmacy, in compliance with House Bill 567 of the 91st General Assembly.

(1) Class J: Shared Services: Shared Service Pharmacy is defined as the processing by a pharmacy of a request from another pharmacy to fill or refill a prescription drug order, or that performs or assists in the performance of functions associated with the dispensing process, drug utilization review (DUR), claims adjudication, refill authorizations, and therapeutic interventions.

(A) A pharmacy may perform or outsource centralized prescription processing services provided the parties:

1. Have the same owner, or have a written contract outlining the services to be provided and the responsibilities and accountabilities of each party in fulfilling the terms of said contract in compliance with federal and state laws and regulations;

2. Maintain separate licenses for each location involved in providing shared services; and

3. Share a common electronic file to allow access to sufficient information necessary or required to fill or refill a prescription drug order. Either share a common database or allow access to each pharmacy’s electronic medication or prescription records. The access must provide real-time online access to the patient’s complete profile for the pharmacies involved.

(B) There must be record keeping systems between shared service pharmacies with real time on-line access to shared services by both pharmacies. Transfer of prescription information between two (2) pharmacies that are accessing the same real-time, on-line database pursuant to the operation of a shared service pharmacy operation shall not be considered a prescription transfer and, therefore, is not subject to the requirements of 4 CSR 220-2.120.

(C) The parties performing or contracting for centralized prescription processing services shall maintain a policy and procedures manual and documentation that implementation is occurring in a manner that shall be made available to the board for review upon request and that includes, but is not limited to, the following:

1. A description of how the parties will comply with federal and state laws and regulations;

2. The maintenance of appropriate records to identify the responsible pharmacist(s) in the dispensing and counseling processes;
3. The maintenance of a mechanism for tracking the prescription drug order during each step in the process;
4. The provision of adequate security to protect the confidentiality and integrity of patient information;
5. The maintenance of a quality assurance program for pharmacy services designed to objectively and systematically monitor and evaluate the quality and appropriateness of patient care, pursue opportunities to improve patient care and resolve identified problems.

(2) A Class J Shared services permit shall not be required if a completed and labeled prescription is delivered from a Missouri licensed pharmacy to another Missouri licensed pharmacy for administration by a pharmacist or other licensed health care professional to the patient on the same premises or physical location as the pharmacy.

(A) The exemption recognized in this subsection only applies if a completed and labeled prescription is delivered to the receiving pharmacy.

(B) If additional manipulation or compounding is required by the receiving pharmacy, receipt of a prescription or order is required and the receiving pharmacy must dispense the product as their own prescription/order. All prescription requirements, record keeping, compounding and labeling requirements must be met.

(C) The receiving pharmacy must maintain documentation of the medication received, the name and address of the pharmacy providing the medication, the date of receipt and the patient’s name.

(D) The receiving pharmacy is responsible for ensuring compliance with all applicable patient counseling requirements.

(E) For purposes of this rule, administration is defined as applying or introducing medication to the body of a patient, whether by injection, infusion, inhalation, ingestion or other means.

(F) Medication administered by a pharmacist must be performed in compliance with all applicable provisions of law.

(G) Notwithstanding any other provision of this rule, licensees shall comply with all applicable controlled substance laws and regulations, including, but not limited to, all applicable security and record keeping requirements.


PURPOSE: The purpose of this rule is to establish minimum standards of operation for Class J: Shared Services Pharmacy, in compliance with House Bill 567 of the 91st General Assembly.

(1) Class J: Shared Services: Shared Service Pharmacy is defined as the processing by a pharmacy of a request from another pharmacy to fill or refill a prescription drug order, or that performs or assists in the performance of functions associated with the dispensing process, drug utilization review (DUR), claims adjudication, refill authorizations, and therapeutic interventions. A Class J Shared Services permit is required if two or more pharmacies are engaged in, or have an arrangement to provide, functions related to the practice of pharmacy for or on behalf of the other pharmacy. These functions may include, but are not limited to: prescription/order receipt, prescription/order clarification or modification, obtaining prescriber authorization, data entry, compounding, dispensing, pharmacist verification, patient counseling, patient profile maintenance, medication therapy services, medication administration, drug utilization review (DUR) and obtaining refill authorization. Both pharmacies participating in the shared services arrangement must have a Class J permit.

(A) A pharmacy may perform or outsource centralized prescription processing services provided the parties:

1. Have the same owner, or have a written contract outlining the services to be provided and the responsibilities and accountabilities of each party in fulfilling the terms of said contract in compliance with federal and state laws and regulations;

2. Maintain separate licenses a separate Class-J classification for each location involved in providing shared services; and

3. Share a common electronic file to allow access to sufficient information necessary or required to fill or refill a prescription drug order. Either share a common database or allow access to each pharmacy's electronic medication or prescription records. The access must provide real-time online access to the patient's complete profile for the pharmacies involved.

(B) There must be record keeping systems between shared service pharmacies with real time on-line access to shared services by both pharmacies. Transfer of prescription information between two (2) pharmacies that are accessing the same real time, on-line database pursuant to the operation of a shared service pharmacy operation shall not be considered a prescription transfer and, therefore, is not subject to the requirements of 4 CSR 220-2.120.
(C) The parties performing or contracting for centralized prescription processing services shall maintain a policy and procedures manual and documentation that implementation is occurring in a manner that shall be made available to the board for review upon request and that includes, but is not limited to, the following:

1. A description of how the parties will comply with federal and state laws and regulations;
2. The maintenance of appropriate records to identify the responsible pharmacist(s) in the dispensing and counseling processes;
3. The maintenance of a mechanism for tracking the prescription drug order during each step in the process;
4. The provision of adequate security to protect the confidentiality and integrity of patient information;
5. The maintenance of a quality assurance program for pharmacy services designed to objectively and systematically monitor and evaluate the quality and appropriateness of patient care, pursue opportunities to improve patient care and resolve identified problems.

(B) Class-J pharmacies operating in compliance with this section are exempt from the requirements of 20 CSR 2220-2.120 and 20 CSR 2220-6.030(4) when transferring prescription information between themselves. A Class-J permit is not required to transfer an individual prescription as authorized by 20 CSR 2220-2.120 pursuant to a request by the patient or the patient's authorized designee.

(C) The parties performing Class-J shared services shall maintain a detailed written description of authorized shared services that includes the name, address and permit number(s) of all pharmacies involved. The parties must maintain a current and accurate policy and procedure manual that includes, but is not limited to, the following:

1. Policies and procedures that identify the duties of each pharmacy, including any functions identified in section (1);
2. A mechanism for tracking the prescription or medication order during each step in the process;
3. Security provisions for protecting the confidentiality and integrity of patient information;
4. Policies and procedures to ensure the safe and appropriate delivery of prescription drugs in compliance with 20 CSR 2200-2.013; and
6. A designation of the pharmacy responsible for offering patient counseling as required by 20 CSR 2220-2.190 and federal law. For purposes of § 338.059, RSM, the name and address of the pharmacy responsible for offering patient counseling must be listed on the prescription label.

(D) Each pharmacy involved in a Class-J arrangement must maintain a quality assurance program that is designed to objectively and systematically monitor and evaluate the quality and appropriateness of pharmacy services and resolve identified problems.

(E) Compounding may only be performed pursuant to a Class-J pharmacy arrangement pursuant to a patient-specific prescription or in anticipation of a patient-specific prescription as authorized by 20 CSR 2220-2.200 and the rules of the Board.

(F) A Class-J permit is not required for pharmacists performing non-dispensing activities authorized by 20 CSR 2220-6.050 outside of a licensed pharmacy.
(2) A Class J Shared services permit shall not be required if a completed and labeled prescription is delivered from a Missouri licensed pharmacy to another Missouri licensed pharmacy for administration by a pharmacist or other licensed health care professional to the patient on the same premises or physical location as the pharmacy.

   (A) The exemption recognized in this subsection only applies if a completed and labeled prescription is delivered to the receiving pharmacy.

   (B) If additional manipulation or compounding is required by the receiving pharmacy, receipt of a prescription or order is required and the receiving product must dispense the product as their own prescription/order. All prescription requirements, record keeping, compounding and labeling requirements must be met.

   (C) The receiving pharmacy must maintain documentation of the medication received, the name and address of the pharmacy providing the medication, the date of receipt and the patient’s name.

   (D) The receiving pharmacy is responsible for ensuring compliance with all applicable patient counseling requirements.

   (E) For purposes of this rule, administration is defined as applying or introducing medication to the body of a patient, whether by injection, infusion, inhalation, ingestion or other means.

   (F) Medication administered by a pharmacist must be performed in compliance with all applicable provisions of law.

   (G) Notwithstanding any other provision of this rule, licensees shall comply with all applicable controlled substance laws and regulations, including, but not limited to, all applicable security and record keeping requirements.

(3) A pharmacy participating in Class-J shared services with a pharmacy that is not under common ownership must notify patients that his/her prescription or medication order was filled or compounded by another pharmacy.

(4) All records required by this rule, including, all policy and procedure manuals, contracts, quality assurance documentation, or other agreements must be maintained for two (2) years and must be made available to the Board or its representative upon request.

20 CSR 2220-6.040 Administration by Medical Prescription Order

PURPOSE: This rule establishes procedures for pharmacists to administer drugs and devices pursuant to a medical prescription order.

(1) A pharmacist who complies with the provisions of this rule may administer drugs and devices pursuant to a medical prescription order, including, vaccines.

(2) Except as otherwise provided by law, The pharmacist may not delegate the medication administration to another person, except to an intern pharmacist intern who has met the qualifications under subsections (3)(B), (C), and (E)(4)(B) – (D) and is working under the direct supervision of a pharmacist qualified to administer drugs pursuant to a by medical prescription order.

(3) Pharmacist Qualifications. A pharmacist who is administering drugs pursuant to a medical prescription order must file a Notification of Intent to administer drugs by medical prescription order with the Board. To file a Notification of Intent, a pharmacist must—

(A) Hold a current, unrestricted license to practice pharmacy in this state Missouri pharmacist license;

(B) Hold a current healthcare provider level cardiopulmonary resuscitation (CPR) certification or Basic Life Support certification issued by the American Heart Association, or the American Red Cross or an equivalent organization. The certificate program must have included a live training component;

(C) Have successfully completed a certificate program in the administration of drugs medication administration and emergency procedures accredited by the Accreditation Council for Pharmacy Education (ACPE) or provided by a governmental entity or a healthcare professional organization or educational institution approved by the State Board of Pharmacy. The certificate program must cover all routes of administration the pharmacist utilizes. To obtain Board approval, the training program must be taught by qualified instructors/a licensed healthcare professional and provide instruction in:

1. Administration techniques which must include hands-on training in routes of administration;
2. Drug storage and handling;
3. Informed consent requirements;
4. Pre- and post-administration assessment and counseling;
5. Biohazard waste disposal, and;
6. Identifying and treating adverse reactions, including anaphylactic reactions and needle sticks.

(D) Pharmacists shall maintain proof of compliance with the requirements of this section for a minimum of two (2) years.
(D) Complete a minimum of two (2) hours of continuing education per calendar year related to administration of drugs. A pharmacist may use the continuing education hours required in this subsection as part of the total continuing education hours required for pharmacist license renewal;

(E) Maintain documentation of the above requirements; and

(F) On a yearly basis prior to administering drugs, notify the State Board of Pharmacy of their qualifications to do so. This notification shall include the types of drugs being administered, and a statement that the pharmacist meets the requirements of subsections (A), (B), (C), and (D) of this section.

(E) If a pharmacist wishes to administer drugs by a route of administration not included in the original certification program, the pharmacist must first be trained in the techniques of that route of administration by a licensed health care practitioner who is authorized to administer medication. Documentation of the required training and training date(s) must be maintained at the pharmacy and available to the Board on request.

(4) General Requirements.

(A) Except as otherwise authorized by law, A pharmacist shall administer drugs vaccines in accordance with current treatment guidelines established by the Centers for Disease Control and Prevention (CDC) or in accordance with manufacturer's guidelines.

(B) A pharmacist shall comply with all state and federal laws and regulations pertaining to Vaccine Information Statements and informed consent requirements.

(C) A pharmacist shall have a current and accurate written policy and procedure manual covering all aspects of the administration of administering drugs by medical prescription order, including the disposal of used and contaminated supplies and appropriate handling of acute adverse events. The manual shall be reviewed annually and be available for inspection by the State Board of Pharmacy or authorized representative. At a minimum, the required policies and procedures must include provisions governing:

1. Drug administration procedures, including, authorized routes of administration,

2. Drug storage;

3. Pre- and post-administration assessment and counseling, including, providing vaccine information statements when applicable;

4. Biohazard waste disposal and disposal of used/contaminated supplies;

5. Identifying and handling acute adverse events or immunization reactions, including, anaphylactic reactions; and

6. Recordkeeping requirements, including, providing notification to the prescriber and primary health care providers, as required by law.

(D) Drugs must be stored within the manufacturer's labeled requirements at all times, including when performing administrations outside of a pharmacy. Vaccines shall be stored in accordance with CDC guidelines at all times.
(E) Pharmacists shall request that a patient remain in the pharmacy a safe amount of time after administering a vaccine to observe any adverse reactions, as required by section 338.010, RSMo.

(5) Requirements of Medical Prescription Order. At a minimum, the medical prescription order from a licensed prescriber must contain at a minimum the following:

(A) The name of the licensed prescriber issuing or authorizing the order;
(B) The name of the patient to receive the drug;
(C) The name of the drug and dose to be administered;
(D) The route of administration;
(E) The date of the original order; and
(F) The date or schedule, if any, of each subsequent administration; and
(G) A statement that the drug is to be administered by a pharmacist.

(6) Record Keeping.

(A) A pharmacist who administering medication pursuant to a medical prescription order shall must maintain the following records regarding each administration. These records must be separate from the prescription files of a pharmacy:

1. The name, address, and date of birth of the patient;
2. The date, route, and anatomic site of the administration;
3. The medication name, and dose, manufacturer, lot number, and expiration date of the drug. For vaccines and biologics, the manufacturer, expiration date, and lot number must also be documented and recorded;
4. For vaccines, the name and address of the patient’s primary health care provider, as identified by the patient. The pharmacist shall document in the patient’s immunization record if a primary health care provider is not provided;
5. The name or identifiable initial of the administering pharmacist. If administered by an intern pharmacist, the identity of the intern and supervising pharmacist; and
6. The nature of an adverse reaction and who was notified, if applicable; and
7. Documentation of a patient’s refusal or failure to remain in or return to the pharmacy after administering a vaccine to observe any adverse reactions.
(B) **Except for proof of compliance with section (3) of this rule,** all records required by this regulation shall be kept by the pharmacist and be available for two (2) years from the date of such record for inspecting and copying by the State Board of Pharmacy and/or its authorized representatives. Records must be kept by the pharmacist at the pharmacy where the prescription order is maintained or may be securely stored offsite at a location designated by the pharmacist. Records maintained at a pharmacy must be produced immediately or within two (2) hours of a request from the Board or the Board’s authorized designee. Records not maintained at a pharmacy must be produced within three (3) business days of a Board request.

(7) **Notification Requirements.**

(A) A pharmacist administering drugs pursuant to a medical prescription order shall notify the prescriber within seventy-two (72) hours patient’s primary health care provider, if provided by the patient, within fourteen (14) days after administration of the following:

1. The identity of the patient;
2. The identity of the drug/vaccine administered;
3. The route of administration;
4. The anatomic site of the administration;
5. The dose administered; and
6. The date of administration.

(B) In the event of any adverse event or reaction experienced by the patient following medication administration, the pharmacist shall notify the prescriber within twenty-four (24) hours after learning of the adverse event or reaction. Notification shall be mandatory and cannot be waived.

(C) A pharmacist administering drugs pursuant to a medical prescription order shall report the administration to all entities as required by state or federal law. Pharmacist administered vaccines must also be reported to the Missouri immunization registry operated by the Missouri Department of Health and Senior Services (ShowMeVax), or its successor.

(D) **Except as otherwise required to comply with (7)(C), notifications required by this section shall be made electronically or in writing.** Alternatively, notifications may be made via a common electronic medication record that is accessible to and shared by both the physician and pharmacist. Documentation of the required notifications, including the notification date, must be kept at the pharmacy or other authorized location where the prescription order is maintained.

(8) **Notification of Intent Refiling.** To continue administration, a Notification of Intent to administer drugs by medical prescription order must be refiled with the Board biennially along with the pharmacist's Missouri pharmacist license. To refile, a pharmacist must:
(A) Hold a current Basic Life Support certification issued by the American Heart Association or the American Red Cross or an equivalent organization. The certification program must have included a live training component; and

(B) Have successfully completed four (4) hours of continuing education (0.4 CEU) related to administering drugs within the applicable pharmacist biennial renewal period/between November 1st and October 31st of the immediately preceding even numbered years. The required continuing education (CE) shall be governed by 20 CSR 2220-7.080 and may be used to satisfy the pharmacist’s biennial pharmacist renewal CE requirements. The initial training program required by subsection (3) of this rule may be used to satisfy the CE requirements of this subsection if the training program was completed within the applicable pharmacist biennial renewal cycle.


20 CSR 2220-6.040 Administration by Medical Prescription Order

PURPOSE: This rule establishes procedures for pharmacists to administer medication pursuant to a medical prescription order.

1. A pharmacist who complies with the provisions of this rule may administer drugs and devices pursuant to a medical prescription order, including, vaccines.

2. Except as otherwise provided by law, a pharmacist may not delegate medication administration to another person, except to an intern pharmacist who has met the qualifications of subsections (4)(B) – (D) and is working under the direct supervision of a pharmacist qualified to administer drugs by medical prescription order.

3. Pharmacist Qualifications. A pharmacist who is administering drugs pursuant to a medical prescription order must first file a Notification of Intent to administer drugs by medical prescription order with the Board. To file a Notification of Intent, a pharmacist must—
   (A) Hold a current Missouri pharmacist license;
   (B) Hold a current healthcare provider level cardiopulmonary resuscitation (CPR) certification or Basic Life Support certification issued by the American Heart Association, the American Red Cross or an equivalent organization. The certificate program must have included a live training component;
   (C) Have successfully completed a certificate program in medication administration and emergency procedures accredited by the Accreditation Council for Pharmacy Education (ACPE) or provided by a governmental entity or a healthcare professional organization or educational institution approved by the Board. To obtain Board approval, the training program must [be taught by qualified instructors/a licensed healthcare professional and] provide instruction in:
      1. Administration techniques which must include hands-on training in routes of administration;
      2. Drug storage and handling;
      3. Informed consent requirements;
      4. Pre- and post-administration assessment and counseling;
      5. Biohazard waste disposal, and;
      6. Identifying and treating adverse reactions, including, anaphylactic reactions and needle sticks.
   (D) Pharmacists shall maintain proof of compliance with the requirements of this section for a minimum of two (2) years.
(E) If a pharmacist wishes to administer drugs by a route of administration not included in the original certification program, the pharmacist must first be trained in the techniques of that route of administration by a licensed health care practitioner who is authorized to administer medication. Documentation of the required training and training date(s) must be maintained at the pharmacy and available to the Board on request.

(4) General Requirements.
   (A) Except as otherwise authorized by law, a pharmacist shall administer vaccines in accordance with current treatment guidelines established by the Centers for Disease Control and Prevention (CDC).
   (B) A pharmacist shall comply with all state and federal laws and regulations pertaining to Vaccine Information Statements and informed consent requirements.
   (C) A pharmacist shall have a current and accurate written policy and procedure manual covering all aspects of administering drugs by medical prescription order. At a minimum, the required policies and procedures must include provisions governing:
      1. Drug administration procedures, including, authorized routes of administration,
      2. Drug storage;
      3. Pre- and post-administration assessment and counseling, including, providing vaccine information statements when applicable;
      4. Biohazard waste disposal and disposal of used/contaminated supplies;
      5. Identifying and handling acute adverse events or immunization reactions, including, anaphylactic reactions; and
      6. Recordkeeping requirements, including, providing notification to the prescriber and primary health care providers, as required by law.
   (D) Drugs must be stored within the manufacturer’s labeled requirements at all times, including when performing administrations outside of a pharmacy. Vaccines shall be stored in accordance with CDC guidelines at all times.
   (E) Pharmacists shall request that a patient remain in the pharmacy a safe amount of time after administering a vaccine to observe any adverse reactions, as required by section 338.010, RSMo.

(5) Requirements of Medical Prescription Order. At a minimum, the medical prescription order from a licensed prescriber must contain the following:
   (A) The name of the licensed prescriber issuing or authorizing the order;
   (B) The name of the patient to receive the drug;
   (C) The name of the drug and dose to be administered;
   (D) The route of administration;
   (E) The date of the original order; and
   (F) The date or schedule, if any, of each subsequent administration.

(6) Record Keeping.
(A) A pharmacist who administering medication pursuant to a medical prescription order must maintain the following records separate from the prescription files of a pharmacy:

1. The name, address, and date of birth of the patient;
2. The date, route, and anatomic site of the administration;
3. The medication name and dose. For vaccines and biologics, the manufacturer, expiration date and lot number must also be documented and recorded;
4. For vaccines, the name and address of the patient's primary health care provider, as identified by the patient. The pharmacist shall document in the patient's immunization record if a primary health care provider is not provided;
5. The identity of the administering pharmacist. If administered by an intern pharmacist, the identity of the intern and supervising pharmacist;
6. The nature of an adverse reaction and who was notified, if applicable; and
7. Documentation of a patient's refusal or failure to remain in or return to the pharmacy after administering a vaccine to observe any adverse reactions.

(B) Except for proof of compliance with section (3) of this rule, all records required by this rule must be kept by the pharmacist for two (2) years from the date of such record. Records must be kept by the pharmacist at the pharmacy where the prescription order is maintained or may be securely stored offsite at a location designated by the pharmacist. Records maintained at a pharmacy must be produced immediately or within two (2) hours of a request from the Board or the Board’s authorized designee. Records not maintained at a pharmacy must be produced within three (3) business days of a Board request.

(7) Notification Requirements.

(A) A pharmacist administering a vaccine pursuant to a medical prescription order shall notify the patient's primary health care provider, if provided by the patient, within fourteen (14) days after administration of the following:

1. The identity of the patient;
2. The vaccine administered;
3. The route of administration;
4. The anatomic site of the administration;
5. The dose administered; and
6. The date of administration.

(B) In the event of any adverse event or reaction experienced by the patient following medication administration, the pharmacist shall notify the prescriber within twenty-four (24) hours after learning of the adverse event or reaction. Notification shall be mandatory and cannot be waived.
(C) A pharmacist administering drugs pursuant to a medical prescription order must report the administration to all entities as required by state or federal law. Pharmacist administered vaccines must also be reported to the Missouri immunization registry operated by the Missouri Department of Health and Senior Services (ShowMeVax), or its successor.

(D) Except as otherwise required by section (7)(C), notifications required by this section must be made electronically or in writing. Alternatively, notifications may be made via a common electronic medication record that is accessible to and shared by both the physician and pharmacist. Documentation of the required notifications, including the notification date, must be kept at the pharmacy or other authorized location where the prescription order is maintained.

(8) Notification of Intent Refiling. To continue administration, a Notification of Intent to administer drugs by medical prescription order must be refiled with the Board biennially along with the pharmacist’s Missouri pharmacist license. To refile, a pharmacist must:

(A) Hold a current Basic Life Support certification issued by the American Heart Association or the American Red Cross or an equivalent organization. The certification program must have included a live training component; and

(B) Have successfully completed four (4) hours of continuing education (0.4 CEU) related to administering drugs within the applicable pharmacist biennial renewal period/between November 1st and October 31st of the immediately preceding even numbered years. The required continuing education (CE) shall be governed by 20 CSR 2220-7.080 and may be used to satisfy the pharmacist’s biennial pharmacist renewal CE requirements. The initial training program required by subsection (3) of this rule may be used to satisfy the CE requirements of this subsection if the training program was completed within the applicable pharmacist biennial renewal cycle.


PURPOSE: This rule establishes the procedures for pharmacists to administer vaccines per written protocol with a physician.

(1) A pharmacist may administer vaccines authorized by Chapter 338, RSMo, pursuant to a written protocol authorized by a physician licensed pursuant to Chapter 334, RSMo, who is actively engaged in the practice of medicine. Unless otherwise restricted by the Board or the governing protocol, pharmacists authorized to immunize pursuant to this rule may administer immunizations at any Missouri licensed pharmacy. Immunizations may be provided at a non-pharmacy location if authorized by the governing protocol.

(A) A pharmacist shall administer vaccines in accordance with current treatment guidelines established by the Centers for Disease Control (CDC) and in accordance with manufacturer’s guidelines, provided that—CDC guidelines shall control in the event of a conflict with manufacturer guidelines. Vaccines shall not be administered to persons under twelve (12) years of age old unless otherwise authorized by law.

(B) A pharmacist shall comply with all state and federal laws and regulations pertaining to Vaccine Information Statements and informed consent requirements.

(C) Vaccines must be stored at all times in accordance with CDC guidelines/recommendations and within the manufacturer’s labeled requirements, including, when administering outside of a pharmacy.

(D) A pharmacist may not delegate the administration of vaccines to another person, except to a pharmacist intern who has met the qualifications under subsections (4)(B) and (C) and is working under the direct supervision of a pharmacist qualified to administer vaccines. Intern pharmacists must maintain proof of compliance with subsections (4)(B) and (C) for a minimum of two (2) years.

(2) A pharmacist may not delegate the administration of vaccines to another person, except to a pharmacist intern who has met the qualifications under subsections (1)(B), (C), and (D) and is working under the direct supervision of a pharmacist qualified to administer vaccines.

(2) The authorizing physician is responsible for the oversight of, and accepts responsibility for, the vaccines administered by the pharmacist.
(4) Pharmacist Qualifications. A pharmacist who is administering a vaccine authorized by Chapter 338, RSMo, must:

(A) Hold a current, unrestricted license to practice pharmacy in this state;

(B) Hold a current cardiopulmonary resuscitation (CPR) certification issued by the American Heart Association or the American Red Cross or equivalent;

(C) Successfully complete a certificate program in the administration of vaccines accredited by the Accreditation Council for Pharmacy Education (ACPE) or a similar health authority or professional body approved by the State Board of Pharmacy;

(D) Maintain documentation of the above certifications;

(E) Complete a minimum of two (2) hours (0.2 CEU) of continuing education as defined per calendar year related to administration of vaccines. A pharmacist may use the continuing education hours required in this subsection as part of the total continuing education hours required for pharmacist license renewal;

(F) Provide documentation of subsections (A), (B), (C), and (E) of this section to the authorizing physician(s) prior to entering into a protocol or administering vaccines; and

(G) On a yearly basis prior to administering vaccines, establish a new protocol with the authorizing physician and notify the State Board of Pharmacy of their qualifications to do so. This notification shall include the types of drugs being administered and a statement that the pharmacist meets the requirements of subsections (A), (B), (C), (E), and (F) of this section.

(3) Pharmacist Qualifications. A pharmacist who is administering a vaccine authorized by Chapter 338, RSMo, by protocol must:

(A) Hold a current Missouri pharmacist license;

(B) Hold a current healthcare provider level cardiopulmonary resuscitation (CPR) or basic life support (BLS) certification issued by the American Heart Association or the American Red Cross or an equivalent organization. The qualifying BLS or CPR certification program must have included a live/in-person CPR skills assessment;
(C) Have successfully completed a certificate program in administering vaccines accredited by the Accreditation Council for Pharmacy Education (ACPE) or a similar health authority or professional body approved by the State Board of Pharmacy. To be approved, non-ACPE programs must include a live/in-person training component and include instruction in:

1. Current CDC guidelines and recommendations for vaccines authorized by Chapter 338, RSMo, including recommended immunization schedules;
2. Basic immunology and vaccine protection;
3. Physiology and techniques for vaccine administration which must include hands-on training in common routes of vaccine administration, including intramuscular, intradermal, subcutaneous and nasal routes of administration;
4. Pre- and post- vaccine screening or assessment; and
5. Identifying and treating adverse immunization reactions;

(D) Have filed a Notification of Intent with the Board of Pharmacy attesting that the pharmacist has complied with sections (3)(A) to (3)(C) of this rule. Notifications of Intent must be filed on the Board’s website or on a form approved by the Board; and

(E) Have a current written protocol with an authorizing physician that complies with this rule.

(5) Administration by Written Protocol with a Missouri Licensed Physician.

(A) A pharmacist may enter into a written protocol with a physician for the administration of vaccines authorized by Chapter 338, RSMo, provided that a pharmacist shall be prohibited from administering vaccines to patients under twelve (12) years of age. The physician must be no further than fifty (50) miles by road, using the most direct route available, from the pharmacist who is administering the vaccine. The written protocol may be valid for a time period not to exceed one (1) year. The protocol must include the following:

1. The identity of the participating pharmacist and physician, including signatures;
2. Time period of the protocol;
3. The identification of the vaccines which may be administered;
4. The identity of the patient or groups of patients to receive the authorized vaccine(s);
5. The identity of the authorized routes and anatomic sites of administration allowed;
6. A provision to create a prescription for each administration under the authorizing physician’s name;

7. A provision establishing a course of action the pharmacist shall follow to address emergency situations including, but not limited to, adverse reactions, anaphylactic reactions, and accidental needle-sticks;

8. A provision establishing a length of time the pharmacist shall observe an individual for adverse events following an injection;

9. A provision establishing the disposal of used and contaminated supplies;

10. The street addresses of the pharmacy or other locations at which the pharmacist may administer the authorized vaccine;

11. Record-keeping requirements and procedures for notification of administration; and

12. A provision that allows for termination of the protocol at the request of any party to it at any time.

(B) The protocol, and any subsequent amendments or alterations, shall be signed and dated by the pharmacist and authorizing physician prior to its implementation, signifying that both are aware of its content and agree to follow the terms of the protocol. The authorizing physician and pharmacist shall each maintain a copy of the protocol from the beginning of implementation to a minimum of eight (8) years after termination of the protocol.

(4) Protocol Requirements.

(A) Pharmacists administering vaccines pursuant to this rule must enter into a written protocol with a Missouri licensed physician for the administration of vaccines as authorized by Chapter 338, RSMo. The written protocol may be valid for a time period not to exceed one (1) year and must be renewed annually. The protocol must include the following:

1. The identity of the participating pharmacist and physician, including signatures;

2. Time period of the protocol;

3. The identification of the vaccines which may be administered;

4. The identity of the patient or groups of patients to receive the authorized vaccine(s);
5. The identity of the authorized routes and anatomic sites of administration allowed;

6. A provision to create a prescription for each administration under the authorizing physician’s name;

7. A provision establishing a course of action the pharmacist shall follow to address emergency situations including, but not limited to, adverse reactions, anaphylactic reactions, and accidental needle sticks;

8. A provision establishing the length of time the pharmacist shall observe an individual for adverse events following an injection;

9. A provision establishing the disposal of used and contaminated supplies;

10. The street addresses of any non-pharmacy locations at which the pharmacist may administer the authorized vaccine;

11. Record-keeping requirements and any required notification procedures; and

12. A provision that allows for termination of the protocol at the request of any party to it at any time.

(B) The protocol, and any subsequent amendments or alterations, shall be manually or electronically signed and dated by the pharmacist and authorizing physician prior to its implementation, signifying that both are aware of its content and agree to follow the terms of the protocol. The authorizing physician and pharmacist shall each maintain a copy of the protocol from the beginning of implementation to a minimum of eight (8) years after termination of the protocol.

(C) Additional pharmacists or immunization locations may be added to an existing protocol, if the amendment is signed and dated by the authorizing physician(s) and, if applicable, any newly added pharmacist(s). Other participating pharmacists shall not be required to re-sign the protocol unless other protocol terms or provisions are changed.

(5) Record Keeping

(A) A pharmacist administering vaccines pursuant to this rule shall maintain a record of each administration which shall include:

1. The name, address, and date of birth of the patient;

2. The date, route, and anatomic site of the administration;

3. The name, dose, manufacturer, lot number, and expiration date of the vaccine;
4. The name and address of the patient’s primary health care provider, as identified by the patient;

5. The name or identifiable initials of the administering pharmacist; The identity of the administering pharmacist or intern pharmacist; and

6. The nature of an adverse reaction and who was notified, if applicable.

7. Documentation that pharmacist interns administering vaccines under the pharmacist’s supervision have complied with section (2) of this rule; and

8. Documentation that any notifications required by this rule have been sent.

(B) If the vaccine was administered on behalf of a pharmacy, the pharmacist shall ensure the records required by subsection (65)(A) of this rule are promptly delivered to the pharmacy.

(C) Within seventy-two hours (72) hours after administration of a vaccine, the administering pharmacist shall obtain a prescription from the authorizing physician for the drug dispensed or shall create a prescription, as authorized by protocol documenting the dispensing of the drug. Notwithstanding any other provision of this rule, prescription records shall be maintained as provided by Chapter 338, RSMo, and the rules of the board.

(D) The records required by this rule shall be maintained securely and confidentially as follows:

1. If the vaccine is administered on behalf of a pharmacy, both the pharmacy and the administering pharmacist shall ensure that all records required by this rule are maintained at the pharmacy separate from the pharmacy’s prescription files of the pharmacy.

2. If the vaccine is not being administered on behalf of a pharmacy, all records shall be maintained securely and confidentially by the administering pharmacist at an address that shall must be identified in the protocol prior to administering the vaccine; and

3. Records shall be maintained for two (2) years from the date of such record and shall be made available for inspecting and copying by the State Board of Pharmacy or the State Board of Registration for the Healing Arts and/or their authorized representatives. Records maintained at a pharmacy must be produced during an inspection by the board State Board of Pharmacy and/or their authorized representatives. Records not maintained at a pharmacy shall be produced within three (3) business days after a request from the State Board of Pharmacy or the State Board of
Registration for the Healing Arts and/or its authorized representative. Failure to maintain or produce records as provided by this rule shall constitute grounds for discipline.

(7) Notification Requirement.

(A) A pharmacist administering vaccines authorized by Chapter 338, RSMo, shall notify the authorizing physician within seventy-two (72) hours after administration of the following:

1. The identity of the patient;
2. The identity of the vaccine(s) administered;
3. The route of administration;
4. The anatomic site of the administration;
5. The dose administered; and
6. The date of administration.

(B) The pharmacist shall provide a written report to the patient’s primary health care provider, if different than the authorizing physician, containing the documentation required in subsection (A) of this section within fourteen (14) days of the administration.

(C) In the event of any adverse event or reaction experienced by the patient pursuant to a written protocol, the pharmacist shall notify the patient’s primary health care provider and authorizing physician, if different, within twenty-four (24) hours after learning of the adverse event or reaction.

(D) A pharmacist administering vaccine(s) shall report the administration to all entities as required by state or federal law.

(E) Documentation that notifications required by this rule have been sent must be maintained as provided in section (6) of this rule.

(6) Notification of Immunizations. Notification of vaccine administration must comply with all state and federal law. All pharmacists provided immunizations must be reported to the Missouri immunization registry operated by the Missouri Department of Health and Senior Services (ShowMeVax). Additionally, pharmacists must comply with the following:

(A) Pharmacists shall notify the protocol physician after administering a vaccine as required by the governing protocol. Notification of vaccine administration must also be provided to the patient’s primary care provider as required by Chapter 338, RSMo.

(B) Pharmacists shall notify the patient’s primary health care provider and, if different, the protocol physician, within twenty-four (24) hours after learning of any adverse event or reaction.
experienced by the patient. Adverse events or reactions must also be reported to the Vaccine
Adverse Event Reporting System (VAERS) or its successor, within thirty (30) days.

(C) Unless otherwise provided by the governing protocol, notification may be made via a
common electronic medication record that is accessible to and shared by both the physician and
pharmacist. Proof of notification must be maintained in the pharmacist’s records as required by
section (6) of this rule.

(7) Notification of Intent Renewal. A Notification of Intent (NOI) to immunize by protocol
must be renewed biennially with the immunizing pharmacist’s Missouri pharmacist license. The
NOI must be submitted on the Missouri Board of Pharmacy’s website or in a form approved by
the Board. To renew a NOI, pharmacists must:

(A) Have a current Missouri pharmacist license;

(B) Have a current cardiopulmonary resuscitation (CPR) or basic life support (BLS)
certification that complies with section (4)(B) of this rule; and

(C) Have completed a minimum of two (2) hours of continuing education (0.2 CEU)
related to administering vaccines or CDC immunization guidelines in a course provided by the
Board or an ACPE accredited continuing education provider. Alternatively, continuing
education may be provided by a governmental entity, healthcare professional organization or
educational institution approved by the Board in advance. Approval requests for non-ACPE
programs must be submitted in accordance with 20 CSR 2220-7.080. To be approved, non-
ACPE programs must provide instruction in one or more of the following:

1. Current CDC guidelines and recommendations for vaccines authorized by Chapter 338,
   RSMo, including, recommended immunization schedules;

2. Basic immunology and vaccine protection;

3. Physiology and techniques for vaccine administration;

4. Pre- and post- vaccine screening or assessment; or

5. Identifying and treating adverse immunization reactions.

(D) The required continuing education may be used to satisfy the pharmacist’s biennial
continuing education requirements.
20 CSR 2220-6.050 Administration of Vaccines Per Protocol

PURPOSE: This rule establishes the procedures for pharmacists to administer vaccines per written protocol with a physician.

(1) A pharmacist may administer vaccines authorized by Chapter 338, RSMo, pursuant to a written protocol authorized by a physician licensed pursuant to Chapter 334, RSMo, who is actively engaged in the practice of medicine. Unless otherwise restricted by the Board or the governing protocol, pharmacists authorized to immunize pursuant to this rule may administer immunizations at any Missouri licensed pharmacy. Immunizations may be provided at a non-pharmacy location if authorized by the governing protocol.

(A) A pharmacist shall administer vaccines in accordance with current treatment guidelines established by the Centers for Disease Control (CDC) and in accordance with manufacturer’s guidelines, provided CDC guidelines shall control in the event of a conflict with manufacturer guidelines. Vaccines shall not be administered to persons under twelve (12) years old unless otherwise authorized by law.

(B) A pharmacist shall comply with all state and federal laws and regulations pertaining to Vaccine Information Statements and informed consent requirements.

(C) Vaccines must be stored at all times in accordance with CDC guidelines/recommendations and within the manufacturer’s labeled requirements, including, when administering outside of a pharmacy.

(D) A pharmacist may not delegate the administration of vaccines to another person, except to a pharmacist intern who has met the qualifications under subsections (4)(B) and (C) and is working under the direct supervision of a pharmacist qualified to administer vaccines. Intern pharmacists must maintain proof of compliance with subsections (4)(B) and (C) for a minimum of two (2) years. (2) The authorizing physician is responsible for the oversight of, and accepts responsibility for, the vaccines administered by the pharmacist.

(3) Pharmacist Qualifications. A pharmacist who is administering a vaccine authorized by Chapter 338, RSMo, by protocol must:

(A) Hold a current Missouri pharmacist license;
(B) Hold a current healthcare provider level cardiopulmonary resuscitation (CPR) or basic life support (BLS) certification issued by the American Heart Association or the American Red Cross or an equivalent organization. The qualifying BLS or CPR certification program must have included a live/in-person CPR skills assessment.

(C) Have successfully completed a certificate program in administering vaccines accredited by the Accreditation Council for Pharmacy Education (ACPE) or a similar health authority or professional body approved by the State Board of Pharmacy. To be approved, non-ACPE programs must include a live/in-person training component and include instruction in:

1. Current CDC guidelines and recommendations for vaccines authorized by Chapter 338, RSMo, including recommended immunization schedules;
2. Basic immunology and vaccine protection;
3. Physiology and techniques for vaccine administration which must include hands-on training in common routes of vaccine administration, including, intramuscular, intradermal, subcutaneous and nasal routes of administration;
4. Pre- and post- vaccine screening or assessment; and
5. Identifying and treating adverse immunization reactions;

(D) Have filed a Notification of Intent with the Board of Pharmacy attesting that the pharmacist has complied with sections (3)(A) to (3)(C) of this rule. Notifications of Intent must be filed on the Board’s website or on a form approved by the Board; and

(E) Have a current written protocol with an authorizing physician that complies with this rule.

(4) Protocol Requirements.

(A) Pharmacists administering vaccines pursuant to this rule must enter into a written protocol with a Missouri licensed physician for the administration of vaccines as authorized by Chapter 338, RSMo. The written protocol may be valid for a time period not to exceed one (1) year and must be renewed annually. The protocol must include the following:

1. The identity of the participating pharmacist and physician, including signatures;
2. Time period of the protocol;
3. The identification of the vaccines which may be administered;
4. The identity of the patient or groups of patients to receive the authorized vaccine(s);
59 5. The identity of the authorized routes and anatomic sites of administration allowed;
60 6. A provision to create a prescription for each administration under the authorizing
61 physician’s name;
62 7. A provision establishing a course of action the pharmacist shall follow to address
63 emergency situations including, but not limited to, adverse reactions, anaphylactic reactions, and
64 accidental needle sticks;
65 8. A provision establishing the length of time the pharmacist shall observe an individual for
66 adverse events following an injection;
67 9. A provision establishing the disposal of used and contaminated supplies;
68 10. The street addresses of any non-pharmacy locations at which the pharmacist may
69 administer the authorized vaccine;
70 11. Record-keeping requirements and any required notification procedures; and
71 12. A provision that allows for termination of the protocol at the request of any party to it at
72 any time.

(B) The protocol, and any subsequent amendments or alterations, shall be manually or
73 electronically signed and dated by the pharmacist and authorizing physician prior to its
74 implementation, signifying that both are aware of its content and agree to follow the terms of the
75 protocol. The authorizing physician and pharmacist shall each maintain a copy of the protocol
76 from the beginning of implementation to a minimum of eight (8) years after termination of the
77 protocol.

(C) Additional pharmacists or immunization locations may be added to an existing protocol, if
78 the amendment is signed and dated by the authorizing physician(s) and, if applicable, any newly
79 added pharmacist(s). Other participating pharmacists shall not be required to re-sign the protocol
80 unless other protocol terms or provisions are changed.

5) Record Keeping.

(A) A pharmacist administering vaccines pursuant to this rule shall maintain a record of each
84 administration which shall include:
86 1. The name, address, and date of birth of the patient;
87 2. The date, route, and anatomic site of the administration;
88 3. The name, dose, manufacturer, lot number, and expiration date of the vaccine;
4. The name and address of the patient’s primary health care provider, as identified by the patient;
5. The identity of the administering pharmacist or intern pharmacist;
6. The nature of an adverse reaction and who was notified, if applicable;
7. Documentation that pharmacist interns administering vaccines under the pharmacist’s supervision have complied with section (2) of this rule; and
8. Documentation that any notifications required by this rule have been sent.

(B) If the vaccine was administered on behalf of a pharmacy, the pharmacist shall ensure the records required by subsection (5)(A) of this rule are promptly delivered to the pharmacy.
(C) Within seventy-two hours (72) hours after administration of a vaccine, the administering pharmacist shall obtain a prescription from the authorizing physician for the drug dispensed or shall create a prescription, as authorized by protocol documenting the dispensing of the drug. Notwithstanding any other provision of this rule, prescription records shall be maintained as provided by Chapter 338, RSMo, and the rules of the board.
(D) The records required by this rule shall be maintained securely and confidentially as follows:
1. If the vaccine is administered on behalf of a pharmacy, both the pharmacy and the administering pharmacist shall ensure that all records required by this rule are maintained at the pharmacy separate from the pharmacy’s prescription files.
2. If the vaccine is not administered on behalf of a pharmacy, records shall be maintained securely and confidentially by the administering pharmacist at an address that must be identified in the protocol prior to administering the vaccine; and
3. Records shall be maintained for two (2) years from the date of such record and shall be made available for inspecting and copying by the State Board of Pharmacy or the State Board of Registration for the Healing Arts and/or their authorized representatives. Records maintained at a pharmacy must be produced during an inspection by the State Board of Pharmacy and/or their authorized representatives. Records not maintained at a pharmacy shall be produced within three (3) business days after a request from the State Board of Pharmacy or the State Board of Registration for the Healing Arts and/or its authorized representative. Failure to maintain or produce records as provided by this rule shall constitute grounds for discipline.
(6) Notification of Immunizations. Notification of vaccine administration must comply with all state and federal law. All pharmacists provided immunizations must be reported to the Missouri immunization registry operated by the Missouri Department of Health and Senior Services (ShowMeVax). Additionally, pharmacists must comply with the following:

(A) Pharmacists shall notify the protocol physician after administering a vaccine as required by the governing protocol. Notification of vaccine administration must also be provided to the patient’s primary care provider as required by Chapter 338, RSMo.

(B) Pharmacists shall notify the patient’s primary health care provider and, if different, the protocol physician, within twenty-four (24) hours after learning of any adverse event or reaction experienced by the patient. Adverse events or reactions must also be reported to the Vaccine Adverse Event Reporting System (VAERS) or its successor, within thirty (30) days.

(C) Unless otherwise provided by the governing protocol, notification may be made via a common electronic medication record that is accessible to and shared by both the physician and pharmacist. Proof of notification must be maintained in the pharmacist’s records as required by section (6) of this rule.

(7) Notification of Intent Renewal. A Notification of Intent (NOI) to immunize by protocol must be renewed biennially with the immunizing pharmacist’s Missouri pharmacist license. The NOI must be submitted on the Missouri Board of Pharmacy’s website or in a form approved by the Board. To renew a NOI, pharmacists must:

(A) Have a current Missouri pharmacist license;

(B) Have a current cardiopulmonary resuscitation (CPR) or basic life support (BLS) certification that complies with section (4)(B) of this rule; and

(C) Have completed a minimum of two (2) hours of continuing education (0.2 CEU) related to administering vaccines or CDC immunization guidelines in a course provided by the Board or an ACPE accredited continuing education provider. Alternatively, continuing education may be provided by a governmental entity, healthcare professional organization or educational institution approved by the Board in advance. Approval requests for non-ACPE programs must be submitted in accordance with 20 CSR 2220-7.080. To be approved, non-ACPE programs must provide instruction in one or more of the following:
1. Current CDC guidelines and recommendations for vaccines authorized by Chapter 338, RSMo, including, recommended immunization schedules;

2. Basic immunology and vaccine protection;

3. Physiology and techniques for vaccine administration;

4. Pre- and post-vaccine screening or assessment; or

5. Identifying and treating adverse immunization reactions.

(D) The required continuing education may be used to satisfy the pharmacist’s biennial continuing education requirements.
TO:       Board Members

FROM:    Kimberly Grinston,
         Executive Director

RE:       Potential Pharmacy Technician Legislation

DATE:     June 5, 2017

Please see the attached proposed drafts of potential pharmacy technician legislation. A few notes:

1) The Tech I draft includes language that incorporates most of the Working Group’s recommendations. If selected, staff has additional questions on how the legislation would apply to nuclear technicians.

2) The Tech II draft would authorize the Board to establish training requirements for the main advanced technician functions discussed by the Working Group. This option would be less extensive should the Board opt not to pursue a comprehensive approach.

3) A third option briefly discussed at a previous meeting was to authorize the Board to approve pilot tech-check-tech or remote technician programs. The agenda includes statutory and rule language from other states that may be helpful should the Board choose this approach.

In the past, legislative proposals were due in July/August. The Boards have been advised to follow the previous deadline until directed otherwise.
Pharmacy technician to register with board of pharmacy, fees, application, renewal--refusal to issue, when--employee disqualification list maintained, use.

338.013. 1. Any person desiring to assist a pharmacist in the practice of pharmacy as defined in this chapter shall apply to the board of pharmacy for registration as a pharmacy technician. Such applicant shall be, at a minimum, legal working age and shall forward to the board the appropriate fee and written application on a form provided by the board. Such registration shall be the sole authorization permitted to allow persons to assist licensed pharmacists in the practice of pharmacy as defined in this chapter.

1. Definitions.

(A) Pharmacy Technician Trainee- Registered pharmacy support staff or a registered pharmacy technician who is in training for a pharmacy technician or an advanced pharmacy technician registration.

(B) Registered Pharmacy Support Staff- An individual with physical access to a pharmacy, or who has the authority or ability to order legend medication for pharmacy use, but does not assist or support a pharmacist in the practice of pharmacy.

Registered Pharmacy Support Staff shall not include individuals with incidental access to the pharmacy while under the direct supervision of a board licensee or registrant, as defined by the Board by rule.

(C) Registered Pharmacy Technician: An individual who assists or supports a pharmacist in the practice of pharmacy, including, but not limited to an individual engaged in dispensing or filling of prescriptions or medical orders.

(D) Registered Advanced Pharmacy Technician- An individual who assists or supports a pharmacist in the practice of pharmacy and who performs advanced
technician functions or exercises increased independence, as defined/authorized by the Board by rule. At a minimum, advanced pharmacy technician duties shall include:

1. Sterile Compounding;
2. Preparation of chemotherapy or nuclear medications or preparation of hazardous injectables; and
3. Remote pharmacy technician activity, as authorized by the Board by rule.

2. Pharmacy support staff, pharmacy technicians and advanced pharmacy technicians must be registered with the board. To be eligible for registration, applicants shall file an application on a form provided by the board with the appropriate fee, undergo a criminal history background check and comply with the following:

(A) Registered Pharmacy Support Staff applicants must be of legal working age;
(B) Registered Pharmacy Technician applicants must be at least sixteen (16) years old and have completed an employer based training program that includes minimum training components, as specified by the Board by rule. —OR—
(B) Registered Pharmacy Technician applicants must be at least sixteen (16) years old and have completed an employer based training program, as provided by the Board by rule. At a minimum, an employer-based training program must include training in the following:

(a) Pharmacy terminology;
(b) Pharmacy calculations;
(c) Dispensing systems;
(d) Labeling requirements,
(e) Applicable state and federal pharmacy and drug laws and regulations;
(f) Record keeping and documentation;
(g) Proper handling and storage of medications, and;
(h) Pharmacy policies and procedures.
(C) Registered Advanced Pharmacy Technicians applicants must be at least sixteen (16) years old and must hold an active pharmacy technician certification issued by a certification entity accredited by the National Commission for Certifying Agencies or, for applicants that will be assisting in the practice of nuclear pharmacy, have
completed a nuclear pharmacy technician certificate program from a provider accredited by the Accreditation Council for Pharmacy Education or its successor.

3. Pharmacy Technician Trainees. The pharmacy shall maintain a list of all pharmacy support staff and registered pharmacy technicians designated as pharmacy technician trainees and the training start date. Once designated, the trainee may engage in registered pharmacy technician or advanced pharmacy technician functions, as authorized by the rules of the Board and the pharmacist-in-charge. A registrant may not be designated as a pharmacy technician trainee for more than one (1) year, provided the pharmacist-in-charge may grant a six (6) month extension for good cause. If training is not completed within the required one (1) year or eighteen (18) months, the registrant may not be re-designated as a trainee for a minimum of six (6) months.

24. The board may refuse to issue a certificate of registration as a pharmacy technician registration authorized by this section to an applicant that has been adjudicated and found guilty, or has entered a plea of guilty or nolo contendere, of a violation of any state, territory or federal drug law, or to any felony or has violated any provision of subsection 2 of section 338.055. Alternately, the board may issue such person a registration, but may authorize the person to work as a pharmacy technician provided that person adheres to certain terms and conditions imposed by the board. The board shall place on the employment disqualification list the name of an applicant who the board has refused to issue a certificate of registration as a pharmacy technician, or the name of a person who the board has issued a certificate of registration as a pharmacy technician but has authorized to work under certain terms and conditions. The board shall notify the applicant of the applicant's right to file a complaint with the administrative hearing commission as provided by chapter 621.

3. If an applicant has submitted the required fee and an application for registration to the board of pharmacy, the applicant for registration as a pharmacy technician may assist a licensed pharmacist in the practice of pharmacy as defined in this chapter may begin performing activities authorized for the registration class once the completed application has been submitted to the board. The applicant shall keep a copy of the
submitted application on the premises where the applicant is employed. If the board refuses to issue a certificate of registration as a pharmacy technician to an applicant, the applicant shall immediately cease assisting a licensed pharmacist in the practice of pharmacy performing the applicable technician activities.

4. A certificate of registration issued by the board or other proof of registration authorized by the board shall be conspicuously displayed in the pharmacy or place of business where the registrant is employed or performing registrant activities.

5. Every pharmacy technician registrant who desires to continue to be registered as provided in this section shall, within thirty days before the registration expiration date, file an application for the renewal, accompanied by the fee prescribed by the board. The registration shall lapse and become null and void thirty days after the expiration date. To renew, registered advanced pharmacy technicians must submit proof that he/she holds a current and active certification identified in section (2)(C).

6. The board shall maintain an employment disqualification list. No person whose name appears on the employment disqualification list shall work as a pharmacy technician, pharmacy support staff registrant, registered pharmacy technician or an advanced registered pharmacy technician, except as otherwise authorized by the board. The board may authorize a person whose name appears on the employment disqualification list to work or continue to work as a pharmacy technician registrant provided the person adheres to certain terms and conditions imposed by the board.

7. The board may place on the employment disqualification list the name of a pharmacy technician registrant who has been adjudicated and found guilty, or has entered a plea of guilty or nolo contendere, of a violation of any state, territory or federal drug law, or to any felony or has violated any provision of subsection 2 of section 338.055.

8. After an investigation and a determination has been made to place a person's name on the employment disqualification list, the board shall notify such person in writing mailed to the person's last known address:
(1) That an allegation has been made against the person, the substance of the allegation and that an investigation has been conducted which tends to substantiate the allegation;

(2) That such person's name has been added in the employment disqualification list of the board;

(3) The consequences to the person of being listed and the length of time the person's name will be on the list; and

(4) The person's right to file a complaint with the administrative hearing commission as provided in chapter 621.

9. The length of time a person's name shall remain on the disqualification list shall be determined by the board.

10. No hospital or licensed pharmacy shall knowingly employ any person whose name appears on the employee disqualification list, except that a hospital or licensed pharmacy may employ a person whose name appears on the employment disqualification list but the board has authorized to work under certain terms and conditions. Any hospital or licensed pharmacy shall report to the board any final disciplinary action taken against a pharmacy technician or the voluntary resignation of a pharmacy technician registrant against whom any complaints or reports have been made which might have led to final disciplinary action that can be a cause of action for discipline by the board as provided for in subsection 2 of section 338.055. Compliance with the foregoing sentence may be interposed as an affirmative defense by the employer. Any hospital or licensed pharmacy which reports to the board in good faith shall not be liable for civil damages.

11. Any person who holds a current and active pharmacy technician registration on or before January 1, 2019 or a later date designated by the Board, may apply to the Board for an advanced technician registration without fee. To be eligible for advanced technician registration under this subsection, the application must be accompanied by a statement from a Missouri licensed pharmacist attesting that the applicant has practiced as a pharmacy technician for a minimum of 400 hours and that such practice included...
in whole or in part, the performance of advanced technician duties, as designated by the Board by rule. Any person registered pursuant to this subsection who fails to maintain their advanced technician registration current and active shall be treated in the same manner as a new applicant and shall comply with all advanced technician registration requirements upon reapplication.

Pharmacy technician to register with board of pharmacy, fees, application, renewal--refusal to issue, when--employee disqualification list maintained, use.

338.013. 1. Any person desiring to assist a pharmacist in the practice of pharmacy as defined in this chapter shall apply to the board of pharmacy for registration as a pharmacy technician. Such applicant shall be, at a minimum, legal working age and shall forward to the board the appropriate fee and written application on a form provided by the board. Such registration shall be the sole authorization permitted to allow persons to assist licensed pharmacists in the practice of pharmacy as defined in this chapter. Pharmacy technicians may engage in the following advanced technician functions subject to standards and requirements established by the Board by rule:

a. Technology assisted final dispensing verification; and

b. Remote pharmacy technician activities.

2. The board may refuse to issue a certificate of registration as a pharmacy technician to an applicant that has been adjudicated and found guilty, or has entered a plea of guilty or nolo contendere, of a violation of any state, territory or federal drug law, or to any felony or has violated any provision of subsection 2 of section 338.055. Alternately, the board may issue such person a registration, but may authorize the person to work as a pharmacy technician provided that person adheres to certain terms and conditions imposed by the board. The board shall place on the employment disqualification list the name of an applicant who the board has refused to issue a certificate of registration as a pharmacy technician, or the name of a person who the board has issued a certificate of registration as a pharmacy technician but has authorized to work under certain terms and conditions. The board shall notify the
applicant of the applicant's right to file a complaint with the administrative hearing commission as provided by chapter 621.

3. If an applicant has submitted the required fee and an application for registration to the board of pharmacy, the applicant for registration as a pharmacy technician may assist a licensed pharmacist in the practice of pharmacy as defined in this chapter. The applicant shall keep a copy of the submitted application on the premises where the applicant is employed. If the board refuses to issue a certificate of registration as a pharmacy technician to an applicant, the applicant shall immediately cease assisting a licensed pharmacist in the practice of pharmacy.

4. A certificate of registration issued by the board shall be conspicuously displayed in the pharmacy or place of business where the registrant is employed.

5. Every pharmacy technician who desires to continue to be registered as provided in this section shall, within thirty days before the registration expiration date, file an application for the renewal, accompanied by the fee prescribed by the board. The registration shall lapse and become null and void thirty days after the expiration date.

6. The board shall maintain an employment disqualification list. No person whose name appears on the employment disqualification list shall work as a pharmacy technician, except as otherwise authorized by the board. The board may authorize a person whose name appears on the employment disqualification list to work or continue to work as a pharmacy technician provided the person adheres to certain terms and conditions imposed by the board.

7. The board may place on the employment disqualification list the name of a pharmacy technician who has been adjudicated and found guilty, or has entered a plea of guilty or nolo contendere, of a violation of any state, territory or federal drug law, or to any felony or has violated any provision of subsection 2 of section 338.055.

8. After an investigation and a determination has been made to place a person's name on the employment disqualification list, the board shall notify such person in writing mailed to the person's last known address:
(1) That an allegation has been made against the person, the substance of the allegation and that an investigation has been conducted which tends to substantiate the allegation;

(2) That such person's name has been added in the employment disqualification list of the board;

(3) The consequences to the person of being listed and the length of time the person's name will be on the list; and

(4) The person's right to file a complaint with the administrative hearing commission as provided in chapter 621.

9. The length of time a person's name shall remain on the disqualification list shall be determined by the board.

10. No hospital or licensed pharmacy shall knowingly employ any person whose name appears on the employee disqualification list, except that a hospital or licensed pharmacy may employ a person whose name appears on the employment disqualification list but the board has authorized to work under certain terms and conditions. Any hospital or licensed pharmacy shall report to the board any final disciplinary action taken against a pharmacy technician or the voluntary resignation of a pharmacy technician against whom any complaints or reports have been made which might have led to final disciplinary action that can be a cause of action for discipline by the board as provided for in subsection 2 of section 338.055. Compliance with the foregoing sentence may be interposed as an affirmative defense by the employer. Any hospital or licensed pharmacy which reports to the board in good faith shall not be liable for civil damages.

Section 333.17723

PUBLIC HEALTH CODE (EXCERPT)
Act 368 of 1978

333.17723 Pilot project to maintain or improve patient care in delivery of pharmacy services and improving patient outcomes.

Sec. 17723.

(1) Subject to this section, the board may approve a pilot project that is designed to utilize new or expanded technology or processes and to provide patients with better pharmacy products or provide pharmacy services in a more efficient manner. The board shall ensure that a pilot project it approves under this section is focused on maintaining or improving patient care in the delivery of pharmacy services and improving patient outcomes. The department may charge petitioners a filing fee sufficient to cover the department's costs incurred while administering and monitoring the pilot project under this section.

(2) The department shall do all of the following:

(a) Establish and administer a process to receive, review, and accept or deny petitions for proposed pilot projects.

(b) Establish time frames for the receipt, review, and approval or denial of petitions for proposed pilot projects.

(c) Designate the individuals who will review and evaluate petitions for proposed pilot projects.

(3) The board shall not approve more than 10 pilot projects under this section. If it determines necessary, the board or department may further limit the number of approved pilot projects based on the scope and type of petitions for proposed pilot projects received.

(4) The board shall not approve a pilot project that does any of the following:

(a) Expands the definition of the practice of pharmacy.

(b) Provides for the therapeutic substitution or substitution of medical devices used
(c) Allows a pharmacy or pharmacist to be involved with a pilot project if the pharmacy's or pharmacist's license is not current or is under investigation for or subject to a sanction for a violation of this act.

(5) The department, in consultation with the board, may grant to a petitioner conducting an approved pilot project under this section an exception to a rule promulgated under this part. The department shall not grant an exception under this subsection from any law relating to the practice of pharmacy. The department shall grant an exception under this subsection for a specified period of time, which period must not exceed 18 months unless extended under subsection (12).

(6) A petitioner who wishes the board to consider a pilot project for approval under this section shall submit to the department a petition that contains all of the following information:

(a) The name, address, telephone number, electronic mail address, and Michigan license number of the pharmacist responsible for overseeing the proposed pilot project.

(b) The specific location where the proposed pilot project will be conducted. The petitioner shall include the Michigan license number of the pharmacy and a statement that the Michigan license of the pharmacy and any pharmacist involved with the pilot project is current, is not under investigation for or subject to a sanction for a violation of this act, and will remain in good standing for the duration of the pilot project.

(c) A detailed summary of the proposed pilot project that includes all of the following:

(i) The goals, hypothesis, and objectives, as applicable, of the proposed pilot project.

(ii) A full explanation of the proposed pilot project and how the project will be conducted.

(iii) The initial time frame for the pilot project, including the proposed start date and length of the project, which initial time frame must not exceed 18 months.

(iv) All background information and literature review, as applicable, to support the proposed pilot project.

(v) If applicable, identification of the rules promulgated under this part from which the petitioner is requesting an exception as provided in subsection (5) in order to complete the proposed pilot project and a request for that exception.

(vi) If applicable, procedures the petitioner will use during the proposed pilot project to ensure that the public's health and safety are not compromised as a result of an exception to a rule being granted under subsection (5).

(vii) The procedures the petitioner will use to protect the identity and privacy of patients in accordance with existing federal and state law and consistent with regulations promulgated under the health insurance portability and accountability act of 1996, Public Law 104-191.

(7) Upon approval of a petition for a pilot project, the department shall specify a time period for the operation of that pilot project, which period must not exceed 18 months unless extended under subsection (11). The department, in consultation with the board, may include appropriate conditions or qualifications on the approval of a pilot project. The department or board may suspend the operation of a pilot project if it determines that the petitioner or any person involved with the pilot project has deviated the operation of the pilot project from the plan of operation.
that was approved.

(8) If determined appropriate for the pilot project approved under this section, the board or department may require the petitioner to notify patients that pharmacy services are being provided as part of a pilot project. If required under this subsection, the petitioner shall notify patients in the manner required by the board or department.

(9) The petitioner shall allow the department to inspect and review pilot project documentation and the pilot project site at any time during the review process and after the pilot project is approved. The pharmacist responsible for overseeing an approved pilot project shall forward all of the following to the department:

(a) Progress reports at intervals specified by the department.

(b) A summary of the results of the project and conclusions drawn from the results of the project within 3 months after completion of the pilot project.

(10) The individuals designated to review and evaluate petitions under subsection (2)(c) shall review the progress reports and the summary of the results of the pilot project submitted under subsection (9). Within 90 days after receipt of the summary of the results of the pilot project under subsection (9), the individuals designated to review and evaluate petitions under subsection (2)(c) shall submit a written report to the department regarding the results of the pilot project. The department shall provide a copy of the written report submitted under this subsection to the board. The individuals designated to review and evaluate petitions under subsection (2)(c) shall submit a copy of the written report to the petitioner at least 2 weeks before the board meeting at which the report will be considered by the board. Upon the request of the petitioner, the board shall allow the petitioner to make a presentation to the board.

(11) If determined appropriate by the board at the meeting at which the written report is considered under subsection (10), and if approved by the department, the specified period of time for conducting a pilot project under subsection (7) may be extended for an additional period of up to 18 months. The board or department shall not grant an extension that would result in a specified period of time for conducting a pilot project under this section to exceed 36 months.

(12) If the department, in consultation with the board, determines that a pilot project for which an exception to a rule has been granted under subsection (5) should be extended so that rules may be promulgated in order to allow the pilot project to be conducted on a permanent basis, the department may extend the exception to the rule for an additional period of up to 18 months.

Popular Name: Act 368

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The Michigan Public Health Code (Code), specifically MCL §333.17723 effective March 30, 2014, provides provisions to allow pharmacies to submit to the Department, a proposed pilot project. These pilot projects should be designed to utilize new or expanded technology or processes and to provide patients with better pharmacy products or provide pharmacy services in a more efficient manner. The focus should be on maintaining or improving patient care in the delivery of pharmacy services and improving patient outcomes. Pilot projects will be reviewed as an exception to a rule promulgated by the Board of Pharmacy. The Board will not grant an exception from any law relating to the practice of pharmacy. Projects that involve expanding the definition of the practice of pharmacy and/or provide for therapeutic substitution or substitution of medical devices used in patient care will not be considered.

**Pilot Project Submission:**

1. A pharmacy may submit a petition for the proposed pilot project, and currently there is no application or monitoring charges for a pilot project through September 30, 2014, the State’s Fiscal Year-End. The Department will evaluate time and expenses related to pilot projects, and may impose fees in a future Fiscal Year. An applicant should submit a petition to the following address:

   Department of Licensing & Regulatory Affairs  
   Bureau of Health Care Services  
   ATTN: MAPS/Pharmacy Section  
   P.O. Box 30454  
   Lansing, MI 48909

The petition must include the following:

   a. The name, address, telephone number, e-mail address, and the Michigan license number of the pharmacy and of the pharmacist responsible for overseeing the proposed pilot project;
   b. Specific location where the proposed pilot project will be conducted, a statement that the license of the pharmacy and pharmacist are current, is not under investigation for or subject to a sanction for any violation of the Code and will remain in good standing for the duration of the pilot program;
   c. Detailed summary of the proposed pilot project that includes the goals, hypothesis and objectives, if applicable, of the proposed pilot project;
   d. Full explanation of the proposed pilot project and how the pilot project will be conducted;
   e. The initial time frame for the pilot project, including proposed start date and length of project, which must not exceed 18 months from the date of initial approval;
   f. All background information and literature review, if applicable, to support the proposed pilot project;
   g. Identification of the rules promulgated from which the requestor is requesting an exception in order to complete the proposed pilot project and a request for that exception, if applicable;
   h. Procedures used to ensure that the public’s health and safety are not compromised as a result of the exception to the rule being granted, if applicable; and,
i. Procedures used to protect the identity and privacy of patients in accordance with existing federal and state law, including HIPAA.

2. Once submitted, the department will send a letter of acknowledgement, advising that the department will review the proposed pilot program and complete the ‘Review of Proposed Pilot Project’ form within 90 days of receipt by the department.

**Department Denial**

a. The department will contact petitioner stating reason(s) for the denial.

**Department Approval**

a. Review pharmacy license and pharmacist license for investigation and/or sanction history;

b. Forward completed and approved ‘Review of Proposed Pilot Project’ form to the Board of Pharmacy for inclusion at the next regularly scheduled meeting;

c. Notify Petitioner of the Board’s project review at least two weeks prior to the scheduled Board of Pharmacy meeting in the event the petitioner would like to provide a presentation to the Board.

d. A department representative will attend the Board of Pharmacy meeting when the pilot project is to be considered.

e. The Board of Pharmacy will review the ‘Review of Proposed Pilot Project’ form to decide whether to approve or deny the proposed pilot project.

**Board of Pharmacy: Project Approval**

a. Board representative will sign the ‘Review of Proposed Pilot Project’ indicating the board’s approval.

b. A department representative will notify the petitioner of the Board’s approval

c. The department will obtain and review required progress reports at intervals specified in the approval.

d. Upon completion of the pilot project, the department will obtain a summary report from the petitioner detailing the results of the project and conclusions drawn from the results of the project.

e. Once the pilot project has ended, the department will complete the ‘Evaluation of Completed Pilot Project’ form and submit it to the Board of Pharmacy for inclusion at the next regularly scheduled meeting for their review.

f. The Board of Pharmacy will review the summary and conclusions of the pilot project. If approved, an extension will be granted to allow the project to continue on a permanent basis while rules are promulgated

**Possible Pilot Project Requirements:**

Notification of approval for the pilot project may include the following requirements:

- A specified time period for the operation of the pilot project (not to exceed 18 months). An extension period of up to an additional 18 months may be granted if Board of Pharmacy rules need to be promulgated in order to allow the pilot project to be conducted on a permanent basis.
- Any additional conditions or qualifications required for the pilot project.
- A requirement to notify patients that pharmacy services are being provided as part of a pilot project, and in a manner required by the department.
• Random inspection(s) by the department to review pilot project documentation and project site at any time during the review process and after the pilot project is approved.
• Submission of progress reports at specified intervals, a summary of the results of the project, and conclusions drawn from the result of the project within three (3) months after completion of the pilot project.

**Board of Pharmacy: Project Denial**
- a. Board representative will sign the ‘Review of Proposed Pilot Project’ indicating the board’s denial.
- b. A department representative will contact the petitioner with the results of the review and the reason(s) for the denial.

3. **NOTE:** The department or board may suspend the operation of the pilot project if it determined that the petitioner or any person involved with the pilot project has deviated from the plan of operation that was approved.

Attachment: Sample Petition format
Pharmacy Pilot Program
Sample Petition

(Please refer to the instructions for further direction.)

I.) **Initial Information:**

[Please refer to Procedure 1(a)]

[Please refer to Procedure 1(b)]

II.) **Pilot Summary/Description:**

[Please refer to Procedure 1(c)]

[Please refer to Procedure 1(d)]

[Please refer to Procedure 1(e)]

III.) **Background Information/Literature Review:**

[Please refer to Procedure 1(f)]

IV.) **Pharmacy Rule Deviation & Reason(s) Why:**

[Please refer to Procedure 1(g)]

V.) **Public Safety/Health/Security:**

[Please refer to Procedure 1(h)]

[Please refer to Procedure 1(i)]

Name: ___________________________________________

Signature: _________________________________________  Date: __________________________
### APPLICATION FOR APPROVAL OF AN INNOVATIVE (PILOT) PROGRAM

Applicant - Please provide the information requested below. (Print or Type) Use full name not initials

<table>
<thead>
<tr>
<th>Title of Pilot Program</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Pharmacy where pilot program is to be conducted</td>
<td>Pharmacy Permit Number</td>
</tr>
<tr>
<td>Street Address</td>
<td>Area Code and Telephone Number</td>
</tr>
<tr>
<td>City</td>
<td>State</td>
</tr>
<tr>
<td>Name/Email of Kansas licensed pharmacist responsible for pilot program</td>
<td>Kansas License Number of Responsible Pharmacist</td>
</tr>
</tbody>
</table>

If requesting that the pilot project be conducted at more than one pharmacy or location, provide a list of additional locations and responsible pharmacists as Attachment 8.

Responsible pharmacist need not be the PIC of the pharmacy, but should be the pharmacist who will most closely oversee and supervise the operation of the pilot program. If the responsible pharmacist does not have administrative/organizational authority for the pharmacy, this application must be cosigned by the pharmacist who does have this authority.

If proprietary/privileged information is included in application please label as such.

Please attach the following additional information and label as indicated. Please write this in lay terms which can be easily understood by non-pharmacists and persons not familiar with computers or other technology to be used in the practice of pharmacy:

<table>
<thead>
<tr>
<th>Label</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attachment 1:</td>
<td>A brief description, narrative, or summary of the new process or procedure for which approval is being sought.</td>
</tr>
</tbody>
</table>
Attachment 2: A listing of the laws or regulations for which waivers are being requested through approval of this pilot program and a brief explanation why each waiver is needed.

Attachment 3: An explanation as to the rationale and objectives for the program, i.e. benefit to the patient or industry. If applicable, this explanation should include how protections for patients will be incorporated into the project and how they will be assessed/measured/reported to the Board.

Attachment 4: A summary of outcomes which will be measured, method for measuring, and timelines for measurements and reporting to the Board, including requested duration of the approval.

Attachment 5: Any measures which will be taken to ensure security of drug product and Confidential/HIPAA information in the execution of the pilot program, if applicable.

Attachment 6: Disclosure of any financial interests, if applicable.

Attachment 7: Any additional supporting information, such as technical or other descriptive literature describing equipment or a process, or information from another state where this process or procedure has been tested, etc.

Attachment 8: List any additional pharmacies, permit numbers, corresponding responsible pharmacists and their license numbers if requesting that the pilot program be conducted at multiple sites.

I attest that the information furnished on this application is true and correct to the best of my knowledge.

Signature of applicant: ____________________________________________________________

Date: __________________________________________________________________________
DRAFT Language – Proposal # (Rx Cares for Missouri)

**Receipt of drugs from unlicensed distributor or pharmacy, unlawful--penalty--pharmacy-to-pharmacy transfers, limit--legend drugs, inventories and records--rulemaking authority**

338.315. 1. Except as otherwise provided by the board by rule, it shall be unlawful for any pharmacist, pharmacy owner or person employed by a pharmacy to knowingly purchase or receive any legend drugs under 21 U.S.C. Section 353 from other than a licensed or registered drug distributor, third party logistics provider or licensed pharmacy. Any person who violates the provisions of this section shall, upon conviction, be adjudged guilty of a class A misdemeanor. Any subsequent conviction shall constitute a class D felony.

2. Notwithstanding any other provision of law to the contrary, the sale, purchase, or trade of a prescription drug by a pharmacy to other pharmacies is permissible if the total dollar volume of such sales, purchases, or trades are in compliance with the rules of the board and do not exceed five percent of the pharmacy's total annual prescription drug sales.

3. Pharmacies shall establish and maintain inventories and records of all transactions regarding the receipt and distribution or other disposition of legend drugs. Such records shall be maintained for two years and be readily available upon request by the board or its representatives.

4. The board shall promulgate rules to implement the provisions of this section. Any rule or portion of a rule, as that term is defined in section 536.010, that is created under the authority delegated in this section shall become effective only if it complies with and is subject to all of the provisions of chapter 536 and, if applicable, section 536.028. This section and chapter 536 are nonseverable and if any of the powers vested with the general assembly pursuant to chapter 536 to review, to delay the effective date, or to disapprove and annul a rule are subsequently held unconstitutional, then the grant of rulemaking authority and any rule proposed or adopted after August 28, 2012, shall be invalid and void.

**Definitions.**

338.330. As used in sections 338.300 to 338.370, the following terms mean:
(1) "Legend drug":

(a) Any drug or biological product:

a. Subject to Section 503(b) of the Federal Food, Drug and Cosmetic Act, including finished dosage forms and active ingredients subject to such Section 503(b); or

b. Required under federal law to be labeled with one of the following statements prior to being dispensed or delivered:

(i) "Caution: Federal law prohibits dispensing without prescription";

(ii) "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian"; or

(iii) "Rx Only"; or

b. Required by any applicable federal or state law or regulation to be dispensed by prescription only or that is restricted to use or dispensed by practitioners only; and

(b) The term "drug", "prescription drug", or "legend drug" shall not include:

a. An investigational new drug, as defined by 21 CFR 312.3(b), that is being utilized for the purposes of conducting a clinical trial or investigation of such drug or product that is governed by, and being conducted under and pursuant to, 21 CFR 312, et. seq.;

b. Any drug product being utilized for the purposes of conducting a clinical trial or investigation that is governed by, and being conducted under and pursuant to, 21 CFR 312, et. seq.; or

c. Any drug product being utilized for the purposes of conducting a clinical trial or investigation that is governed or approved by an institutional review board subject to 21 CFR Part 56 or 45 CFR Part 46;

(2) "Out-of-state wholesale drug distributor", a wholesale drug distributor with no physical facilities located in the state;

(3) "Pharmacy distributor", any licensed pharmacy, as defined in section 338.210, engaged in the delivery or distribution of legend drugs to any other licensed pharmacy where such delivery or distribution constitutes at least five percent of the total gross sales of such pharmacy;

(4) "Wholesale drug distributor", anyone engaged in the delivery or distribution of legend drugs from any location and who is involved in the actual, constructive or attempted transfer of a drug or drug-related device in this state, other than to the ultimate consumer. This shall include, but not be limited to, drug wholesalers, repackagers and manufacturers which are engaged in the
delivery or distribution of drugs in this state, with facilities located in this state or in any other state or jurisdiction. A wholesale drug distributor shall not include any common carrier or individual hired solely to transport legend drugs. Any locations where drugs are delivered on a consignment basis, as defined by the board, shall be exempt from licensure as a drug distributor, and those standards of practice required of a drug distributor but shall be open for inspection by board of pharmacy representatives as provided for in section 338.360.

(5) “Third-party Logistics Provider”, an entity that provides or coordinates warehousing, or other logistics services of a product on behalf of a drug manufacturer, wholesale distributor, or dispenser of a legend drug, but does not take ownership of the product, nor have responsibility to direct the sale or disposition of the product.

License required, temporary licenses may be granted--out-of-state distributors, reciprocity allowed, when.

338.333. 1. Except as otherwise provided by the board of pharmacy by rule in the event of an emergency or to alleviate a supply shortage, no person or distribution outlet shall act as a wholesale drug distributor, or pharmacy distributor, or third party logistics provider without first obtaining license to do so from the Missouri board of pharmacy and paying the required fee. The board may grant temporary licenses when the wholesale drug distributor, or pharmacy distributor, or third party logistics provider first applies for a license to operate within the state. Temporary licenses shall remain valid until such time as the board shall find that the applicant meets or fails to meet the requirements for regular licensure. No license shall be issued or renewed for a wholesale drug distributor, or pharmacy distributor, or third party logistics provider to operate unless the same shall be operated in a manner prescribed by law and according to the rules and regulations promulgated by the board of pharmacy with respect thereto. Separate licenses shall be required for each distribution or third party logistics site owned or operated by a wholesale drug distributor, or pharmacy distributor, or third party logistics provider unless such drug distributor, or pharmacy distributor, or third party logistics provider meets the requirements of section 338.335.

2. An agent or employee of any licensed or registered wholesale drug distributor, or pharmacy distributor, or third party logistics provider need not seek licensure under this section and may lawfully possess pharmaceutical drugs, if the agent or employee is acting in the usual course of his or her business or employment.
3. The board may permit out-of-state wholesale drug distributors, third party logistics provider or out-of-state pharmacy distributors to be licensed as required by sections 338.210 to 338.370 on the basis of reciprocity to the extent that an out-of-state wholesale drug distributor or out-of-state pharmacy distributor the entity both:

(1) Possesses a valid license granted by another state pursuant to legal standards comparable to those which must be met by a wholesale drug distributor, or pharmacy distributor or third party logistics provider of this state as prerequisites for obtaining a license under the laws of this state; and

(2) Distributes into Missouri from a state which would extend reciprocal treatment under its own laws to a wholesale drug distributor, or pharmacy distributor or third party logistics provider of this state.

Out-of-state distributors, licenses required, exception.

338.337. It shall be unlawful for any out-of-state wholesale drug distributor, or out-of-state pharmacy acting as a distributor or third party logistics provider to do business in this state without first obtaining a license to do so from the board of pharmacy and paying the required fee, except as otherwise provided by section 338.335 and this section. Application for an out-of-state wholesale drug distributor’s or out-of-state third party logistics provider’s license under this section shall be made on a form furnished by the board. The issuance of a license under sections 338.330 to 338.370 shall not change or affect tax liability imposed by the Missouri department of revenue on any out-of-state wholesale drug distributor or out-of-state pharmacy entity. Any out-of-state wholesale drug distributor that is a drug manufacturer and which produces and distributes from a facility which has been inspected and approved by the Food and Drug Administration, maintains current approval by the federal Food and Drug Administration, and has provided a copy of the most recent Food and Drug Administration Establishment Inspection Report to the board, and which is licensed by the state in which the distribution facility is located, or, if located within a foreign jurisdiction, is authorized and in good standing to operate as a drug manufacturer within such jurisdiction, need not be licensed as provided in this section but such out-of-state distributor shall register its
business name and address with the board of pharmacy and pay a filing fee in an amount established by the board.

**Sale of drugs, out-of-state distributor, license required.**

338.340. No person acting as principal or agent for any out-of-state wholesale drug distributor, or out-of-state pharmacy distributor, or out-of-state third party logistics provider shall sell or distribute drugs in this state unless the wholesale drug distributor or pharmacy distributor entity has obtained a license pursuant to the provisions of sections 338.330 to 338.370.
Renewal of license or permit--late renewal or failure to renew, effect--continuing education requirements--inactive license issued when--changed to active, procedure.

338.060. 1. Every licensed pharmacist or permit holder who desires to continue in the practice of this profession shall, within thirty days before the license expiration date, file an application for the renewal before the license expiration date, which application shall be accompanied by the fee prescribed in sections 338.010 to 338.198.

2. If any pharmacist fails, after the expiration of the pharmacist's license, to make application to the board for its renewal, the pharmacist's name shall be removed from the register of licensed pharmacists, and such person, in order to again become registered as a licensed pharmacist, shall be required to pay all delinquent fees. Any pharmacist who fails to renew the pharmacist's license within two years of its expiration and then desires to be preregistered shall be treated in the same manner as a person who has never been licensed. Any registered pharmacist whose certificate of registration has expired while the pharmacist has been engaged in active duty with the United States Army, United States Navy, United States Air Force, the Marine Corps, Coast Guard, or any other branch of the armed services or the state militia called into the service or training of the United States of America, or in training or education under the supervision of the United States preliminary to induction into the military services may have the pharmacist's certificate of registration renewed without paying any lapse, renewal or registration fee or without passing any examination, if within one year after the termination of such service, training or education, other than by dishonorable discharge, the pharmacist furnishes the board with an affidavit to the effect that the pharmacist has been so engaged and that the pharmacist's service, training or education has terminated.

3. Except as provided in subsection 5 of this section, when applying for a renewal of the license as required by the provisions of this section, each licensed pharmacist shall submit proof
of the completion of at least fifteen thirty hours of board-approved continuing education courses during each twelve month biennial renewal period immediately preceding the date of the application for renewal of the license. The board shall prescribe the form to be completed. No license shall be renewed unless the holder thereof has complied with the provisions of this subsection.

4. The proof of completion of such continuing education shall be in such form as the board may require. The approved courses shall include those offered by correspondence, but the board shall approve all courses of instruction which may be used to satisfy the education requirements of subsection 3 of this section.

5. Each licensed pharmacist may, instead of submitting proof of the completion of the required continuing education courses, apply for an inactive license at the time the pharmacist makes application for the renewal of the pharmacist’s license and pay the required renewal fee. An inactive license shall then be issued, and may be renewed biennially. While the inactive license is in effect the pharmacist shall not practice pharmacy. The inactive license may be changed to a regular license without other examination whenever the pharmacist submits proof of the completion of the total number of continuing education courses required for each biennial renewal period since the pharmacist was last licensed on an active basis.


Prior revisions: 1929 § 13145; 1919 § 4717; 1909 § 5769
DRAFT Language – Proposal # (Charitable Pharmacies)

Equipment required--manner of operation of pharmacy--compliance with state and federal laws required.

338.250. 1. No pharmacy shall be licensed under the provisions of this chapter unless it is equipped with proper pharmaceutical equipment and reference manuals, so that the practice of pharmacy may be accurately and properly performed. The board shall prescribe the minimum of technical equipment which the pharmacy shall at all times possess. Such requirements may vary, depending upon the population served, but shall be consistently and uniformly enforced. No permit shall be issued or renewed for the operation of a pharmacy unless the pharmacy shall be operated in a manner and according to the rules and regulations prescribed by law and by the Missouri board of pharmacy with respect to obtaining and maintaining such a permit. Any pharmacy that receives or possesses drugs or devices shall be held responsible for compliance with all laws within this chapter as well as state and federal drug laws on all drugs received or possessed, including but not limited to drugs and devices received or possessed pursuant to a consignment arrangement.

2. The Board may issue a temporary charitable pharmacy permit to a Missouri licensed pharmacy or pharmacist to operate a charitable pharmacy at a specified physical location, provided a temporary charitable permit shall not be issued for more than a seven (7) day period and may not be renewed or reissued unless otherwise authorized by the Board.

3. The Board shall promulgate rules to implement the provisions of this section. Any rule or portion of a rule, as that term is defined in section 536.010, that is created under the authority delegated in this section shall become effective only if it complies with and is subject to all of the provisions of chapter 536 and, if applicable, section 536.028. This section and chapter 536 are nonseverable and if any of the powers vested with the general assembly pursuant to chapter 536 to review, to delay the effective date, or to disapprove and annul a rule are subsequently held
unconstitutional, then the grant of rulemaking authority and any rule proposed or adopted after August 28, 2018, shall be invalid and void.

338.055. 1. The board may refuse to issue any certificate of registration or authority, permit or license required pursuant to this chapter for one or any combination of causes stated in subsection 2 of this section or if the designated pharmacist-in-charge, manager-in-charge, or any officer, owner, manager, or controlling shareholder of the applicant has committed any act or practice in subsection 2 of this section. The board shall notify the applicant in writing of the reasons for the refusal and shall advise the applicant of his or her right to file a complaint with the administrative hearing commission as provided by chapter 621.

2. The board may cause a complaint to be filed with the administrative hearing commission as provided by chapter 621 against any holder of any certificate of registration or authority, permit or license required by this chapter or any person who has failed to renew or has surrendered his or her certificate of registration or authority, permit or license for any one or any combination of the following causes:

   (1) Use of any controlled substance, as defined in chapter 195, or alcoholic beverage to an extent that such use impairs a person’s ability to perform the work of any profession licensed or regulated by this chapter;

   (2) The person has been finally adjudicated and found guilty, or entered a plea of guilty or nolo contendere, in a criminal prosecution under the laws of any state or of the United States, for any offense reasonably related to the qualifications, functions or duties of any profession licensed or regulated under this chapter, for any offense an essential element of which is fraud, dishonesty or an act of violence, or for any offense involving moral turpitude, whether or not sentence is imposed;

   (3) Use of fraud, deception, misrepresentation or bribery in securing any certificate of registration or authority, permit or license issued pursuant to this chapter or in obtaining permission to take any examination given or required pursuant to this chapter;
(4) Obtaining or attempting to obtain any fee, charge, tuition or other compensation by fraud, deception or misrepresentation;

(5) Incompetence, misconduct, gross negligence, fraud, misrepresentation or dishonesty in the performance of the functions or duties of any profession licensed or regulated by this chapter;

(6) Violation of, or assisting or enabling any person to violate, any provision of this chapter, or of any lawful rule or regulation adopted pursuant to this chapter;

(7) Impersonation of any person holding a certificate of registration or authority, permit or license or allowing any person to use his or her certificate of registration or authority, permit, license, or diploma from any school;

(8) Denial of licensure to an applicant or disciplinary action against an applicant or the holder of a license or other right to practice any profession regulated by this chapter granted by another state, territory, federal agency, or country whether or not voluntarily agreed to by the licensee or applicant, including, but not limited to, surrender of the license upon grounds for which denial or discipline is authorized in this state;

(9) A person is finally adjudged incapacitated by a court of competent jurisdiction;

(10) Assisting or enabling any person to practice or offer to practice any profession licensed or regulated by this chapter who is not registered and currently eligible to practice under this chapter;

(11) Issuance of a certificate of registration or authority, permit or license based upon a material mistake of fact;

(12) Failure to display a valid certificate or license if so required by this chapter or any rule promulgated hereunder;

(13) Violation of any professional trust or confidence;

(14) Use of any advertisement or solicitation which is false, misleading or deceptive to the general public or persons to whom the advertisement or solicitation is primarily directed;

(15) Violation of the drug laws or rules and regulations of this state, any other state or the federal government;
(16) The intentional act of substituting or otherwise changing the content, formula or brand of any drug prescribed by written or oral prescription without prior written or oral approval from the prescriber for the respective change in each prescription; provided, however, that nothing contained herein shall prohibit a pharmacist from substituting or changing the brand of any drug as provided under section 338.056, and any such substituting or changing of the brand of any drug as provided for in section 338.056 shall not be deemed unprofessional or dishonorable conduct unless a violation of section 338.056 occurs;

(17) Personal use or consumption of any controlled substance unless it is prescribed, dispensed, or administered by a health care provider who is authorized by law to do so.

3. After the filing of such complaint, the proceedings shall be conducted in accordance with the provisions of chapter 621. Upon a finding by the administrative hearing commission that the grounds, provided in subsection 2 of this section, for disciplinary action are met, the board may, singly or in combination, assess an administrative civil penalty, require satisfactory completion of a continuing professional education program as the board may specify, censure or place the person named in the complaint on probation on such terms and conditions as the board deems appropriate for a period not to exceed five years, or may suspend, for a period not to exceed three years, or revoke the license, certificate, or permit. The board may impose additional discipline on a licensee, registrant, or permittee found to have violated any disciplinary terms previously imposed under this section or by agreement. The additional discipline may include, singly or in combination, an administrative civil penalty, require satisfactory completion of a continuing professional education program, censure, placing the licensee, registrant, or permittee named in the complaint on additional probation on such terms and conditions as the board deems appropriate, which additional probation shall not exceed five years, or suspension for a period not to exceed three years, or revocation of the license, certificate, or permit.
4. If the board concludes that a licensee or registrant has committed an act or is engaging in a course of conduct which would be grounds for disciplinary action which constitutes a clear and present danger to the public health and safety, the board may file a complaint before the administrative hearing commission requesting an expedited hearing and specifying the activities which give rise to the danger and the nature of the proposed restriction or suspension of the licensee's or registrant's license. Within fifteen days after service of the complaint on the licensee or registrant, the administrative hearing commission shall conduct a preliminary hearing to determine whether the alleged activities of the licensee or registrant appear to constitute a clear and present danger to the public health and safety which justify that the licensee's or registrant's license or registration be immediately restricted or suspended. The burden of proving that the actions of a licensee or registrant constitute a clear and present danger to the public health and safety shall be upon the state board of pharmacy. The administrative hearing commission shall issue its decision immediately after the hearing and shall either grant to the board the authority to suspend or restrict the license or dismiss the action.

5. If the administrative hearing commission grants temporary authority to the board to restrict or suspend the licensee's or registrant's license, such temporary authority of the board shall become final authority if there is no request by the licensee or registrant for a full hearing within thirty days of the preliminary hearing. The administrative hearing commission shall, if requested by the licensee or registrant named in the complaint, set a date to hold a full hearing under the provisions of chapter 621 regarding the activities alleged in the initial complaint filed by the board.

6. If the administrative hearing commission dismisses the action filed by the board pursuant to subsection 4 of this section, such dismissal shall not bar the board from initiating a subsequent action on the same grounds.

7. Any civil penalty imposed by the board under subsection 3 of this section shall not exceed two thousand five hundred dollars for each offense. Each day of a continued violation constitutes a separate offense, with a maximum penalty of twenty-five
thousand dollars. In determining the amount of penalty to be imposed, the Board may consider any of the following:

1. Whether the amount imposed will be a substantial deterrent to the violation;
2. The circumstances leading to the violation;
3. The severity of the violation and the risk of harm to the public;
4. The economic benefits gained by the violator as a result of noncompliance; and
5. The interest of the public.

8. Any disciplinary order imposing a civil penalty is subject to judicial review upon the filing of a petition under section 536.100 by any person subject to the penalty.

9. Failure to pay a civil penalty shall be grounds for denying, disciplining or refusing to renew or reinstate a license, registration or permit. If the penalty is not timely paid, the board may notify the attorney general. The attorney general may commence an action to recover the amount of the penalty, including reasonable attorney fees and costs. In such action, the validity and appropriateness of the final order imposing the civil penalty shall not be subject to review.

10. Penalties collected under this section shall be handled in accordance with Section 7 of Article IX of the Missouri Constitution. Such penalties shall not be considered a charitable contribution for tax purposes.