THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

January 26, 2018

Claudette E. Dalton, MD
Chair, Committee on Ethics and Professionalism
Federation of State Medical Boards
400 Fuller Wiser Road, Suite 300
Euless, TX 76039

Re: Position of the Federation of State Medical Boards: Compounding of Medications by Physicians

Dear Dr. Dalton:

The Pew Charitable Trusts is pleased to offer comments on the position statement of the Federation of State Medical Boards (FSMB) regarding Compounding of Medications by Physicians.[1] Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including that of compounded drugs.

Compounded drugs can be an important tool for physicians treating patients whose medical needs cannot be fulfilled by FDA-approved products. However, as the draft FSMB statement acknowledges, patients have suffered serious adverse events linked to contaminated and substandard compounded drugs (lines 13-14). In 2012-13, the nation suffered its worst known public health crisis associated with compounded drugs. Seventy-six people died and approximately 778 individuals in 20 states were stricken with meningitis or other infections. While this was the largest outbreak of infections associated with compounded drugs, there have been many other instances – resulting from compounding in a wide variety of settings – where compounded drugs have harmed or killed patients.[2] As written, FSMB's statement may suggest that outsourcing facilities have been the only source of adverse events (lines 13-14); alterations to clarify that outsourcing facilities, pharmacies, and physician compounders have all been sources of safety concerns would more accurately convey the health risk at stake.

FSMB has taken an important and welcome step in crafting a position statement that recognizes the important roles physicians play as prescribers, purchasers, and compounders. By choosing compounded medications only when clinically necessary, purchasing compounded drugs from high-quality suppliers

[1] Federation of State Medical Boards, Committee on Ethics and Professionalism, "Position of the Federation of State Medical Boards: Compounding of Medications by Physicians" (draft, Jan. 2018), https://www.fsmb.org/Media/Default/PDF/For_Comment_Draft_Position_Statement_on_Physician_Compounding.pdf.
[2] The Pew Charitable Trusts, "U.S. Illnesses and Deaths Associated with Compounded Medications or Repackaged Medications, 2001-17" (2017), http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/us-illnesses-and-deaths-associated-with-compounded-medications-or-repackaged-medications.

whenever possible, and adopting rigorous quality processes when they must compound drugs themselves, physicians can have a meaningful impact on improving the quality of compounded drugs and ensuring the safety of patients who need them.

Physicians as Prescribers of Compounded Drugs

Compounded drugs are inherently higher-risk than FDA-approved products because of differences in the ways that they are tested and made. Compounded drugs have not undergone FDA premarket review for safety, effectiveness, and quality, and they lack a premarket inspection and finding of manufacturing quality. Thus, as the FSMB draft statement contemplates, compounded drugs should only be used to meet a patient's specific medical need (lines 28-29) that cannot be met by FDA-approved drugs (lines 57-59).

The clinical need supporting use of a compounded medication should be documented in the medical records (lines 45-46), and may also need to be documented elsewhere to support regulatory requirements. Federal and state authorities responsible for overseeing the production of compounded drugs may, in some circumstances, need providers to verify the need for the compounded product. For example, restrictions that prevent traditional compounders from producing drugs that are "essentially a copy" of FDA approved drugs do not apply where that drug produces a "significant difference" for the patient.[3] Similar restrictions for outsourcing facilities do not apply if the drug produces a "clinical difference" for the patient,[4] and outsourcing facilities may only compound from bulk substances when there is a "clinical need" to do so.[5] It is appropriate for physicians to make these clinical determinations, and thus physicians should keep records of these determinations as required to ensure compliance with applicable law. To support regulators' efforts to advance patient safety, FSMB's statement should acknowledge the role that physicians may need to play in documenting the need for compounded drugs, as required by those authorities.

The combinations of ingredients in compounded products are not required to be tested for safety or effectiveness, and thus may expose patients to unknown risks. FSMB's draft statement appropriately indicates that physicians must limit the active ingredients in prescribed compounded drugs to include only those that are essential (lines 44-45), and not include unnecessary substances (lines 46-47). Physicians will be more able to limit patients' exposure to unnecessary risks by using compounded drugs only when required and not using unnecessary ingredients, and thus only exposing patients to these unapproved drugs when the additional risks are justified by the circumstances.

Significantly, FSMB's draft statement addresses reimbursement, and is clear that physicians should not add or request unnecessary substances in order to ensure higher reimbursement (lines 46-48). It would be helpful for the statement to also make the related point that compounding is not a safe solution to

[3] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353a(b)(2).
[4] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353b(d)(2).
[5] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353b(a)(2)(A)(i). An exception to this restriction on compounding from bulk ingredients applies if the drug compounded from the bulk drugs substance is in shortage. Ibid. at (ii).

high drug prices.[6] It is important that the drugs physicians need be available at reasonable prices, but undermining the approval process by supporting a market for compounded drugs that compete with approved products exposes patients to additional and unnecessary risk and is not in their best interest.

Physicians as Purchasers of Compounded Drugs

Different quality standards apply to different types of compounding. When pharmacies or physicians prepare compounded drugs for individual patients pursuant to a prescription, they are subject to state standards,[7] and to Federal prohibitions against making drugs under insanitary conditions.[8] Office stock products carry distinct risks for patients because rather than being used immediately, they are often stored for a period of time before use, which increases the opportunity for any contaminants to grow to dangerous levels. Also, these drugs are frequently produced in bulk – sometimes at significant scale – multiplying the potential public health consequences of any error. To mitigate these risks, as FSMB's draft statement recognizes, federal law makes outsourcing facilities subject to quality standards similar to those that apply to approved drugs: current Good Manufacturing Practices (cGMP) (lines 54-57).

We applaud FSMB for recognizing that by prioritizing the purchasing of quality drug products, physicians make an impact on patient safety and the compounding industry. Because outsourcing facilities are required to comply with cGMP, physicians improve patients' ability to access quality compounded drugs by developing relationships with outsourcing facilities (lines 52-54). As the FSMB statement notes, physician compliance with Federal and state laws regarding the compounding and dispensing of drugs is a critical way physicians can help ensure the safety of compounded drugs (lines 61-63). By only purchasing legal supplies of the compounded drugs physicians must keep on hand, physicians both protect their patients and support the development of the outsourcing facility sector as a safe supplier of compounded office stock drugs.

Physicians as Compounders

Patients have been harmed by drugs improperly compounded in physician office settings. For example, 41 patients developed septic arthritis when a private outpatient practice in New Jersey compounded intra-articular injections in a manner that violated recommended infection prevention practices,[9] and twelve oncology patients in Illinois contracted bacterial bloodstream infections from parenteral infusion

[6] The Pew Charitable Trusts, "Compounding is Not a Safe Solution to Rising Drug Prices" (2016), http://www.pewtrusts.org/en/research-and-analysis/analysis/2016/09/28/compounding-is-not-a-safe-solution-to-rising-drug-prices.

[7] Most states have adopted standards established by the U.S. Pharmacopeial Convention. USP chapters <797> and <795> apply, respectively, to pharmacy compounding of sterile and nonsterile preparations, and chapter <800> to the compounding, handling, and administration of drugs that present physical or health hazards.

[8] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 351(a)(2)(A).

[9] Kathleen Ross et al., "Outbreak of Septic Arthritis Associated with Intra-Articular Injections at an Outpatient Practice — New Jersey, 2017," *Morbidity and Mortality Weekly Report* 66, no. 29 (2017): 777-779, http://dx.doi.org/10.15585/mmwr.mm6629a3.

products that were exposed to a contaminated sink.[10] Thus, to avoid exposing patients to harm, physicians who engage in (or supervise) compounding must: 1) limit compounding to circumstances where it is necessary; 2) have knowledge, and ensure their staff have knowledge, of applicable laws and quality processes; 3) comply with standards designed to ensure quality; and 4) submit to appropriate oversight of compounding activity.

Physicians should engage in compounding only when necessary for patient care

FSMB's proposed framework properly recognizes that compounding should not be a physician's first choice. Physicians should only compound drugs when no FDA-approved options are available to the patient (lines 57-59), and, where possible, should purchase from outsourcing facilities (lines 53-54). The FSMB draft statement also appropriately encourages physicians to limit compounding to necessary volumes (lines 61- 62). To protect patient safety, physicians must only make compounded drugs for their own patients – not for other providers' patients (lines 29-31), and must only do so for individual patients when a specific need arises (line 29). Also, to minimize the risk of contamination, physicians must not compound large quantities of drugs in anticipation of patients who exhibit a particular set of symptoms or for retail sale (lines 32-33) or engage in more than limited quantities of anticipatory compounding (lines 40-42).

Physicians and their staff must have knowledge of applicable laws and quality standards

To protect patient safety, physicians who engage in compounding must comply with Federal and state laws (lines 62-63) and with the quality standards established by the U.S. Pharmacopeia (lines 66-67). Physicians are not only responsible for knowing the law and appropriate quality standards themselves, but must also ensure that staff know what is expected of them (lines 31-32, 69-72). It would improve FSMB's draft statement to explicitly acknowledge that although physicians and other traditional compounders are primarily regulated by the states, they are also subject to Federal restrictions against compounding under insanitary conditions and thus should be aware of Federal guidance in addition to state law and USP standards.

Physicians should employ proper technique to prevent contamination and other errors

Compounding conditions and practices must be designed to prevent contamination. FSMB's draft statement includes several directives that will help physicians minimize the risk of contamination. For example, the statement expresses a preference that physicians limit themselves to non-sterile compounding, and notes that when physician compounding of sterile drugs best serves the patient's medical needs, physicians must employ aseptic techniques (lines 61-65). Patient harm can be minimized by disposing of ingredients and final products when the "By Use Date" (BUD) indicates the products have expired (lines 20-22).

[10] BR Yablon et al., "Outbreak of Pantoea agglomerans Bloodstream Infections at an Oncology Clinic-Illinois, 2012-2013," *Infection Control & Hospital Epidemiology* 38, no. 3 (2017): 314-319, http://dx.doi.org/10.1017/ice.2016.265.

Contamination is not the only potential cause of adverse events. Super potent drugs – those with too much of an active ingredient – can also lead to patient harm or death. Thus, the implementation and stringent enforcement of protocols that ensure ingredients are added in the proper proportions is essential (lines 23-25).

In some circumstances, technique alone will be insufficient to prevent contamination or error. FSMB's statement should indicate that physicians who engage in compounding must commit to ensuring that they have all equipment and materials needed to comply with applicable standards, and that their facilities are adequate to meet physical space requirements. Thus, for example, if a physician chooses to engage in compounding that must be performed under a hood per USP standards, it is important that the physician invest in that equipment. Physicians without the capacity to meet applicable standards should seek alternative sources for compounded drugs.

Some exceptions to otherwise applicable standards apply to physicians, including, for example, when products are compounded for immediate use.[11] It would improve FSMB's statement to indicate that physicians operating under exceptions to otherwise applicable law and standards should document the conditions making the exception appropriate. For example, physicians who only compound under immediate use provisions, and thus do not obtain equipment that would be necessary for compounding drugs that are not administered immediately, should have clear written procedures for labeling drugs and ensuring their use or disposal within the appropriate timeframe.

Physicians should submit to appropriate oversight of compounding activity

All compounders – regardless of setting – should be subject to inspection to ensure compliance with applicable law and regulation. Site inspections are the most important tool states use to assess compliance with laws and regulations on compounding, whether in a community pharmacy, specialty pharmacy, or hospital setting. An advisory committee of state pharmacy regulators that Pew convened in 2014 recommended, as one of its best practices, that states inspect sterile compounding facilities annually and non-sterile compounders every two years. As state medical boards do not typically inspect compounding practices within physician offices, Pew applauds FSMB for acknowledging the importance of working closely with state boards of pharmacy to close regulatory gaps (lines 80-82). It would be helpful for FSMB's statement to explicitly indicate that physicians who engage in compounding must submit to inspection by relevant authorities, which may include boards of pharmacy as well as the Food and Drug Administration.

[11] An exemption to USP <797> standards permits the compounding of low-risk sterile drug products intended for immediate use. United States Pharmacopeial Convention, "General Chapter <797> Pharmaceutical Compounding – Sterile Preparations." Also, FDA recently released a plan indicating that it intends to define circumstances under which compounding creates "negligible" risk and thus would be exempted from insanitary conditions requirements. U.S. Food and Drug Administration, "2018 Compounding Policy Priorities Plan," accessed Jan. 24, 2018, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm.

Thank you for your efforts to protect patient safety by helping to ensure that compounding activity is held to standards appropriate to the level of risk. As you continue to refine your position, please feel free to contact Elizabeth Jungman at The Pew Charitable Trusts at ejungman@pewtrusts.org or (202) 540-6443.

Sincerely,

Elizabeth Jungman
Director, Public Health Programs
The Pew Charitable Trusts