February 1, 2018

Steven Schierholt
Executive Director
State of Ohio Board of Pharmacy
77 South High Street, 17th Floor
Columbus, OH 43215

Re: Proposed Changes to Ohio Administrative Code Chapter 4729:7

Dear Director Schierholt:

On behalf of the undersigned medical associations, representing thousands of Ohio physicians, we are grateful for the opportunity to comment on the recently amended prescriber compounding rules.

First, we sincerely appreciate the pharmacy board's decision to revisit the compounding rules. The proposed changes to rules regarding exemptions to the requirement to obtain a Terminal Distributor of Dangerous Drugs (TDDD) License, and the separation of non-sterile compounding from sterile compounding have been positively received by physicians. However, there are several issues that were not addressed in the re-drafted rules and we would like to take this opportunity to reiterate many of our outstanding concerns.

While all physicians agree that compounding activities should be performed in the safest manner possible, it is important to note that the legislative and regulatory backlash against prescriber compounding began not as a result of physicians mishandling compounded medications, but rather as the result of the contamination of compounded products made by a compounding pharmacy. Throughout the several years of drafting and redrafting compounding rules in Ohio, the Ohio State Board of Pharmacy and the State Medical Board of Ohio have yet to provide data that shows Ohio physicians are not compounding properly in physician offices. Physicians are trained to respond and react to evidence-based findings and, as we have stated previously, physicians believe that in-office compounding activities in Ohio have been safely performed for decades and do not require such stringent regulations.

National Level Compounding Initiatives and Reviews

Many federal regulatory agencies and organizations are currently researching the best approaches to address physician compounding. The Ohio pharmacy board has largely relied on United States Pharmacopeia (USP) policies to dictate physician compounding in Ohio, but the Food and Drug Administration (FDA) has recently acknowledged a need to revise draft USP guidance documents related to compounding. The FDA plans to better define the circumstances under which drugs are being mixed and applied in a manner that creates negligible patient risk, and therefore wouldn't be subject to the same compliance policy under the agency's risk-based approach to implementing these requirements. They have also recognized the need for a balanced approach to regulations. Any attempts by the Ohio pharmacy board to set new policy prior to publication of these updated guidance documents may create an undue burden on physicians who routinely combine drugs and medicine in a manner that creates negligible patient risk.

The pharmacy board relies, in large part, on a 2012 Centers for Disease Control and Prevention (CDC) study[1] to demonstrate why these rules justify the adverse impact to physicians. The CDC study highlighted by the pharmacy board examines the safety of single use vials. The vast majority of in-office compounding is performed using MULTIPLE dose vials which are intended for multiple uses and have preservatives as well as manufacturer specific expiration dates for those reasons. In response to previous drafts of the compounding rules, the pharmacy board was provided with numerous studies[2]

[1] https://www.cdc.gov/injectionsafety/PDF/CDC-SDV-Position05022012.pdf

[2] *11 studies previously submitted to the pharmacy board in reference to compounding rules:*

1. Matsumoto AH1, Reifsnyder AC, Hartwell GD, Angle JF, Selby JB Jr, Tegtmeyer CJ. *Reducing the discomfort of lidocaine administration through pH buffering.* J Vasc Interv Radiol. 1994 Jan-Feb;5(1):171-5.
2. Pascuet E1, Donnelly RF, Garceau D, Vaillancourt R. *Buffered lidocaine hydrochloride solution with and without epinephrine: stability in polypropylene syringes.* Can J Hosp Pharm. 2009 Sep;62(5):375-80.
3. Johnson SM1, Saint John BE, Dine AP. *Local anesthetics as antimicrobial agents: a review.* Surg Infect (Larchmt). 2008 Apr;9(2):205-13. doi: 10.1089/sur.2007.036. Review.
4. Colaric KB1, Overton DT, Moore K. *Pain reduction in lidocaine administration through buffering and warming.* Am J Emerg Med. 2000 Mar;18(2):235-6.
5. Osaki T1, Osaki MH1, Osaki TH1, Sant'Anna AE1, Yu MC1, Hofling-Lima AL1. *Absence of bacterial or fungal growth in vials of reconstituted botulinum toxin type A after storage.* Aesthet Surg J. 2015 Feb;35(2):189-93. doi: 10.1093/asj/sju072.
6. Alam M1, Bolotin D, Carruthers J, Hexsel D, Lawrence N, Minkis K, Ross EV. *Consensus statement regarding storage and reuse of previously reconstituted neuromodulators.* Dermatol Surg. 2015 Mar;41(3):321-6.
7. Hexsel D, Rutowitsch MS, de Castro LC, do Prado DZ, Lima MM. *Blind multicenter study of the efficacy and safety of injections of a commercial preparation of botulinum toxin type A reconstituted up to 15 days before injection.* Dermatol Surg. 2009 Jun;35(6):933-9; discussion 940.

providing information on the safety, stability and storage recommendations related to compounded products. We recommend that the pharmacy board review these studies to better understand our interpretation.

The FDA, USP, and CDC are not the only federal entities who are exploring this issue, in fact, the United States House Energy and Commerce Health Subcommittee held a hearing on January 30th titled "Examining Implementation of the Compounding Quality Act."[3] While most of the testimony and subsequent questioning from members of the Subcommittee focused on compounding activities specific to outsourcing compounding facilities and pharmacies, the overarching theme of much of the hearing was a need for a balanced approach to compounding regulations. The hearing emphasized consideration of the risks of the compounding activity in relation to the setting in which the drugs are being dispensed and/or used when setting regulatory restrictions. In other words, the regulations that apply to large outsourcing facilities and pharmacies should not necessarily also apply to physician offices where the risks of patient harm are substantially lessened. Notably, the testimony also highlighted patient concerns about access. When regulations are too burdensome, making the procurement and production of compounded drugs difficult, that can ultimately affect access and patient care.

As the issue of prescriber compounding is very much in a state of exploration and review, and there are studies available that prove the safety of many of the compounding activities regulated under the board's proposed and current rules, we strongly suggest that the Ohio pharmacy board rescind all compounding rules until the national regulatory authorities have determined the appropriate level of oversight needed.

Specific Comments on Draft Rules

While we continue to assert that the draft and existing rules should be rescinded until further guidance has been published from national compounding experts and regulatory bodies, we offer the following comments regarding the draft rules.

Ohio Administrative Code 4729:7-1-01

While we are mostly satisfied with the definitions provided, we would like to provide the following suggested changes:

8. Larson PO, Ragi G, Swandby M, Darcey B, Polzin G, Carey P. *Stability of buffered lidocaine and epinephrine used for local anesthesia*, J Dermatol Surg Oncol. 1991 May;17(5):411-4.

9. Liu A, Carruthers A, Cohen JL, Coleman WP 3rd, Dover JS, Hanke CW, Moy RL, Ozog DM. *Recommendations and current practices for the reconstitution and storage of botulinum toxin type A.* J Am Acad Dermatol. 2012 Sep;67(3):373-8.

10. Melman D, Siegel DM. *Prefilled syringes: safe and effective*, Dermatol Surg. 1999 Jun;25(6):492-3.

11. Pate DA, Shimizu I, Akin R, Snodgrass K, Emrick A. *Safety of Prefilled Buffered Lidocaine Syringes With and Without Epinephrine.* Dermatol Surg. 2016 Mar;42(3):361-5. doi: 10.1097/DSS.0000000000000624.

[3] https://energycommerce.house.gov/hearings/examining-implementation-compounding-quality-act/

(A)(3)

This definition of compounding includes “reconstituting”. While a very limited number of sole shareholder physicians will be exempt from obtaining a TDDD for reconstituting medications, under the draft rules, they will be held to the USP guidelines for reconstituting medications.

There appears to be differing opinions at the federal level over whether reconstitution should be included in the definition of compounding:

> **FDA Definition** [4]
>
> “combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. “**Compounding does not include mixing, reconstituting,** or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling"
>
> **USP Definition**[5]
>
> The preparation, mixing, assembling, altering, packaging, and labeling of a drug or drug-delivery device” **Specifically includes: “Reconstitution** or manipulation of commercial products that may require the addition of one or more ingredients.”

Due to the uncertainty surrounding the definition on a national level, and the need for additional investigation over whether reconstitution needs to be held to the same standard of other compounding activities, we suggest that the pharmacy board remove the word “reconstituting” from section (A)(3). This suggestion is in accordance with the board’s current compounding rules that exempt the reconstitution of non-sterile and sterile compounding drugs.

(A)(8)

We suggest that the board consider defining “Immediate-Use” as used in proposed rule 4729:7-3-03. Section (A)(8) defines “immediate administration” and we feel that, due to the similar terminology, adding an “immediate-use” definition would help alleviate any possible confusion.

(A)(9)

We suggest the following amendment to the definition of “non-sterile compounded drug” in order to better define what activities constitute non-sterile compounding:

> “Non-sterile compounded drug” means a dangerous drug preparation intended to be non-sterile. *This definition includes, but is not limited to, the production of solutions, suspensions, ointments and creams, powders, suppositories, capsules, and tablets.*

[4] FDA FAQ on compounding published 10/06/2015 3. [21 USC 321 (k) and (m)].

[5] USP <795> Pharmaceutical Compounding-Nonsterile Preparations

Ohio Administrative Code 4729:7-3-01

While we appreciate the board's attempt to exempt certain providers from the requirement to obtain a TDDD license, we reiterate our previous position that certain, lower-risk compounding procedures should be exempt as well. The following compounding procedures have been identified by physicians as procedures that have been safely performed in physician offices for decades with no evidence of patient safety risks:

- Diluting prescription drugs with sterile saline for injection based on physician's clinical judgement and adjusted to meet the patient's need.
- Tumescent anesthesia.
- Buffering lidocaine with epinephrine and sodium bicarbonate for in-office surgical procedures.
- Diluting steroid with lidocaine or saline for cyst, joint or scar injection.
- Lidocaine mixed with Rocephin to decrease the injection pain.
- Diluting or creating allergens for injection or skin testing.
- Mixing of Albuterol/Atrovent in one nebulizer treatment to form a duoneb.

A recent (2016) study[6] examined the *"Safety of Prefilled Buffered Lidocaine Syringes With and Without Epinephrine".* This study found that prefilled lidocaine syringes are not subject to bacterial or fungal growth after being stored for 4 weeks and refilled syringes of lidocaine remain safe to use for up to 4 weeks. The study recommends that any current regulations placed on the disposal of these solutions should be revisited. This study reiterates what physicians in Ohio already know. There are many lower-risk compounding activities that should not be subject to additional oversight by the pharmacy board.

Ohio Administrative Code 4729:7-3-02 (B)

As stated above, we feel that the board should not place overly burdensome USP 797 regulations on physicians who compound lower-risk sterile drugs. Complying with the requirements included in USP 797 have the potential to drive up the cost of patient care, either due to the requirement to purchase expensive equipment or the need to have compounded medication prepared at a compounding pharmacy. It is well known that medications compounded at off-site pharmacies are considerably more expensive for patients than medications compounded on-site. In addition, USP 797 is currently under review, and with the appointment of experts to the USP compounding workgroup who are Dermatologists, we expect significant revision.

Ohio Administrative Code 4729:7-3-03

While we appreciate the board's decision to retain the immediate-use exception, many physicians feel that the 6-hour time frame should not apply to every sterile non-hazardous compounding activity. As previously stated, the board should exempt several lower-risk compounding procedures from the 6-hour requirement and allow those procedures to be performed in accordance within the prevailing, evidence-based, standard of care. As these lower-risk procedures have been safely performed in physician offices without harm to patients, physicians should be able to continue practicing without being subject to an unjustified 6-hour time frame. Physicians would be bound by the beyond-use date on the manufacturer's label. If a beyond-use date does not exist, the compounded drug products could only be used for six hours following preparation.

[6] https://www.ncbi.nlm.nih.gov/pubmed/26859654

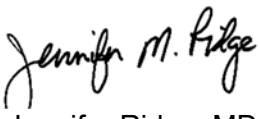
Ohio Administrative Code 4729:7-3-05

Physicians appreciate the reasoning behind the pharmacy board's record keeping rule. However, this rule places an unnecessary administrative burden on physician offices. Physicians are already required to follow OAC 4729-9-22, Records of Dangerous Drugs. We suggest lessening the requirement by requiring physicians to keep a log of medications that were compounded in the patient's medical record which includes the lot numbers so that physicians can easily contact affected patients in the event of a recall.

We appreciate the opportunity to provide comments on the pharmacy board's amended compounding rules. If you have any questions, Jennifer Hayhurst, OSMA's Director of Regulatory Affairs, will be acting as the coordinator for our groups. Ms. Hayhurst can be reached at 614-527-6766 or via email at jhayhurst@osma.org

Sincerely,

Robyn F. Chatman MD, MPH
President
Ohio State Medical Association



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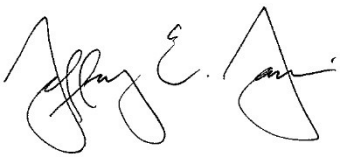

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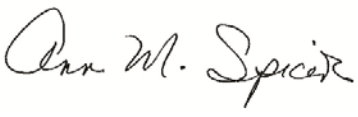

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