

## FDA ISSUES NEW DRAFT MOU FOR 503A COMPOUNDERS GOVERNING CROSS-BORDER DISPENSING AND COMMENTS RELATED TO CGMP COMPLIANCE FOR OUTSOURCING FACILITIES

On September 7, 2018, the United States Food and Drug Administration (“FDA”) issued a revised draft [Memorandum of Understanding](#) (“MOU”) that would govern interstate dispensing and distribution of “inordinate amounts” of compounded prescription drugs by certain compounding physicians and pharmacies. The concept of this MOU first appeared in the Compliance Policy Guidance issued by the FDA in 1992. In that Compliance Policy Guidance, the FDA considered “traditional compounders” that participated in “distributing inordinate amounts of compounded products out of state” to be engaged in activities “normally associated with a manufacturer,” thus implicating concerns related to the unauthorized manufacture of prescription drugs. This MOU concept was later codified in 1997 and retained when the statute was reaffirmed in 2013.<sup>[1]</sup> This MOU is also contemplated by the Federal Food, Drug, and Cosmetic Act (“FDCA”)<sup>[2]</sup> and applies to traditional compounders that carry out limited anticipatory and patient-specific compounding commonly referred to as “503A Compounders” as distinct from compounding “Outsourcing Facilities” governed under section 503B of the FDCA.

Pharmacies that are 503A Compounders may only “distribute” a compounded drug outside of the state if: i) the state in which the 503A Compounder is located “...has entered into an MOU with the [FDA] which addresses the distribution of inordinate amounts of compounded drug products interstate...”; or ii) such distribution “...out of the State... [occurs] in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.”<sup>[3]</sup> This revised MOU would therefore govern the permissible scope of out-of-state “distribution” of compounded drugs in states that enter into the MOU. Notably, the MOU contains a rather expansive definition of “distribution,” which addresses both delivery/shipping a drug to a facility in addition to dispensing a drug to a patient. This definition has evolved over the drafts of the MOU (as outlined below) and affected facilities will want to consider the impact of this broad definition when ascertaining the percentages of drugs “distributed” interstate.

More specifically, the revisions to the MOU would:

- Increase the limits on the proportion of compounded drugs that 503A Compounders may dispense or distribute from 30 percent to 50 percent per month in states that have signed the MOU and request the reporting by states of certain information about compounded drug prescriptions distributed or dispensed intrastate and interstate; and
- Affirm the FDA’s expectation that each state will continue to have day-to-day oversight over compounding pharmacies and physicians in its respective state, which may include investigating complaints and advising the FDA when such state receives reports of serious adverse drug experiences or serious product quality issues such as drug contamination.

The FDA now seeks additional public feedback to the current MOU, especially with regard to the more recent revisions. Stakeholders, including compounding pharmacies, physicians and pharmacists, should continue to monitor developments in this space and provide their comments to the FDA no later than **December 10, 2018**.

Finally, stakeholders should anticipate updated FDA draft guidance for public comment, describing the FDA’s policies concerning Current Good Manufacturing Practice (“CGMP”) requirements for Outsourcing Facilities. While the FDA has not yet released the specifics, the FDA has suggested the upcoming guidance will outline a flexible, risk-based approach to CGMP for Outsourcing Facilities under which the FDA generally would not apply all of the same requirements to lower-risk products, or smaller volumes of products, that are produced by Outsourcing Facilities.

This article will address each of the above provisions in more detail and provide guidance and background to industry stakeholders in drafting their comments. Finally, this article will provide some practical advice and next steps to stakeholders seeking to stay current with FDA guidance on drug compounding.

## BACKGROUND AND DISCUSSION

Compounded drugs are customized medications made based on a specific prescription for an individual patient by mixing, altering, or combining ingredients together in the exact strength and dosage form required by that individual patient. Because compounded drugs are not FDA-approved and due to the nature of their preparation, compounded drugs are at higher risk for contamination and other threats to patient safety. These risks were illustrated by the 2012 nationwide fungal meningitis outbreak. This tragic outbreak led to more than 750 cases of illness and the deaths of 64 individuals. A certain compounding facility had used a compounded drug for injection that was supposed to be sterile but had become contaminated before distribution to patients and providers. As a result of this outbreak, the FDA has taken a more proactive role in regulating compounded drugs.

To that end, the FDA intended to improve its draft MOU from 2015 and 1999 to address concerns about patient access and preserve critical safety provisions to prevent future public health tragedies. The FDA issued an initial draft MOU in January 1999. Since then, the 2015 draft and this current draft redefined “inordinate amounts” to increase the percentage distributed and/or dispensed and revises the definition of “distribution.” For reference, the key provisions of the three MOUs are summarized to highlight the evolving view of the FDA in this space:

MOU Comparison of Drafts			
	1999	2015	2018
Inordinate Amount	Where the number of compounded drugs dispensed or distributed interstate annually is equal to or greater than 20 percent of all drugs dispensed by the facility. This draft proposed a 20 percent total annual interstate limit, and interstate quantities of individual drugs (e.g., different dosage strengths) could not exceed 5 percent even if the total distributed was less than 20 percent.	Where the number of units of compounded human drug products distributed interstate during any calendar month is equal to or greater than 30 percent of the number of units of compounded and non-compounded drug products distributed or dispensed both intrastate and interstate during that same month.	Where the number of prescription orders for compounded drug products distributed interstate during any calendar month is greater than 50 percent of the number of prescription orders for compounded drug products distributed or dispensed both intrastate and interstate by such pharmacy or physician during that same month.

Distribution	Distribution excluded “local” interstate distribution to patients within 50 miles of the compounding pharmacy, and interstate distribution in response to a public health emergency or catastrophic event.	Means any time a compounded drug leaves the facility where it was made, regardless of whether the drug is also deemed to be “dispensed.” FDA does “not intend to consider” prescriptions dispensed to a patient where that patient carries a drug across state lines after dispensing at the compounding facility.	Means any drug product sent out of the facility in which the drug was compounded. Such distribution may include, but is not limited to, delivery or shipment to a physician’s office, hospital or other health care setting for administration and dispensing the drug product by sending it to a patient for the patient’s own use.
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The MOU highlights four main areas of updates, as outlined below.

1. *503A Compounders may dispense or distribute up to 50 percent per month of their compounded drugs interstate without reporting by states.*

Under the draft MOU from 2015, 503A Compounders that dispensed or distributed 30 percent or more of all of their compounded drug products interstate, also known as an inordinate amount, would face adverse actions from the state authorities.

As revised, the MOU would raise the limits on the proportion of drugs that may be distributed or dispensed interstate by 503A Compounders from 30 percent to 50 percent. First, states would only identify 503A Compounders that distribute more than 50 percent of their total prescription orders interstate and report certain information about the volume of compounded drugs distributed interstate and the number of states in which the compounder is licensed. In turn, the FDA will use this information to develop risk-based oversight priorities with the greatest public health impacts. The FDA intends to use this information to prioritize its inspections of 503A Compounders based on risk. Second, states would have greater flexibility over gathering information on inordinate amounts. Third, states would no longer be required to take action when a 503A Compounder distributes inordinate amounts interstate. Instead, the state would have the option of taking action using a more flexible, risk-based approach.

2. *503A Compounders in states that do not sign the MOU continue to have a 5 percent limit on interstate shipments of compounded drugs by a 503A Compounder, but this does not apply to Outsourcing Facilities or drugs compounded for animals.*

Currently, Section 503A of the FDCA limits the out-of-state distribution of compounded drugs by a 503A Compounder to 5 percent of total prescription orders dispensed or distributed by the traditional compounder. This 5 percent restriction would remain in place for traditional compounders located in states that do not sign the MOU with the FDA once it is finalized.

The FDA notes that the 5 percent limit does not apply to drugs compounded by Outsourcing Facilities and compounded drugs for animals.

3. *States will continue to have day-to-day oversight over compounding pharmacies and physicians located in their respective states.*

The FDA anticipates that state authorities such as state boards of pharmacy maintain primary responsibility for regular, day-to-day oversight of state-licensed 503A Compounders.

The MOU and other FDA guidance will offer clarity to states about investigating complaints associated with compounded drug products that have been distributed out of state. States signing the MOU will agree to investigate complaints and notify the FDA when they receive reports of serious adverse drug experiences or serious product quality issues. These states would also be responsible for maintaining records of complaints and investigations.

More, both 503A Compounders and Outsourcing Facilities will want to continue to consider the impact of potential state law restrictions on compounding, both in the state in which the drugs are compounded and in the state to which the drugs are delivered.

4. *Outsourcing Facilities will be accountable for meeting CGMP requirements, as addressed in upcoming draft guidance from the FDA.*

In addition to its updates to the MOU, the FDA has also indicated it will provide new guidance for Outsourcing Facilities registered with the FDA that are subject to CGMP regulations and requirements. The FDA designed these requirements to ensure proper design, monitoring and control of pharmaceutical manufacturing processes and facilities. The requirements permit manufacturers to have some flexibility in methods of implementing controls while maintaining standards and protecting the public and consumers from harm. In its statement, the FDA noted its intent to issue a revised draft guidance about the CGMP requirements for Outsourcing Facilities in the coming months. Once released, stakeholders may submit comments for the FDA to take into consideration.

One objective of the revised guidance is to make it more feasible for compounders to register and operate as Outsourcing Facilities. To this end, the FDA will propose a flexible, risk-based approach to CGMP for Outsourcing Facilities that would meet the minimum standards to protect patients while simultaneously being tailored to the nature of the operation such as the risk and volume of the products produced by the facilities. If more compounding pharmacies and physicians can become Outsourcing Facilities, the FDA foresees greater physician access since Outsourcing Facilities can compound and distribute drugs for “office stock” or for use in a physician’s office. Outsourcing Facilities also have other benefits and flexibilities, such as the ability to compound drugs without first receiving a patient-specific prescription.

## PRACTICAL TAKEAWAYS

The FDA encourages all interested stakeholders to comment on the revised draft MOU and to review the [Federal Register notice](#) that explains the provisions of the revised draft MOU, along with how to submit comments. Comments may be submitted with confidential information that would not be made public. Stakeholders should work with their advocacy teams on responses and submit comments electronically or by paper/written format no later than **December 10, 2018**.

Once finalized, the MOU will be offered to states for signatures during a proposed 180-day period. Please note that during this period, the FDA does not intend to enforce the 5 percent out-of-state distribution limitation for 503A Compounders in states that do not sign onto the MOU. 503A Compounders that distribute compounded drugs interstate should monitor this process closely and ensure that their state governments sign onto the MOU if it is relevant to their scope of practice. These 503A Compounders should leverage their trade associations and other networks to lobby for state government participation. If states do not sign onto the MOU and the 180-day period ends, 503A Compounders will only be able to distribute out-of-state in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by that 503A Compounder.

Finally, Outsourcing Facilities should remain alert for any new FDA guidance related to CGMP compliance.

If you have any questions or would like additional information about this topic, please contact:

- **Todd A. Nova** at 414-721-0464 or [tnova@hallrender.com](mailto:tnova@hallrender.com);
- **Kristen H. Chang** at 414-721-0923 or [kchang@hallrender.com](mailto:kchang@hallrender.com); or
- Your regular Hall Render attorney.

[1] 21 U.S.C. 353a(b)(3)(B).

[2] See 21 U.S.C. 353a(b)(3).

[3] 21 U.S.C. 353a(b)(3).