October 23, 2014

Texas State Board of Pharmacy
333 Guadalupe, Suite 3600
Austin, TX 78701

Attention: Allison Benz

Dear Members:

In response to the proposed changes to Class B Nuclear Pharmacy, I believe that all of the changes to 22 TAC §§291.52 – 291.54 should be rejected.

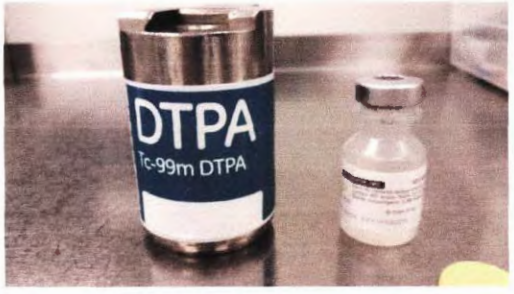
These changes do not clarify the requirements for compounding sterile non-radiopharmaceuticals. Sterile non-radiopharmaceuticals or sterile radiopharmaceuticals are injected into patients the same way sterile preparations are done in hospital pharmacies and home healthcare facilities. Whether they are radioactive or not is irrelevant to the safety of the patient, which I would hope is the ultimate goal of every practicing pharmacist. There are pharmacies that are Class B pharmacies that are compounding sterile radiopharmaceuticals as well as non-radiopharmaceuticals and doing so from raw materials to sterile to sterile transfers. The shields and delivery "pigs" (which are the way radiopharmaceuticals are delivered) are re-used over and over again. They are sometimes returned with blood inside them from uncapped, returned syringes. The sterility and cleanliness of these items cannot be over-emphasized. To remove the "non-radiopharmaceuticals from the sterile USP <797> requirements is a step backwards in pharmacy. Those preparations are the same type of preparations that hospitals draw up and dispense routinely. If they are not drawn up in a USP<797> cleanroom in the pharmacy they are drawn up at the bedside or nurses station and injected in a matter of minutes, these are done so under the guidelines of "immediate use" criteria. By this proposed change the non-radiopharmaceuticals discussed, if drawn by a Class B pharmacy, would be drawn under less than adequate standards of air quality and room testing. Also, most Class B pharmacies are not within any institution and the doses would have to be delivered to the facility. Depending on when the doses were drawn relative to when the "runs" are processed and delivered it could be as long as 6 to 8 hours after the dose was drawn. The "other agencies" that are referenced deal with the radiation exposure to employees and the public, as well as the safe transport of these

medications…..They have nothing to do with the sterility, stability, quality control or pharmaceutical regulations of these dispensed medications.

Every pharmacy, no matter the classification or location of the pharmacy, if they dispense medication to any individual within the borders of Texas, should be inspected by the board for compliance in all aspects of the law. The lack of inspections has allowed pharmacies to do business within the state of Texas but not uphold the standards set forth by the board and the Federal regulations (ie. USP <797>, and <795>). This lack of inspections has allowed pharmacies to dispense medications that have not been properly prepared and/or tested and therefore jeopardized the safety of patients.

Greater than 95% of the radiopharmaceuticals dispensed are injected into patients. Therefore, from a patient safety standpoint the USP <797> standard (which has been backed by the FDA in the DQSA) should be the bare minimum under which any sterile preparation should be prepared and dispensed. That does not differentiate between radioactive or non-radioactive, and does state that even sterile to sterile should be done in an ISO Class 5 environment within a ISO Class 7 buffer area and an Class 8 ante room.

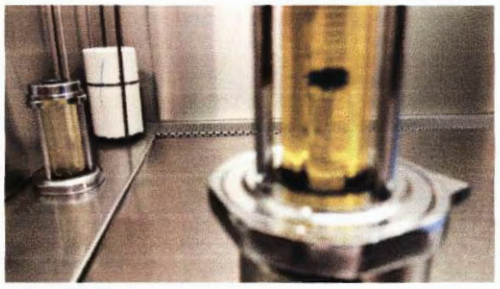
Attached are photos of the shields a nuclear pharmacy uses to compound kits and the requirements for shielding that do not allow for adequate checks for "floaties" or "inspection of the final preparation".



This is a picture of a vial shield used to compound "kits"

Looking down into an open shield to see there is no ability to visualize the contents after closing.

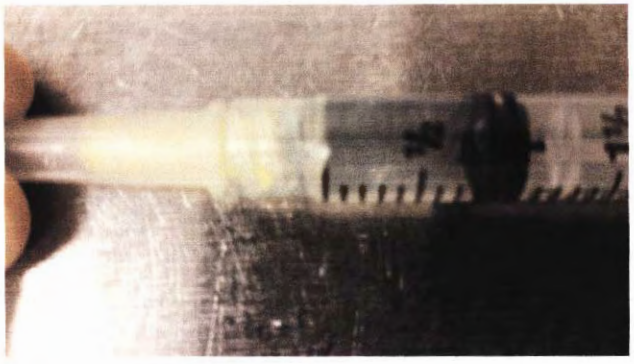
Shows a syringe inside of a syringe shield used to compound "kits"



Shows the syringe up close thru a syringe shield

L-block lead glass shield and dose calibrator used inside of a LFH

A "pig" used to transport doses to nuclear medicine clinics and departments for use in patients.



Syringe with a white contaminate in the syringe

The same syringe inside of a syringe shield with the picture taken directly over the syringe not looking through the leaded glass L-block, to show the difficulty of seeing contaminates through the required shielding. This helps emphasize the importance of using ALL engineering controls to limit the potential for contamination. (All USP <797> guidelines).

If there are any questions, please feel free to contact me at my email or phone number listed below.

Respectfully yours,

Byron Jay Ashworth RPh.
Radiation Safety Officer
USP<797> Expert Panel Member
GE Healthcare
Dallas, TX
214-689-8600
Bjay.Ashworth@gmail.com

-----Original Message-----
From: Thomas, Jane (GE Healthcare)
Sent: Tuesday, October 28, 2014 6:26 AM
To: Allison Benz
Subject: sterile compounding

October 28, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

RE: Proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies

There are no material differences between compounding sterile products, whether in the practice of retail, hospital, surgery, or nuclear pharmacy. USP <797> standards should apply to all pharmacies engaged in compounded sterile products. The Texas State Board of Pharmacy rule §291.133 is aligned with USP <797> standards and this rule should be applied and enforced across all licensed compounding nuclear pharmacies for all sterile compound preparations. Furthermore, all nuclear pharmacies should be inspected routinely to ensure patients in Texas receive consistent quality.

Proposed rule changes to sections §291.52 and §291.53 Nuclear pharmacy sterile compounded preparations with or without a radioactive component should have the same quality. I urge the TSBP to reject all of the proposed rule changes to sections §291.52 and §291.53.

Proposed rule change to section §291.54
Regular inspections are necessary to maintain the same quality across all nuclear pharmacies in Texas to better protect Texas patients. I urge the TSBP to approve the proposed rule change in section §291.54.

As a pharmacist in Texas, please include my comments for the proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies in the November Board Meeting.

Sincerely,

Jane Thomas, Pharm D
License #48138

-----Original Message-----
From: Haecker, Nathan (GE Healthcare)
Sent: Tuesday, October 28, 2014 7:27 AM
To: Allison Benz
Subject: Proposed rules change to §§291.52 - 291.54

October 28, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

Proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies

USP <797> standards should apply to all pharmacies engaged in compounded sterile products, whether in the practice of retail, hospital, surgery, or nuclear pharmacy. "Standards" should not be dependent on the title of practice. The Texas State Board of Pharmacy rule §291.133 is aligned with USP <797> standards to ensure that all patients receive the same quality product regardless of where it was compounded. If concessions to these standards start to be made for one mode of practice, it opens the door for others to follow. These rules were instituted to increase patient safety and should be applied across all licensed compounding nuclear pharmacies for all sterile compound preparations.

Proposed rule changes to sections §291.52 and §291.53 Nuclear pharmacy sterile compounded preparations with or without a radioactive component should have the same quality. I urge the TSBP to reject all of the proposed rule changes to sections §291.52 and §291.53.

Proposed rule change to section §291.54
Regular inspections are necessary to maintain the same quality across all nuclear pharmacies in Texas to better protect Texas patients. I urge the TSBP to approve the proposed rule change in section §291.54.

As a pharmacy technician in Texas, please include my comments for the proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies in the November Board Meeting.

Sincerely,
Nathan Haecker, CPhT
Texas Registration # 109134

October 23, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

As a nuclear pharmacist in Texas please include my comments for the proposed rules change to 22 TAC §§291.52 - 291.54 for Class B pharmacies in the November 4th Board Meeting.

Proposed Change (Opposed)
22 TAC §291.52, and §291.53
The Texas State Board of Pharmacy proposes amendments to §291.52, concerning Definitions; §291.53, concerning Personnel; and §291.54, concerning Operational Standards. The amendments to §291.52, if adopted, update the definitions. The amendments to §291.53, if adopted, clarify the requirements for compounding sterile non-radiopharmaceuticals.

Comments: All of the changes to sections 22 TAC §291.52 and §291.53 should be rejected. There is no difference between a sterile radiopharmaceutical and a sterile non-radiopharmaceutical. Radiopharmaceutical injectable sterile preparations are prepared in identical fashion as non-radiopharmaceutical/pharmaceutical injected sterile preparations. Nuclear (Class B) Pharmacies prepare between 0% to <1% of sterile non-radiopharmaceuticals and this is an effort to completely prevent Texas nuclear pharmacies from complying with §291.133 and ultimately <USP>797 compliance. Over 98% of radiopharmaceuticals are sterile injectable unit doses which are injected into human patients that are prepared in one location and sent out to many medical facilities in a given market. This accounts for thousands of sterile radiopharmaceutical preparations that are sent out each day by the thirty-six nuclear pharmacies in Texas.

The real truth is that radiopharmaceuticals are higher risk due to the extra shielding and reuse of lead lined syringe shields. These shields must be cleaned properly before they are recirculated for shipping radioactive sterile preparations. There are many other concerns that come from shipping sterile injectable products from a centralized nuclear pharmacy. In summary, the potential for cross contamination and outbreak of a microbial source from a single centralized nuclear pharmacy is very high. In 2004 a Maryland nuclear pharmacy infected 16 patients (14 men and 2 women) at three different health care facilities with Hepatitis C virus from a single preparation of technetium Tc-99m Sestamibi. See more at: http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=1857#sthash.Uc5Qazu6.dpuf

No other regulatory body besides the Texas State Board of Pharmacy is qualified to regulate <USP>797 compliance concerning the sterility, potency, and quality of pharmaceutical preparations prepared in a Texas licensed pharmacy. The other regulatory agencies over nuclear pharmacies are all concerned with radiation exposure, transportation and security with the focus mainly on public and occupational safety.

Proposed Change (Support)
22 TAC §291.54
The amendments to §291.54, if adopted, require nuclear pharmacies to be inspected prior to renewal.

Comments: This proposed change in Section 22 TAC §291.54 should be approved. Every pharmacy in the State of Texas should be inspected routinely. I am in full support of the change requiring an inspection upon renewal of Class B pharmacies. I believe the TSBP will see a huge discrepancy in quality between different suppliers of radiopharmaceuticals from Nuclear (Class B) pharmacies in Texas.

Summary

I am writing as a concerned Texas nuclear pharmacist with 17 years of experience in Texas and 20 years in the nuclear pharmacy industry. The regulation and the enforcement of radiopharmaceuticals must be performed by a qualified agency to protect patients in Texas. Several thousand Texans are injected with radiopharmaceuticals each day and those patients should receive a consistent high quality product. All sterile compounded preparations from a licensed pharmacy should have the same quality. There is no difference between the starting components for a sterile radiopharmaceutical preparation and a sterile non-radiopharmaceutical/pharmaceutical. Nuclear pharmacies are capable of complying with TAC 22 §291.133 and should be expected to maintain the same quality for all sterile preparations.

Please contact me if you would like to discuss further and if my schedule allows I plan to attend the November TSBP board meeting.

Sincerely,

Donald D. Warner, R.Ph.
License # 34285
709 Crested Butte Trail
Flower Mound, TX 75028
warners4ou@verizon.net

From: Finch, Christina (GE Healthcare)
Sent: Tuesday, October 28, 2014 1:58 PM
To: Allison Benz
Subject: proposed rule change

Dear Ms. Benz:

RE: Proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies

There are no material differences between compounding sterile products, whether in the practice of retail, hospital, surgery, or nuclear pharmacy. USP <797> standards should apply to all pharmacies engaged in compounded sterile products. The Texas State Board of Pharmacy rule §291.133 is aligned with USP <797> standards and this rule should be applied and enforced across all licensed compounding nuclear pharmacies for all sterile compound preparations. Furthermore, all nuclear pharmacies should be inspected routinely to ensure patients in Texas receive consistent quality.

Proposed rule changes to sections §291.52 and §291.53

Nuclear pharmacy sterile compounded preparations with or without a radioactive component should have the same quality. I urge the TSBP to reject all of the proposed rule changes to sections §291.52 and §291.53.

Proposed rule change to section §291.54

Regular inspections are necessary to maintain the same quality across all nuclear pharmacies in Texas to better protect Texas patients. I urge the TSBP to approve the proposed rule change in section §291.54.

As a pharmacist in Texas, please include my comments for the proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies in the November Board Meeting.

Sincerely,

Christina R. Finch, RPh
License # 43057
Pharmacy Manager
GE Healthcare
7920 Elmbrook Dr Ste 116
Dallas TX 75247

-----Original Message-----
From: Dang, Vu (GE Healthcare)
Sent: Tuesday, October 28, 2014 12:09 PM
To: Allison Benz
Subject: Nuclear Pharmacy USP 797 Compliance

Hello Ms. Benz,

I am a Board Certified radiopharmacist here in the state of Texas. I have been practicing for four years in various nuclear pharmacy settings including the nuclear medicine department at Brooke Army Medical Center in San Antonio, and GE Healthcare here in Dallas, TX. I am writing you today because I have been made aware of pending changes regarding Class B compliance laws pertaining to USP 797.

I want to inform you that although radiopharmaceuticals have little to no pharmacological effect and are extremely safe for patient use they are however, administered intravenously and sometimes intrathecally. In a very simplistic explanation, radiopharmaceuticals are compounded by adding a sterile radioactive solution to a sterile drug vial, often using normal saline as a diluent. Although the ingredients are sterile in form, it is imperative that the user practice strict aseptic technique. This process should also be done in an environment that is under constant control from various pathogens. Gamma radiation does not kill/inhibit microbial growth contrary to popular belief.

As such, it is my belief that the same rules that would apply to traditional compounding pharmacies should also apply to Class B pharmacies. By mandating that all Class B pharmacies comply with any and all USP 797 guidelines we would be protecting the thousands of patients in the state of Texas that are imaged/treated in nuclear medicine daily. We would be doing a serious disservice to the very patients we swore to treat and serve by allowing Class B radiopharmacies to operate with no regard for current USP 797 guidelines. Thank you for your time.

Vu Dang
Pharm.D., BCNP

GE Healthcare
Dallas, TX

October 28, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

RE: Proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies

All pharmacies that engage in the compounding of sterile products, whether in the practice of retail, hospital, surgery or nuclear medicine, should be required to abide by the standards set forth in USP <797>. These standards were instituted to improve the quality of product and to increase patient safety. The Texas State Board of Pharmacy rule §291.133 is aligned with USP <797> standards and this rule should be applied and enforced across all licensed compounding nuclear pharmacies for all sterile compound preparations, including radiopharmaceutical preparations. Furthermore, all nuclear pharmacies should be inspected routinely to ensure patients in Texas receive consistent quality.

Proposed rule changes to sections §291.52 and §291.53

Nuclear pharmacy sterile compounded preparations with or without a radioactive component should have the same quality. I urge the TSBP to reject all of the proposed rule changes to sections §291.52 and §291.53.

Proposed rule change to section §291.54

Regular inspections are necessary to maintain the same quality across all nuclear pharmacies in Texas to better protect Texas patients. I urge the TSBP to approve the proposed rule change in section §291.54.

As a pharmacy technician in Texas, please include my comments for the proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies in the November Board Meeting.

Sincerely,

M. Louise Haecker

Margaret Louise Haecker, CPhT
Texas Registration #109111

-----Original Message-----
From: Chu, Huy (GE Healthcare)
Sent: Wednesday, October 29, 2014 12:49 PM
To: Allison Benz
Subject: Proposed changes to Nuclear Pharmacy

October 29, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

RE: Proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies

There are no material differences between compounding sterile products, whether in the practice of retail, hospital, surgery, or nuclear pharmacy. USP <797> standards should apply to all pharmacies engaged in compounded sterile products. The Texas State Board of Pharmacy rule §291.133 is aligned with USP <797> standards and this rule should be applied and enforced across all licensed compounding nuclear pharmacies for all sterile compound preparations. Furthermore, all nuclear pharmacies should be inspected routinely to ensure patients in Texas receive consistent quality.

Proposed rule changes to sections §291.52 and §291.53 Nuclear pharmacy sterile compounded preparations with or without a radioactive component should have the same quality. I urge the TSBP to reject all of the proposed rule changes to sections §291.52 and §291.53.

Proposed rule change to section §291.54
Regular inspections are necessary to maintain the same quality across all nuclear pharmacies in Texas to better protect Texas patients. I urge the TSBP to approve the proposed rule change in section §291.54.

As a pharmacist in Texas, please include my comments for the proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies in the November Board Meeting.

Sincerely,

Huy Chu, PharmD

License # 49414

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

October 29, 2015

Re: Proposed rules change to 22 TAC §§291.52 - 291.54 for Class B pharmacies

Dear Ms. Benz:

As a member of 2005-2010 and 2010-2015 USP Compounding Expert Committee, please include my comments for the proposed rules change to 22 TAC §§291.52 - 291.54 for Class B pharmacies in the November 4th Board Meeting.

Proposed Change (Opposed) 22 TAC §291.52, and §291.53

The Texas State Board of Pharmacy proposes amendments to §291.52, concerning Definitions; §291.53, concerning Personnel; and §291.54, concerning Operational Standards. The amendments to §291.52, if adopted, update the definitions. The amendments to §291.53, if adopted, clarify the requirements for compounding sterile non-radiopharmaceuticals.

Comments: All of the changes to sections 22 TAC §291.52 and §291.53 should be rejected. According to USP Chapter <1> Injections: *"Parenteral articles are prepared scrupulously by methods designed to ensure that they meet Pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms. An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration."*

The only mechanism that the Texas Board of Pharmacy has to ensure that parenteral articles, be they radiopharmaceuticals or non-radiopharmaceuticals, to meet this compendial expectation is through robust state regulations that are modeled after USP Chapter <797> Pharmaceutical Compounding-Sterile Preparation. There is no difference between a sterile radiopharmaceutical and a sterile non-radiopharmaceutical. Radiopharmaceutical injectable sterile preparations are prepared in identical fashion as non-radiopharmaceutical injected sterile preparations.

Nuclear (Class B) Pharmacies as a whole prepare a very low percentage of sterile non-radiopharmaceuticals and this is an effort to completely exempt Texas nuclear pharmacies from complying with §291.133 and ultimately <USP>797 compliance which is designed to protect patients from receiving contaminated medication. Over 98% of radiopharmaceuticals are sterile injectable unit doses which are injected into human patients that are prepared in one location and sent out to many medical facilities in a given market. This accounts for thousands of sterile radiopharmaceutical preparations that are sent out each day by the thirty-six nuclear pharmacies in Texas.

It is critical to understand that radiopharmaceuticals are at higher risk of contamination due difficulty in achieving adequate vial septa disinfection, which are punctured dozens of times during the production of compounded doses, the extra lead shielding and reuse of lead lined syringe shields.

A study published by Weatherman, et. al.,[1] has shown that radiopharmaceuticals are not inherently antimicrobial and prone to contamination during handling and compounding. (See attached article) In the study, almost 1% doses showed evidence of contamination when tested. The ideal benchmark of contamination for aseptically prepared doses should be 0.1% and in a state where thousands of doses are dispensed daily, nuclear pharmacies are dispensing dozens of contaminated doses to patients. It is the duty of the Texas Board of Pharmacy to protect the citizens of the state from receiving contaminated injectable medication. No other regulatory body besides the Texas State Board of Pharmacy is qualified to regulate <USP>797 compliance concerning the sterility, potency, and quality of pharmaceutical preparations prepared in a Texas licensed pharmacy. The other regulatory agencies responsible for regulating nuclear pharmacies are concerned with other issues that include: radiation exposure, transportation and security with the focus mainly on public and occupational safety.

Proposed Change (Support) 22 TAC §291.54

The amendments to §291.54, if adopted, require nuclear pharmacies to be inspected prior to renewal.

Comments: This proposed change in Section 22 TAC §291.54 should be approved. Every pharmacy in the State of Texas should be inspected routinely. "People respect what others inspect." I am in full support of the change requiring an inspection upon renewal of Class B pharmacies. I believe the TSBP will see a significant discrepancy in quality between different suppliers of radiopharmaceuticals from Nuclear (Class B) pharmacies compared to other pharmacies providing compounded sterile preparation's in Texas. A national USP 797 Compliance Study conducted annually by CriticalPoint has shown that aseptic compounding practices in states that require compliance with USP Chapter <797> have a statistically significant higher compliance rate than in states that don't require compliance.

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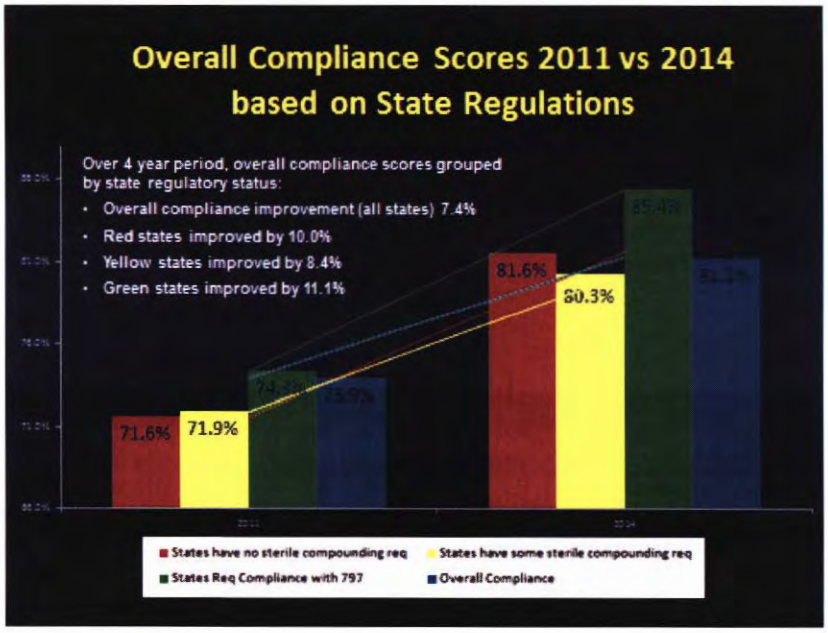
[1] Weatherman KD, Augustine S, Christoff J, and Galbraith W. Establishing Benchmark Rates of Microbial and Bacterial Endotoxin Contamination for Radiopharmaceuticals Compounded in Commercial Nuclear Pharmacy Settings. *Int J Pharm Compd. 2013; 17: 168-174.*



Summary

I am writing as a concerned pharmacist with 31 years of sterile compounding experience. The regulation and the enforcement of radiopharmaceuticals must be performed by a qualified agency to protect patients in Texas. Several thousand Texans are injected with radiopharmaceuticals each day and those patients should receive a consistent high quality compounded sterile preparation. All sterile compounded preparations from a licensed pharmacy should have the same quality. There is no difference between the starting components for a sterile radiopharmaceutical preparation and a sterile non-radiopharmaceutical/pharmaceutical. Nuclear pharmacies are capable of complying with TAC 22 §291.133 and should be expected to maintain the same quality for all sterile preparations.

I sincerely appreciate your consideration of this letter. Please contact me if you would like to discuss further.

Sincerely,

Eric S. Kastango. MBA, RPh, FASHP
President/CEO-Clinical IQ, LLC and CriticalPoint, LLC
235 Main Street, Ste 292
Madison, NJ 07940

235 Main Street, Ste 292
Madison, NJ 07940
(p) 973.765.9393 (f) 866.538.4783

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

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

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 apyrogenicity 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 2004[1] 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.

The authors' affiliations are: ***Kara D. Weatherman,*** *Purdue University College of Pharmacy, West Lafayette, Indiana;* ***Samuel Augustine****, Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska;* ***Jeffrey Christoff****, Ohio Northern University College of Pharmacy, Ada, Ohio;* ***Wendy Gailbraith****, University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma.*

nuclear pharmacies and nuclear medicine departments alike.

Per *USP* <797>, most radiopharmaceuticals are considered "low-risk" compounded preparations.[2] 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.[2] 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 [AUTHOR: NOTE] 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

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 endotoxinicity, 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, 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.[3] 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 Amebocyte 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 ^{99}Mo / ^{99m}Tc 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 ENDOTOXIN SAMPLES
Myoview	106	105[x]
Cardiolite	171	168*
Sestamibi (generic)	14	14
MDP (all brands)	168	163*[x]
HDP	67	67
MAA	172	170*[x]
Sulfur Colloid (SC)	147	141*[x]
$NaTcO_4$ (Lanth/Covid)	166	165[x]
Choletec	204	199*[x]
Mebrofenin (generic)	59	59
Hepatolite	38	38
DTPA	93	93
MAG- 3	83	83
Neurolite	8	8
Filtered SC	18	17[x]
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

TABLE 2. Sterility Testing Results.

RADIOPHARMACEUTICAL	NUMBER OF STERILITY SAMPLES	+ GROWTH STERILITY TEST
Myoview	106	0
Cardiolite	171	6
Sestamibi (generic)	14	0
MDP (all brands)	168	0
HDP	67	1
MAA	172	3
Sulfur Colloid (SC)	147	1
TcO4 (Lanth/Covid)	166	2
Choletec	204	0
Mebrofenin (generic)	59	0
Hepatolite	38	0
DTPA	93	0
MAG- 3	83	0
Neurolite	8	0
Filtered SC	18	0
DMSA	2	0
TOTALS:	**1516**	**13 (0.86%)**

TABLE 3. Distribution of Positive Sterility Tests.

RP KIT		TSB DAY 3	FTM DAY 3	TSB DAY 7	FTM DAY 7	TSB DAY 14	FTM DAY 14
Cardiolite	1	-	-	+	+	+	+
	2	-	-	+	+	+	+
	3	-	-	-	-	-	+
	4	-	-	-	-	-	+
	5	-	-	-	-	-	+
	6	-	-	-	+	-	+
HDP	1	-	-	-	+	-	-
MAA	1	-	+	-	+	-	+
	2	-	-	-	-	+	-
	3	-	+	-	+	-	+
Sulfur	1	-	-	+	-	+	-
Colloid							
$NaTcO_4$	1	-	+	-	+	-	+
	2	-	-	-	+	-	+

TABLE 4. Bacterial Endotoxin Testing Results.

RADIOPHARMACEUTICAL	NUMBER OF BACTERIAL ENDOTOXIN SAMPLES	+ GEL BACTERIAL ENDOTOXIN TEST
Myoview	105	0
Cardiolite	168	0
Sestamibi (generic)	14	0
MDP (all brands)	163	0
HDP	67	0
MAA	170	0
Sulfur Colloid (SC)	141	2
$NaTcO_4$ (Lanth / Covid)	165	0
Choletec	199	1
Mebrofenin (generic)	59	0
Hepatolite	38	0
DTPA	93	1
MAG-3	83	0
Neurolite	8	0
Filtered SC	17	0
DMSA	2	0
TOTALS:	**1492**	**4 (0.27%)**

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[4] and 2005.[5] 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 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.

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October 30, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

RE: Proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies

There are no material differences between compounding sterile products, whether in the practice of retail, hospital, surgery, or nuclear pharmacy. USP <797> standards should apply to all pharmacies engaged in compounded sterile products. The Texas State Board of Pharmacy rule §291.133 is aligned with USP <797> standards and this rule should be applied and enforced across all licensed compounding nuclear pharmacies for all sterile compound preparations. Furthermore, all nuclear pharmacies should be inspected routinely to ensure patients in Texas receive consistent quality.

Proposed rule changes to sections §291.52 and §291.53

Nuclear pharmacy sterile compounded preparations with or without a radioactive component should have the same quality. I urge the TSBP to reject all of the proposed rule changes to sections §291.52 and §291.53.

Proposed rule change to section §291.54

Regular inspections are necessary to maintain the same quality across all nuclear pharmacies in Texas to better protect Texas patients. I urge the TSBP to approve the proposed rule change in section §291.54.

As a pharmacy technician in Texas, please include my comments for the proposed rules change to §§291.52 - 291.54 concerning nuclear pharmacies in the November Board Meeting.

Sincerely,

Anthony M Gould, Jr.

Full Name: **Anthony Maurice Gould, Jr.** ***CPhT***
License # **130827**

Via FAX

October 29, 2014

Gay Dodson, Executive Director
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, TX 78701

RE: Comments on Agenda Item C.1.6, Tab 07
Amendments to 291.133 Concerning Nuclear Pharmacies Compounding Sterile Preparations

Dear Executive Director Dodson,

NuTech, Inc., a corporation operating three Class B pharmacies in Tyler, College Station, and Wichita Falls, TX appreciates the opportunity to make comments on the proposed amendments to the Texas Pharmacy Act and the Texas Occupations Code regarding Class B pharmacies. These comments represent issues that we feel need clarification and/or elaboration before adoption of this amendment. I plan to be in attendance at the meeting to answer any questions the Board might have regarding our comments.

NuTech appreciates the clarification afforded by the exclusion of Class B pharmacies from lines 34-36 of the proposed amendment. A clarification was indeed needed, as NuTech has considered its compounding of sterile products within the scope of the 291.133 as currently written since its adoption by the Board. NuTech agrees with the wisdom of excluding Class B pharmacies preparing sterile compounded preparations from this clause.

However, we believe that inclusion of the new statement in lines 34-36 prompts a need for other clarifications to the following ambiguities:

- Must a Class E-S pharmacy that also compounds sterile radioactive preparations for sale and/or distribution in Texas still comply with Class B rules? Must it comply with 291.133 in the compounding of its radioactive preparations?
- What specific characteristic(s) define(s) a "Class B" pharmacy and determine with which class of rules it must comply in specific circumstances? Should these terms not be defined within the text of the rules? Should not "Class B" pharmacy be defined in its own rules just as Class E is in its rules?

- How does the phrase "sterile non-radioactive preparation" from line 35 relate to the definition of a "radiopharmaceutical" as defined in 291.51, which includes "non-radioactive kits"? Could either an in-state or non resident pharmacy use the definition in 291.51 to make a case that is practicing as a Class B pharmacy in compounding these kits and therefore not within the scope of lines 34-36 and rule 291.133?
- **Most importantly, if Class B and Class E-S pharmacies compounding radioactive sterile preparations are exempt from the scope of 291.133(d)(1)C) and (D), which limit the compounding of copies of commercially-available products to specific circumstances and conditions, will that practice no longer be prohibited or limited since there is no reference to it in the Class B rules or any rules with which they must comply?**

We believe that without clarification, the effect of the simple deletion of Class B from the wording and the addition of the new wording in lines 34-36 will open the door to consequences and abuses that the Board did not foresee or intend. Unfortunately, we know from our experience that the nuclear pharmacy industry is not immune to pharmacies and pharmacists who search out ambiguities in the law and exploit them for financial gain.

Director Dodson, NuTech strongly believes that these questions must be addressed before the final adoption of this amendment to avoid the possibility of ambiguities that allow misinterpretation, manipulation, and exploitation of Board of Pharmacy rules in the future. We believe that clarifications should be in the text of the rules themselves rather than simply relying on a Board interpretation at some point in the future. We recommend that the adoption and implementation of this amendment be delayed until the ambiguities raised by these questions can be addressed.

We again thank you for the opportunity to comment on these proposals, and hope that the Board will consider them seriously. I can be reached at the NuTech office at 903-592-8635, on my cell at 903-530-2722, or by email at monty@nutechrx.com.

Yours in Pharmacy,

Monty Ingram, BCNP
Compliance Coordinator
NuTech, Inc.

October 29, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

As a nuclear pharmacist in Texas please include my comments for the proposed rules change to 22 TAC §§291.52 - 291.54 for Class B pharmacies in the November 4th Board Meeting.

Proposed Change (Opposed)
22 TAC §291.52, and §291.53
The Texas State Board of Pharmacy proposes amendments to §291.52, concerning Definitions; §291.53, concerning Personnel; and §291.54, concerning Operational Standards. The amendments to §291.52, if adopted, update the definitions. The amendments to §291.53, if adopted, clarify the requirements for compounding sterile non-radiopharmaceuticals.

Comments:

Currently the Texas State Board of Pharmacy is being asked to consider specific exemptions to current rules and standards concerning the compounding of sterile preparations. The exemptions/changes propose that nuclear pharmacies should be given special consideration when compounding sterile and non-sterile non-radiopharmaceutical preparations. I believe an effort is being made to rename/reclassify radioactive sterile radiopharmaceutical preparations to avoid following some of the current guidelines set by USP 797 and TSBP. I intend to question the validity of special treatment or exemptions based on the presence or non-presence of radioactivity. There are currently no compelling reasons for exempting radiopharmaceutical compounds from the standards set by both USP (797) and The Texas State Board of Pharmacy.

Radiopharmaceuticals are typically chemical combination of a non-radioactive molecule connected to a radioactive substance. The radioactive component of this mixture undergoes radioactive decay according to specific half-lives. Typical isotopes (radioactive substance) used in nuclear pharmacy have short half-lives ranging from seconds to hours. Please note that is decay does not reduce or change the volume of the liquid in a vial or unit dose syringe. The same amount of fluid will remain in the vial or syringe regardless of the half-life duration of the isotope. The idea that short half-lives preclude radiopharmaceuticals to sterility testing is at best ignorant or at worst intellectually dishonest.

Another common misconception is that the radioactivity (ionizing radiation) emitted from a radiopharmaceutical sterilizes, sanitizes, or reduces the population of potentially infectious pathogens. This is simply not true. A gamma ray (ionizing radiation) can kill an infectious pathogen, but the killing cannot keep pace with the exponential growth doubling of a bacterial population. It would be analogous to hiring an exterminator to kill 40, and only 40, ants in your backyard.

Currently the risk level of compounding of most radiopharmaceuticals is considered medium risk. This is based on the initial compounding instructions of adding 2 sterile ingredients (2 septum punctures) to a sterile vial of powdered radiopharmaceutical. In reality the septum of this vial is punctured at least 5 to 30 more additional times during the act of obtaining individualized doses and a sample for quality control analysis. The use of leaded glass syringe shields and lead/tungsten vial shields are used to protect the person from excess ionizing radiation, but can expose the syringes and vials to reduced first air flow and increased turbulent conditions. Most radiopharmaceuticals ingredients cannot include preservatives due to stability issues related to the chemistry involved. All of these factors are compelling reasons that the standards set by USP 797 should be a requirement when compounding radiopharmaceuticals.

Summary:

Nuclear pharmacy is a very specific and commonly misunderstood specialty of pharmacy practice. The rules and practice guidelines are set by a combination of regulatory enforcement by an impressively long list of regulatory agencies including but not limited to the NRC, DOT, DEA, pharmacy boards, DEA, and FAA. While this fact does lead to a complicated mixture of regulatory actions that are followed in the practice of nuclear pharmacy, very few of these agencies are concerned with the sterility of the products we produce. Please consider the above information while pondering the proposed changes.

Sincerely,

Ricky Aguilar, Pharm D, Nuclear Pharmacist
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GE Healthcare
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October 29, 2014

Allison Benz, R.Ph., M.S.
Director of Professional Services
Texas State Board of Pharmacy
333 Guadalupe Street, Suite 3-600
Austin, Texas 78701

Dear Ms. Benz:

RE: Proposed rules change to 22 TAC §§291.52 - 291.54 for (Class B) nuclear pharmacies

GE Healthcare is pleased to have the opportunity to provide Texas State Board of Pharmacy comments on the proposed rules change to 22 TAC §§291.52 - 291.54 for (Class B) nuclear pharmacies concerning sterile compounded radiopharmaceuticals oversight.

GE Healthcare, a unit of General Electric Company, has expertise in medical imaging, information technologies, medical diagnostics, patient monitoring systems, performance improvement, drug discovery, and biopharmaceutical manufacturing technologies.

Through our Life Sciences Core Imaging segment, the 31 GE Healthcare US radiopharmacies provide sterile compounded radiopharmaceuticals to healthcare practitioners. These products are primarily used for diagnostic imaging. GE Healthcare is also an FDA registered manufacturer of finished drug products pursuant to our approved NDA's.

GE Healthcare believes that radiopharmaceutical sterile compounding at nuclear pharmacies should be held to the same standards as all other practices of pharmacy for compounding. For adequate consumer protection, all states should align their regulations with, and enforce, current USP <797> standards across all licensed compounding pharmacies for sterile radiopharmaceutical products. From an aseptic processing standpoint no material differences exist between compounding sterile products, whether in the practice of retail, hospital, surgery, or nuclear pharmacy and the standards of USP <797> should apply to all pharmacies engaged in compounded sterile products.

Currently, GE Healthcare radiopharmacies do not compound higher-risk level preparations as defined by <USP>797. GE Healthcare pharmacies prepare only FDA approved sterile products and our activities are limited low and medium risk compounded sterile products. We

respectfully suggest that when establishing the context of the appropriate regulation for (Class B) nuclear pharmacies that the same quality standards be applied to sterile radiopharmaceutical and pharmaceutical compounded preparations. Due to the nature of radioactive material there are unique concerns for nuclear pharmacies and those unique concerns should be addressed in specific rules for nuclear pharmacy practice, but there should not be a complete exclusion from following pharmacy sterile compounding rules such as §291.133 that are in line with <USP 797> standards. We respectfully ask that for radiopharmaceutical compounded preparations as relating to nuclear pharmacy practice, Texas State Board of Pharmacy please consider the following five areas of concern for nuclear pharmacy practice.

1. **Specific Patient Names** - Radiopharmaceuticals are currently dispensed as compounded prescription preparations to nuclear medicine departments within clinics and hospitals for physician use and administration without specific patient names in most cases, and are administered for a specific time and activity. Radiopharmaceuticals decay rapidly after compounding due to the short half-life isotope utilized most in compounded radiopharmaceuticals. Therefore if administered too early, the dose would be above prescribed activity/dose and if too late a sub-diagnostic activity/dose. This approach helps prevent delays in procedures and decay of limited radioisotopes, particularly in situations such as when a patient is unavailable or schedule changes occur. If specific patient names are required under a definition of pharmacy compounding, it would be feasible radiopharmacy practice to obtain the specific patient name within 72 hours of delivery of the compounded sterile radiopharmaceutical to the site, this would allow for situations when doses are used under emergency situations or on weekends and holidays when facilities might not be open during regular business hours.

2. **Preparations Per Batch** - Due to the low milliliter volume dispensed for compounded sterile radiopharmaceutical preparations, the number of preparations obtained from one compounded sterile batch of an FDA approved radiopharmaceutical, prepared as specified in package insert (PI), can be as high as fifty. Rules should therefore allow for a maximum of fifty preparations from a single batch where products such as radiopharmaceuticals are involved (e.g. pharmacy bulk vial packaging for the preparation of unit dose radiopharmaceuticals).

3. **Wholesale Distribution Licensure** - One commercially available radiopharmaceutical is classified as a CII controlled substance and under current DEA regulations must only be distributed utilizing DEA Form 222. By regulation, this status prohibits dispensing of the product as a prescription under a pharmacy license. For this reason, all GE Healthcare radiopharmacies have a distributor and/or wholesaler license in addition to a pharmacy license. Nuclear pharmacies in compliance with DEA requirements for a particular drug in this situation should not be prohibited from being a distributor or wholesaler as that would prevent local distribution of such a product.

4. **Minor Variations** – GE Healthcare believes that the term “minor variations” in radiopharmaceutical compounding should be more clearly defined to provide guidance to compounding radiopharmacies. These minor variations from the manufacturers

package insert should accommodate a specific patient need. The addition of excipient products to extend shelf-life of a product should increase the risk category of compounded radiopharmaceuticals. The fractionations or splitting of a radiopharmaceutical kit and storage under any condition until the fractionated amount can be further compounded at a later time should be considered high-risk compounding.

5. **Unapproved Manufacturing** – The compounding of a radiopharmaceutical kit that appears to be the same as a manufactured product and is compounded in large batches that are distributed in large volumes through interstate commerce is essentially manufacturing drug products under the cover of pharmacy compounding. These pharmacies manufacture unapproved copies of commercially available FDA approved drugs in single dose and multi-dose formulations on a regional or national basis is not pharmacy compounding. Pharmacy rules should be in place to prevent these counterfeit copies of commercially available radiopharmaceutical kits.

Proposed rule changes to sections 22 TAC §291.52 and §291.53

Nuclear pharmacies are capable of complying with TAC 22 §291.133 and should be expected to maintain the same quality for all sterile preparations. There are no differences between the starting components for a sterile radiopharmaceutical preparation and a sterile pharmaceutical compounded preparation. All sterile compounded preparations with or without a radioactive component should have the same quality. GE Healthcare recommendation is that all proposed rule changes to sections 22 TAC §291.52 and §291.53 be rejected.

Proposed rule change in Section 22 TAC §291.54

Routine inspections are necessary to maintain the same quality across all practices of pharmacy in order to maintain the same quality for sterile compounded products. GE Healthcare recommendation is that the proposed rule change in Section 22 TAC §291.54 be approved.

We appreciate the opportunity to provide comments and input to the Texas State Board Pharmacy on compounding of sterile radiopharmaceuticals and can provide additional clarification if necessary.

Sincerely,

Rich DeVeau
GM Pharmacy Operations
Life Sciences Core Imaging
GE Healthcare