

December 10, 2018

BY ELECTRONIC SUBMISSION: www.regulations.gov
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA draft Memorandum of Understanding regarding distributions of compounded drug products (Docket No. FDA-2018-N-3065)

Dear Sir or Madam:

The Pew Charitable Trusts is pleased to offer comments on the revised Draft Memorandum of Understanding (MOU) the FDA issued on September 7, 2018. Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including pharmaceutical compounding.

Since the publication of the FDA's 1992 Compliance Policy Guide, interstate distribution of compounded drugs has been one of a set of factors that is considered when seeking to identify facilities that exceed the scope of traditional compounding.¹ The Food and Drug Administration Modernization Act of 1997 first established the FDA/State MOU mechanism to address interstate distribution of "inordinate amounts" of compounded drug products. That legislation created a choice: a drug could either be compounded in a state that enters into an MOU with the FDA that "addresses the distribution of inordinate amounts of compounded drug products interstate" and "provides for appropriate investigation" of complaints from interstate recipients of those products, or the compounder would not be allowed to dispense or distribute compounded drugs out of state in quantities that exceed 5 percent of its total prescription orders. This provision was subsequently retained when Congress updated federal compounding law through the Drug Quality and Security Act in 2013.

The FDA's proposal is a significant departure from prior drafts, which would have limited the volume of compounded drugs that could flow across state lines. As we discuss in our comments below, the proposed MOU trades limitations on the volume of compounded drugs shipped interstate for better information about those shipments. While this tradeoff could facilitate oversight by encouraging states to better understand compounding activity within their borders and providing the FDA with information necessary to prioritize inspections, the prospect of unlimited volumes of compounded drugs crossing state lines makes robust oversight critical. If states cannot provide this oversight, in general or for specific groups—like physicians—the proposed MOU will not fill its statutory role in protecting patients from the risks attendant to significant distribution of inordinate amounts of compounded drug products.

¹ Food and Drug Administration Compliance Policy Guide 7132.16. 1992.

The proposed MOU will allow unlimited interstate distribution of compounded drug products, increasing the risk of harm if oversight is inadequate

The proposed MOU would require states that enter into the MOU to identify compounders in their jurisdiction (using surveys, reviews of compounding records during inspections of compounding pharmacies, or other mechanisms available to the State) that are distributing inordinate amounts of compounded drugs interstate and inform the FDA about those compounders. However, importantly, the proposed MOU does not require states to take action to limit the interstate distribution of inordinate amounts of compounded drug products by these compounders. This is a significant change from prior iterations of the MOU, which set a limit on interstate distribution of compounded drugs in states that signed it. Although the limit was higher than the 5 percent cap for compounders in states that do not sign the MOU, it would nevertheless have set hard limits on the interstate distribution of compounded drugs. The proposed MOU, in effect, will allow pharmacies and physicians to produce and distribute an unlimited volume of compounded drugs interstate under quality standards that are set and enforced primarily by states.

By shifting away from restricting the volume of compounded drugs that can be shipped across state lines, and thus permitting unlimited sales from state-regulated facilities, the proposed MOU inevitably increases the risk of harm if oversight is inadequate. As Pew and the National Association of Boards of Pharmacy recently reported, between 2015 and 2018, the number of states conducting annual inspections of sterile compounding pharmacies fell from 26 to 22.² If regulators in one state fail to identify dangerous lapses in adherence to compounding quality standards, patients nationwide can be harmed. The most widely known example of this was the 2012-2013 fungal meningitis outbreak, which sickened at least 793 people and killed more than 70.³ While the source of the outbreak was traced to a single Massachusetts compounding pharmacy, all the patients that were harmed were located outside of the state. Since that time, there have been other cases of serious illness, injury, and death associated with contaminated compounded drug products shipped interstate.⁴

Allowing unlimited interstate distribution increases the potential for harm to the public. Pew recognizes, however, that there are practical challenges with implementing strict limits on interstate distribution. Setting such limits would significantly affect or even shut down established businesses and would potentially expose the FDA to legal challenges. That in turn could compromise the agency's ability to implement the MOU provisions, including the 5 percent restriction, because the FDA has committed to not enforcing the 5 percent rule until the MOU is final. On balance, the approach the FDA has taken in the MOU, while imperfect, is a practical and reasonable approach, at least in the near term, to reducing the potential for harm from unrestricted interstate distribution of compounded drugs.

² The Pew Charitable Trusts, "State Oversight of Drug Compounding," (2018), https://www.pewtrusts.org/-/media/assets/2018/02/drug_safety_assesment_web.pdf

³ U.S. Food and Drug Administration, "January 31, 2018: New England Compounding Center Pharmacist Sentenced for Role in Nationwide Fungal Meningitis Outbreak," accessed Dec. 5, 2018, <https://www.fda.gov/ICECI/CriminalInvestigations/ucm594800.htm>.; Jess Bidgood, "Pharmacist Gets 9-Year Prison Term in Deadly Meningitis Outbreak," *New York Times*, June 26, 2017, <https://www.nytimes.com/2017/06/26/us/pharmacy-meningitis-deaths-steroids-crisis.html>.

⁴ The Pew Charitable Trusts, "U.S. Illnesses and Deaths Associated With Compounded Medications or Repackaged Medications, 2001-17" (2018), <https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2017/us-illnesses-and-deaths-associated-with-compounded-medications-or-repackaged-medications>.

The FDA has proposed a trade-off—allowing unlimited interstate distribution in states that sign the MOU but requiring those states to report pharmacies that ship inordinate amounts of compounded drug products out of state—which may facilitate state participation and potentially give the FDA important insight into which pharmacies should be prioritized for federal oversight. Whether the trade-off is successful in meeting those public health goals will depend on:

1. How many states sign the MOU—the more states that sign the MOU, the more information the FDA will have on compounders that ship inordinate amounts of compounded drug products interstate;
2. Whether the states that sign the MOU conduct regular inspections of compounding pharmacies to find out whether those pharmacies are distributing inordinate amounts, and report them to the FDA; and
3. Whether the FDA uses this information to help determine its inspection and enforcement priorities for patient-specific compounders in states that sign the MOU.

The proposed MOU would help the FDA identify compounders that primarily serve patients in other states, and prioritize their inspections accordingly

The FDA currently has no formal mechanism for identifying compounders that dispense or distribute significant amounts of compounded drug products interstate. In past research, Pew has also found that states vary in terms of how much knowledge they have regarding the compounding facilities in their jurisdiction, and have varying ability to meaningfully respond to safety deficiencies.⁶ The MOU would provide the FDA with a better understanding of the compounding landscape by requiring states that sign it to inform the FDA of any compounders in their state that distribute greater than 50 percent of the number of prescription orders for compounded drug products interstate. This information will in turn make it easier for the agency to prioritize its oversight activities and focus on those compounders who would pose the greatest risk to public health if they were not compounding under appropriate standards.

In the previous MOU draft, the threshold for inordinate amount was set at 30 percent. While we supported that proposal, we accept the logic behind increasing the threshold for what constitutes “inordinate amounts” from 30 to 50 percent of total prescription orders. While the state retains primary oversight responsibility over all state-regulated pharmacies, when compounders are distributing most of their product out-of-state, the greatest exposure to potential harm is to out-of-state patients. In those circumstances it makes sense to have additional federal insight into compounding operations to better equip the FDA to protect interstate patients if the state fails to do so. Defining “inordinate amounts” at 50 percent will give the FDA information allowing it to identify those facilities that do more interstate than intrastate business, which promotes public health by allowing the agency to target its resources on facilities where violations would affect patients beyond the state borders.

The information the FDA gains under the MOU is valuable only if the agency has the resources to implement an effective inspectional program on facilities that pose the most widespread risk and makes implementation of this program a priority. And states must have—or develop—mechanisms to provide the FDA with the information the agency will need to prioritize inspections of those facilities. If after a reasonable time period (e.g., 3-5 years) the FDA has not been able to inspect facilities using the information gained from states that sign it and effectively regulate compounders that distribute large

amounts of compounded drug products interstate, the agency should consider returning to a hard cap on interstate shipments above a pre-set volume.

Successful implementation of the proposed MOU will require robust state mechanisms for collecting information on compounding pharmacies

In order to provide the FDA with the information required under the proposed MOU, states will need robust mechanisms in place to collect annual information on the amount of drugs dispensed or distributed by pharmacies in their jurisdiction. Without these data, states will not be able to accurately identify compounders distributing inordinate amounts of compounded drugs or provide the FDA with the information necessary to inform inspectional priorities. Because the FDA is trading access to information for putting a hard cap on interstate distribution, the proposed compromise is only reasonable if states can provide actionable information.

However, states face challenges in collecting these data. A 2016 Pew report found that states have varying degrees of knowledge regarding sterile compounders within their respective jurisdictions.⁵ The MOU suggests that states may consider surveys, reviews of records during inspections, or other mechanisms to identify those pharmacies. It will be important to ensure that these mechanisms result in robust data. For example, because voluntary surveys typically have low response rates, the FDA can recommend that states make survey participation mandatory, perhaps as a condition of license renewal. Additionally, although inspections may be a useful way to verify survey responses, they are not conducted annually in every pharmacy. It may be necessary for states to adopt other mechanisms to collect or verify information from pharmacies during periods of time when they are not scheduled to be inspected. Funding will be a challenge for these proposals, so states may need to explore mechanisms—such as additional licensing fees for compounders—to finance the data collection necessary to give compounders the additional flexibility they will have if their states participate in the MOU.

Regardless of the mechanism(s) by which states collect information, the FDA's proposal that states collect information on the total number (not just the percentage) of prescription orders for compounded drugs distributed both within the state and interstate is good policy that will give the agency a more accurate overview of the public health risk posed by compounding operations. Percentage is not a perfect proxy for operational scale and including the total number of prescription orders provides important additional context. Widespread distribution of compounded drugs also undermines the drug approval process, placing patients at greater risk of harm if they have access to fewer FDA approved drugs and more unapproved compounded drugs.

Additionally, the FDA should consider whether there should be a reciprocal obligation for the agency to provide information to states about pharmacies located in other states that distribute inordinate amounts into their state.

If states cannot effectively oversee physician compounding, physicians should be limited to 5 percent interstate distribution

⁵ The Pew Charitable Trusts, "National Assessment of State Oversight of Sterile Drug Compounding" (2016), http://www.pewtrusts.org/~media/assets/2016/02/national_assessment_of_state_oversight_of_sterile_drug_compounding.pdf.

The proposed MOU imposes minimal obligations on states to oversee or even understand physician compounding. States that sign the MOU are not required to know which physicians in their jurisdiction are compounding. Moreover, when patients are harmed, rather than investigate the root cause of a complaint, the state would only be required to notify the appropriate regulator in the state and would notify the FDA only if the complaint involves a serious adverse event—there is no obligation on the state to follow-up on patient harm from drugs compounded by physicians.

Compared to their authority over compounding pharmacies, states generally have limited ability to regulate compounding that happens in physician offices. A 2016 Pew report found that most state boards of pharmacy were not certain if meaningful oversight of physician compounding—by state medical boards or otherwise—existed in their respective states.⁶ Additionally, the report found that there is little to no clarity on which quality standards apply to sterile compounding in physicians’ offices, and there are often no mechanisms to track adverse events associated with drugs that are compounded in these settings.

Despite recognizing that states may have limited ability to track or control physician compounding, the FDA is proposing to permit physicians in states that sign the MOU to distribute unlimited amounts of compounded drug products interstate. We are unaware of circumstances where there is a clinical need for physicians to distribute substantial volumes of compounded drug products across state lines. Yet the FDA’s proposal would permit physicians to set up a business supplying compounded drug products interstate, and those businesses would compete against (and potentially undercut) compounding pharmacies, which are subject to more robust regulation. The MOU would not obligate states to track this activity, so neither state regulators nor the FDA would have knowledge of such practices.

If physicians are not subject to the same oversight as pharmacists/pharmacies are, they should not receive the same flexibility to distribute compounded drug products interstate that pharmacies in states that enter the MOU would have. In states that cannot commit to tracking and overseeing physician activity, the FDA should limit interstate distribution for physicians to the 5 percent that would apply if the physician was in a state that had not signed the MOU. To accomplish this, the agency could permit states to sign a pharmacy-only MOU, which would allow pharmacies in that state to exceed the 5 percent limit, but not physicians. Alternatively, the FDA could address physician compounding separately within the same MOU. For example, in states that sign the MOU with regard to pharmacists but that cannot effectively track, set quality standards for, inspect and take enforcement action against, and investigate complaints regarding physician compounders, “inordinate amounts” could be set at 5 percent for physicians, and distribution of more than 5 percent would not be allowed.

Additional Comments and Clarifications

- **Clarifying state and federal roles:** The MOU should also be explicit that states retain jurisdiction over, and the obligation to oversee, compounders that distribute inordinate amounts of compounded drug products interstate to the same extent that they oversee compounders that distribute most of their compounded drug products intrastate. States should not view oversight of such compounders as solely being the FDA’s responsibility, as the states have the responsibility to oversee their licensees whether they operate within the state or out of the state.

⁶ Ibid.

- **Inordinate amounts:** The FDA’s revisions to how “inordinate amounts” are calculated are also helpful and clarifying. Under the new draft MOU, both the numerator (i.e., the number of prescription orders shipped interstate) and the denominator (i.e., all prescription orders dispensed or distributed) would only include compounded drugs. This helps to level the playing field by avoiding giving significantly more leeway to pharmacies that, in addition to compounding, also dispense or distribute significant quantities of manufactured products. Including all drug products in the calculation of inordinate amounts would, in effect, allow these pharmacies to ship much higher quantities of compounded drugs interstate without surpassing the 50 percent threshold. The FDA’s revised language avoids this result.
- **Prescription order:** The term “prescription order” needs to be defined in a way that will minimize the potential for gamesmanship. If compounders demonstrate atypical prescription patterns—for example, by distributing a large supply of compounded drug products per order interstate while dispensing smaller but more numerous orders of compounded drug products intrastate, thus sending a high volume of drugs interstate while still maintaining a low percentage of interstate orders—the state should be compelled to flag the compounder to the FDA for possible inspection if it has reason to believe, based on other metrics, that a significant portion of the compounder’s drugs are being shipped interstate. Adding to the definition that prescription orders must be typical in amount and duration, as determined by whether intrastate and interstate prescriptions are generally similar, will be clarifying to compounders who ship significant quantities of compounded drug products interstate.
- **Compounded drug products:** The term “compounded drug products” is used many times throughout the document and most of the state’s obligations under the MOU pertain to acts that must be performed with regard to “compounded drug products.” However, this term is not defined in the draft MOU and is defined very differently—if at all—from one state to the next. Because the limitation on distributing inordinate amounts interstate applies to drug products deemed to be “compounded” under section 503A, the FDA should provide a uniform definition for the term in the MOU or in corresponding guidance provided to the states.
- **Non-adherence and termination:** The MOU should clarify the FDA’s authority to determine non-adherence to the terms of the MOU. In case of termination, the FDA should clarify when compounding pharmacies will become subject to the 5 percent limit: the date of posting of the termination notice online, the date the termination request was sent, or some other date.
- **Dispensing vs. Distribution:** Pew supported the FDA’s prior articulation of the terms dispense and distribute, which would have considered any product leaving the compounding facility to have been distributed. Patient-specific drugs are dispensed directly to patients and are also distributed to providers for administration—such as when a hospital compounder distributes product to a patient in a ward, or a community pharmacist fills a patient specific order for a clinic. While we view the FDA’s revision—which now exempts drugs dispensed directly to a patient in person from the definition of distribution—as being unnecessary, we don’t see the change as having a significant impact on public health, provided that guardrails are in place to

prevent distribution in the guise of such dispensing. For example, a third party in the same state as the compounder should not be able to receive prescriptions from the compounder and then mail compounded drugs to patients interstate without those transactions factoring into the calculation of whether a compounder distributes an inordinate amount interstate.

- **Maintaining Records:** The proposed MOU provides a 3-year period for the maintenance of complaint records; however, the FDA should consider requiring maintenance of complaint records until the end of the time period that any state law would permit a lawsuit from an injured patient (which we understand to be 6 years).
- **Information Collection and Disclosure:** The MOU should recommend that the submission and disclosure information for inordinate amounts include the names of states that the compounding pharmacy/physician distributes to. The MOU currently recommends submitting the number (not names) of states.

We thank you again for the opportunity to provide comments.

Sincerely,

A handwritten signature in blue ink, appearing to read "Elizabeth Jungman", with a long horizontal flourish extending to the right.

Elizabeth Jungman, J.D., M.P.H.
Director, Public Health Programs