



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-N-0030]

Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State Board of Pharmacy or Other Appropriate State Agency and the Food and Drug Administration; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability; withdrawal.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing the availability of a final standard memorandum of understanding (MOU) entitled “Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the [insert State Board of Pharmacy or Other Appropriate State Agency] and the U.S. Food and Drug Administration” (final standard MOU). The final standard MOU describes the responsibilities of a State Board of Pharmacy or other appropriate State agency that chooses to sign the MOU in investigating and responding to complaints related to drug products compounded in such State and distributed outside such State and in addressing the interstate distribution of inordinate amounts of compounded human drug products.

DATES: The announcement of the MOU is published in the *Federal Register* on **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. FDA is withdrawing its revised draft standard MOU that published on September 10, 2018 (83 FR 45631), as of **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: Submit electronic comments on the final standard MOU to Docket No. FDA-2015-N-0030. Submit written comments on the final standard MOU to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document. Submit written requests for single copies of the final standard MOU to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft document.

FOR FURTHER INFORMATION CONTACT: Alexandria Fujisaki, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5169, Silver Spring, MD 20993-0002, 240-402-4078.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following sections of the FD&C Act: (1) section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements), (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and (3) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

One of the conditions to qualify for the exemptions listed in section 503A of the FD&C Act is that (1) the drug product is compounded in a State that has entered into an MOU with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to drug products distributed outside such State; or (2) if the drug product is compounded in a State that has not entered into such an MOU, the licensed pharmacist, pharmacy, or physician does not distribute, or cause to be distributed, compounded drug products out of the State in which they are compounded in quantities that exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (5 percent limit) (see section 503A(b)(3)(B)(i) and (ii) of the FD&C Act). Another condition to qualify for the exemptions listed in section 503A of the FD&C Act is that the drug is compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient (section 503A(a) of the FD&C Act). This MOU does not alter this condition.

Section 503A(b)(3)(B) of the FD&C Act directs FDA to develop, in consultation with the National Association of Boards of Pharmacy (NABP), a standard MOU for use by the States in complying with section 503A(b)(3)(B)(i).

FDA is withdrawing the revised draft standard MOU entitled “Memorandum of Understanding Addressing Certain Distributions of Compounded Drug Products Between the State of [insert State] and the U.S. Food and Drug Administration,” which was issued in September 2018 (2018 revised draft standard MOU). The 2018 revised draft standard MOU is superseded by the final standard MOU.

II. Previous Efforts to Develop a Standard MOU

In the *Federal Register* of January 21, 1999 (64 FR 3301), FDA announced the availability for public comment of a draft standard MOU, developed in consultation with NABP (1999 draft standard MOU). Over 6,000 commenters submitted comments on the 1999 draft standard MOU. Because of litigation over the constitutionality of the advertising, promotion, and solicitation provision in section 503A of the FD&C Act,¹ the draft standard MOU was not completed. In 2013, section 503A of the FD&C Act was amended by the Drug Quality and Security Act (DQSA) (Pub. L. 113-54) to remove the advertising, promotion, and solicitation provisions that were held unconstitutional, and FDA took steps to implement section 503A, including to continue to develop the standard MOU. In the *Federal Register* of February 19, 2015 (80 FR 8874), FDA withdrew the 1999 draft standard MOU and issued the 2015 draft standard MOU for public comment. FDA received more than 3,000 comments on the 2015 draft standard MOU. In the *Federal Register* of September 10, 2018 (83 FR 45631), FDA withdrew the 2015 draft standard MOU and issued the 2018 revised draft standard MOU for public comment. FDA received 38 comments during the comment period on the 2018 revised draft standard MOU. By this notice, FDA is withdrawing the 2018 revised draft standard MOU and issuing a final standard MOU, which the Agency developed in consultation with NABP for use by the States in complying with section 503A(b)(3)(B).

III. Final Standard MOU

In consultation with NABP, FDA has developed a final standard MOU. FDA considered the comments submitted on the 2015 draft standard MOU and 2018 revised draft standard MOU,

¹ The conditions of section 503A of the FD&C Act originally included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were challenged in court and held unconstitutional by the U.S. Supreme Court in 2002. See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

as well as comments on the MOU provisions it received in connection with a draft guidance on section 503A of the FD&C Act entitled “Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act” (2013 draft 503A guidance) (see 78 FR 72901, December 4, 2013). Below, FDA has summarized and discussed key provisions of the final standard MOU and, where appropriate, summarized changes that the Agency made in the final standard MOU. Drug products intended for veterinary use, repackaged drug products, biological products subject to licensure through a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262), and drug products compounded by outsourcing facilities under section 503B of the FD&C Act are not the subject of the final standard MOU.

A. Investigation of Complaints Relating to Compounded Human Drug Products Distributed

Outside the State

The final standard MOU provides that a State Board of Pharmacy or other appropriate State agency that enters into the MOU agrees to:

- Investigate complaints of adverse drug experiences and product quality issues relating to human drug products compounded at a pharmacy in the State and distributed outside the State. Investigations performed by the State Board of Pharmacy or other appropriate State agency under this MOU will include taking steps to assess whether there is a public health risk associated with the compounded drug product and whether such risk is adequately contained. Investigations will be performed pursuant to the State Board of Pharmacy’s or other appropriate State agency’s established investigatory policies and procedures, including those related to prioritizing complaints, provided they are not in conflict with the terms of the MOU;

- If the complaint is substantiated, take action that the State Board of Pharmacy or other appropriate State agency considers to be appropriate and warranted, in accordance with and as permitted by State law, to ensure that the relevant pharmacy investigates the root cause of the problem that is the subject of the complaint and undertakes sufficient corrective action to address any identified public health risk relating to the problem, including the risk that future similar problems may occur;
- Maintain records of the complaints it receives regarding adverse drug experiences or product quality issues relating to human drug products compounded at a pharmacy, the investigation of each complaint, and any response to or action taken as a result of a complaint, beginning when the State Board of Pharmacy or other appropriate State agency receives notice of the complaint. The State Board of Pharmacy or other appropriate State agency will maintain these records for at least 3 years. The 3-year period begins on the date of final action on a complaint, or the date of a decision that the complaint requires no action.
- Notify FDA by submission to an Information Sharing Network or by email to StateMOU@fda.hhs.gov as soon as possible, but no later than 5 business days, after receiving a complaint involving a serious adverse drug experience or serious product quality issue relating to a human drug product compounded at a pharmacy and distributed outside the State, and provide FDA with certain information about the complaint, including the following: name and contact information of the complainant, if available; name and address of the pharmacy that is the subject of the complaint; and a description of the complaint, including a description of any compounded human drug product that is the subject of the complaint;

- Share with FDA, as permitted by State law, the results of the investigation of a complaint after the State Board of Pharmacy or other appropriate State agency concludes its investigation of a complaint assessed to involve a serious adverse drug experience or serious product quality issue. This information includes the following: the State Board of Pharmacy's or other appropriate State agency's assessment of whether the complaint was substantiated, if available; and a description and the date of any actions the State Board of Pharmacy or other appropriate State agency has taken to address the complaint;
- Notify the appropriate regulator of physicians within the State of complaints of which the State Board of Pharmacy or other appropriate State agency receives that involve an adverse drug experience or product quality issue relating to human drug products compounded by a physician and distributed outside the State. The State Board of Pharmacy or other appropriate State agency will also notify FDA by submission to an Information Sharing Network or by email to StateMOU@fda.hhs.gov as soon as possible, but no later than 5 business days, after receiving the complaint of the following information, if available: name and contact information of the complainant; name and address of the physician that is the subject of the complaint; and description of the complaint, including a description of any compounded human drug product that is the subject of the complaint.

The types of complaints of compounded drug products that should be investigated include any adverse drug experience and product quality issues. Even non-serious adverse drug experiences and product quality issues can be indicative of problems at a compounding facility that could result in product quality defects leading to serious adverse drug experiences if not corrected. For example, inflammation around the site of an injection can indicate drug product

contamination from inadequate sterile practices at the compounding pharmacy. If the pharmacy or physician has inadequate sterile practices, other more serious contamination could result in serious adverse drug experiences.

The final standard MOU does not include specific directions to the State Boards of Pharmacy or other appropriate State agencies relating to how to conduct their investigation of complaints. Rather, as recommended by comments submitted to FDA previously, the details of such investigations are left to the State Board of Pharmacy's or other appropriate State agency's discretion. For example, a State Board of Pharmacy or other appropriate State agency may review an incoming complaint describing an adverse drug experience and determine that such a complaint does not warrant further investigation. In other cases, a State Board of Pharmacy or other appropriate State agency may determine that an incoming complaint contains insufficient information and investigate further to determine appropriate action.

The State Board of Pharmacy or other appropriate State agency signing the final standard MOU would agree to notify FDA about certain complaints and provide FDA with certain information about the complaints so FDA could investigate the complaints itself, or take other appropriate action. The 2018 revised draft standard MOU provided that notification would occur as soon as possible, but no later than 3 business days of receipt of the complaint. The final standard MOU provides that notification will occur as soon as possible, but no later than 5 business days after the State Board of Pharmacy or other appropriate State agency receives the complaint. This period will continue to facilitate early Federal/State collaboration on serious adverse drug experiences and serious product quality issues that have the potential to affect patients in multiple States, while providing for notification in a timeframe that is more feasible for the State Boards of Pharmacy or other appropriate State agencies. FDA increased the time

for notifying FDA in the final standard MOU in response to comments expressing concern about having sufficient time to process complaints and notify FDA. We note that FDA has staff on call 24 hours a day to receive information in emergency situations.

Comments on the 2015 draft MOU expressed concern with certain provisions regarding States entering into the MOU and agreeing to take action not permitted by State law or implying that, after taking action, the State made a legal determination that a complaint had been resolved. The revised draft standard MOU clarified that the State should investigate and take action that the State considers to be appropriate with respect to the complaint in accordance with and as permitted by State law. FDA also clarified that, by signing the MOU, the State agrees to take steps to assess whether there is a public health risk associated with the compounded drug product and whether such risk is adequately contained rather than make definitive determinations of risk or confirm containment. The final standard MOU retains these revisions that addressed the concerns from comments on the 2015 draft.

B. Distribution of Inordinate Amounts of Compounded Human Drug Products Interstate

For purposes of the final standard MOU, a pharmacy has distributed an inordinate amount of compounded human drug products interstate if the number of prescription orders for compounded human drug products that the pharmacy distributed interstate during any calendar year is greater than 50 percent of the sum of the number of prescription orders for compounded human drug products that the pharmacy sent out of (or caused to be sent out of) the facility in which the drug products were compounded during that same calendar year and the number of prescription orders for compounded human drug products that were dispensed (e.g., picked up by a patient) at the facility in which they are compounded during that same calendar year (Fig. 1). This concept is called the 50 percent threshold.

Figure 1. Calculating an Inordinate Amount

$$\frac{A}{B} = X, \text{ where:}$$

A = Number of prescription orders for compounded human drug products that the pharmacy distributed interstate during any calendar year

B = The sum of the number of prescription orders for compounded human drug products (i) that the pharmacy sent out of (or caused to be sent out of) the facility in which the drug products were compounded during that same calendar year; plus (ii) the number of prescription orders for compounded human drug products that were dispensed (e.g., picked up by a patient) at the facility in which they were compounded during that same calendar year

If X is greater than 0.5, it is an inordinate amount and is a threshold for certain information identification and reporting under the MOU.

The final standard MOU provides that State Boards of Pharmacy or other appropriate State agencies that enter into the MOU will agree to:

- On an annual basis, identify, using surveys, reviews of records during inspections, data submitted to an Information Sharing Network, or other mechanisms available to the State Board of Pharmacy or other appropriate State agency, pharmacies that distribute inordinate amounts of compounded human drug products interstate.
- For pharmacies that have been identified as distributing inordinate amounts of compounded human drug products interstate during any calendar year, the State Board of Pharmacy or other appropriate State agency will identify, using data submitted to the Information Sharing Network or other available mechanisms, during that same calendar year:
 - The total number of prescription orders for sterile compounded human drug products distributed interstate;

- The names of States in which the pharmacy is licensed;
- The names of States into which the pharmacy distributed compounded human drug products; and,
- Whether the State inspected for and found during its most recent inspection that the pharmacy distributed compounded human drug products without valid prescription orders for individually identified patients.
- Within 30 business days of identifying a pharmacy that has distributed inordinate amounts of compounded human drug products interstate, the State Board of Pharmacy or other appropriate State agency will notify FDA, by submission to an Information Sharing Network or by email to StateMOU@fda.hhs.gov, and will include the following information:
 - Name and address of the pharmacy that distributed inordinate amounts of compounded human drug products interstate;
 - The number of prescription orders for compounded human drug products that the pharmacy sent out of (or caused to be sent out of) the facility in which the drug products were compounded during that same calendar year;
 - The number of prescription orders for compounded human drug products that were dispensed (e.g., picked up by a patient) at the facility in which they are compounded during that same calendar year;
 - Total number of prescription orders for compounded human drug products distributed interstate during that same calendar year;
 - Total number of prescription orders for sterile compounded human drug products distributed interstate during that same calendar year;

- The names of States in which the pharmacy is licensed as well as the names of States into which the pharmacy distributed compounded human drug products during that same calendar year; and
- Whether the State Board of Pharmacy or other appropriate State agency inspected for and found during its most recent inspection that the pharmacy distributed compounded human drug products without valid prescriptions for individually identified patients during that same calendar year.
- If the State Board of Pharmacy or other appropriate State agency becomes aware of a physician who is distributing any amount of compounded human drug products interstate, it will notify the appropriate regulator of physicians within the State. The State Board of Pharmacy or other appropriate State agency will, within 30 days of identifying a physician who is distributing any amount of compounded human drug products interstate, also notify FDA by submission to an Information Sharing Network or by email to StateMOU@fda.hhs.gov.

Section 503A of the FD&C Act reflects Congress' recognition that compounding may be appropriate when it is based on receiving a valid prescription order or notation approved by the prescribing practitioner for an identified individual patient. However, drug products compounded under section 503A are not required to demonstrate that they are safe or effective, have labeling that bears adequate directions for use, or conform to CGMP. Congress, therefore, imposed strict limitations on the distribution of drug products compounded under section 503A to protect the public health and the integrity of the drug approval process.

In particular, Congress did not intend for compounders operating under these statutory provisions to grow into conventional manufacturing operations making unapproved drugs,

operating a substantial proportion of their business interstate, without adequate oversight. Although other provisions of the FD&C Act (e.g., the adulteration provisions regarding drugs prepared, packed, or held under insanitary conditions) apply to drugs compounded by State-licensed pharmacies and physicians that may qualify for the exemptions under section 503A of the FD&C Act, and although FDA may take action in appropriate cases against compounders whose drugs violate these provisions or that operate outside of the conditions in section 503A, Congress recognized that these compounders are primarily overseen by the States. However, if a substantial proportion of a compounder's drug products are distributed outside a State's borders, adequate regulation of those drug products poses significant challenges to State regulators. States face logistical, regulatory, and financial challenges inspecting compounders located outside of their jurisdiction. In addition, if a compounder distributes drug products to multiple States, it can be very difficult to gather the scattered information about possible adverse drug experiences or product quality issues associated with those drug products, connect them to the compounder, and undertake coordinated action to address a potentially serious public health problem.

Therefore, as a baseline measure, section 503A(b)(3)(B)(ii) of the FD&C Act limits the distribution of compounded drug products outside of the State in which they are compounded to 5 percent of the total prescription orders dispensed or distributed by a licensed pharmacist, pharmacy, or physician. It then directs FDA, in consultation with NABP, to develop a standard MOU that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to drug products compounded in and distributed outside such State. Development of the standard MOU involves FDA describing what inordinate amounts means and providing a mechanism for

addressing distribution of inordinate amounts of compounded human drug products interstate, as long as the State agrees to appropriately investigate complaints relating to drug products compounded in and distributed out of the State. The 5 percent limitation in section 503A(b)(3)(B)(ii) does not apply to drug products compounded in a State that has entered into the standard MOU under section 503A(b)(3)(B)(i).

In the 2015 draft standard MOU, FDA proposed that distribution interstate up to a 30 percent limit would not be inordinate, and that States entering into the MOU would agree to take action regarding pharmacists, pharmacies, or physicians that distribute inordinate amounts of compounded drug products interstate. FDA received a number of comments indicating that certain pharmacies, such as pharmacies located near State borders and home infusion pharmacies, distribute more than 30 percent of their compounded human drug products to patients interstate because, for example, the patients are located in another nearby State, or because few pharmacies compound a particular drug product to treat an uncommon condition for patients dispersed throughout the country. The comments noted that the proposed definition of inordinate amounts and the proposed provision in which States agree to take action could prevent such pharmacies from fulfilling patients' medical needs for the drug products that they supply. Other comments expressed concern about instances in which pharmacies are located near a State border and distribute compounded drug products to the other side of that border. FDA also received general comments questioning the Agency's basis for the 30 percent limit and indicating that it was too low. Some comments suggested that FDA increase the limit, including a suggestion to increase it to 50 percent.

The 2018 revised draft standard MOU addressed these comments in two respects. First, it removed the provision in the 2015 draft standard MOU that States agree to take action with

respect to the distribution of inordinate amounts of compounded human drug products interstate. Second, it changed what is considered “inordinate amounts” from a 30 percent limit to a 50 percent threshold. In the final standard MOU, the States are not agreeing to take action with respect to distribution of inordinate amounts of compounded human drug products interstate, but, instead, to notify FDA of pharmacies that have distributed an inordinate amount of compounded human drug products interstate. The Agency does not intend to take action against a pharmacy located in a State that has entered into the MOU solely because the pharmacy has exceeded the threshold for inordinate amounts. Rather, the State Board of Pharmacy or other appropriate State agency entering into the final standard MOU agrees to collect further information on pharmacies that have distributed inordinate amounts interstate and provide this information to FDA to help inform Agency inspectional priorities. The State Board of Pharmacy or other appropriate State agency also agrees to notify FDA and the appropriate state regulator of physicians if it becomes aware of physicians distributing any amount of compounded human drug products interstate.

We note that States generally have day-to-day oversight responsibilities over State-licensed pharmacies, pharmacists, and physicians. In general, FDA considers a State-licensed pharmacy or physician to be primarily overseen by the State, which is responsible both for regulation of the compounder and protection of its citizens who receive the compounded drug products. However, as discussed above, if a substantial proportion of a compounder’s drug products is distributed outside a State’s borders, adequate regulation of those drugs poses significant challenges to State regulators. In such cases, although State oversight continues to be critical, additional oversight by FDA may afford an important public health benefit.

As stated above, the final standard MOU uses 50 percent as the threshold beyond which the amount of compounded human drug products distributed interstate by a pharmacy would be

considered inordinate. The 50 percent threshold is the threshold that, with regard to pharmacies, triggers an information identification and reporting obligation once it is reached. The Agency believes that more than 50 percent is an appropriate measure of “inordinate amounts” because it marks the point at which pharmacies are distributing the majority of their compounded human drug products interstate, and the regulatory challenges associated with interstate distributors discussed above become more pronounced. At this point, the risk posed by the distribution practices of the compounder may weigh in favor of additional Federal oversight in addition to State oversight.

FDA recognizes that, in some cases, pharmacies may distribute more than 50 percent of a small quantity of compounded human drug products to contiguous States. Although such pharmacies have exceeded the inordinate amounts threshold in the final standard MOU, FDA would consider other information, such as the number of patients that will receive the compounded human drug products, if available, when assessing the pharmacy’s priority for risk-based inspection. Accordingly, when a State Board of Pharmacy or other appropriate State agency identifies a pharmacy that distributes an inordinate amount of compounded human drug products interstate, the final standard MOU provides that the State entity will supply the Agency with certain information as described above. In addition, if the State Board of Pharmacy or other appropriate State agency becomes aware of a physician who is distributing any amount of compounded human drug products interstate, the State entity will notify both the appropriate regulator of physicians within the State and FDA. FDA intends to use this information to prioritize its oversight of compounders based on risk, focusing on those that appear likely to distribute large volumes of compounded human drug products, particularly when the distribution

is to multiple States, the drug products are intended to be sterile, and there is information about a lack of valid prescriptions for individually identified patients.

The calculation of inordinate amounts in the final standard MOU, with clarifying changes to the language, is the same as the calculation proposed in the 2018 revised draft standard MOU, with the exception of a change in the timeframe used in the calculation from 1 month to 1 year and removing drugs compounded by physicians from the calculation made by the State Board of Pharmacy or other appropriate State agency. The 2015 draft standard MOU provided that a compounder is considered to have distributed an inordinate amount of compounded drug products interstate if the number of units of compounded 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 by such compounder during that calendar month. FDA received comments noting that because the calculation includes both compounded and non-compounded drug products, in many cases, a substantial factor in whether a compounder has distributed an inordinate amount of compounded drug products interstate is whether the compounder offers non-compounded drug products. For example, under that policy, many specialty compounding pharmacies that engage in distribution of compounded human drug products interstate and only distribute compounded drug products would be able to distribute fewer compounded drug products interstate before reaching an inordinate amount than a pharmacy that also fills prescriptions for non-compounded drug products, even if both pharmacies produced the same amount of compounded drug products. After considering the public comments, FDA does not believe that including non-compounded drug products within the calculation of inordinate amounts would help address the public health concerns associated with sending compounded human drug products interstate that

Congress sought to address in section 503A(b)(3)(B) of the FD&C Act. Non-compounded drug products were excluded from the calculation of inordinate amounts in the 2018 revised draft MOU. This final standard MOU maintains this exclusion.² FDA removed drug products compounded by physicians from the inordinate amount calculation to clarify that the State Board of Pharmacy or other appropriate State agency signing the MOU does not agree to gather information about the distribution of compounded drug products interstate by physicians or to calculate inordinate amounts of drug products compounded by a physician and distributed interstate. Instead, the State Board of Pharmacy or other appropriate State agency signing the MOU agrees that if it becomes aware that a physician is distributing any amount of compounded human drug products interstate it will notify the State authority that regulates physicians and FDA. This focus on States calculating inordinate amounts of pharmacy compounding reflects FDA's understanding and feedback from State regulators that the distribution interstate of compounded drug products mainly involves pharmacy compounders.

FDA received comments on the 2018 revised draft MOU expressing concern about calculating inordinate amounts by calendar month. After considering these comments and recognizing the possibility for significant monthly fluctuations, we have provided for annual calculation of inordinate amounts in the final standard MOU.

This 50 percent threshold does not function as a limit on the distribution of compounded human drug products interstate, but, instead, is a threshold for triggering information gathering about pharmacy distribution of compounded drugs by the State Board of Pharmacy or other

² FDA also intends to exclude non-compounded drugs from the calculation of the 5 percent limit in section 503A(b)(3)(B)(ii).

appropriate State agency and provision to FDA. The information gathered will be considered by the Agency for the purpose of helping to inform its risk-based inspection priorities.

C. Definitions

Appendix A retains the definitions of “adverse drug experience,” “serious adverse drug experience,” “product quality issue,” and “serious product quality issue” from the 2018 revised draft standard MOU.

To clarify the meaning of “distribution of inordinate amounts of compounded drug products interstate,” the proposed definition of “distribution” in the 2018 revised draft standard MOU has been omitted and “distribution of compounded human drug products interstate” and “inordinate amounts” are defined. “Distribution of compounded human drug products interstate” means that a pharmacy or physician has sent (or caused to be sent) a compounded drug product out of the state in which the drug was compounded. A pharmacy has distributed an “inordinate amount” of compounded human drug products interstate if the number of prescription orders for compounded human drug products that the pharmacy distributed interstate during any calendar year is greater than 50 percent of the sum of: (1) the number of prescription orders for compounded human drug products that the pharmacy sent out of (or caused to be sent out of) the facility in which the drug products were compounded during that same calendar year; plus (2) the number of prescription orders for compounded human drug products that were dispensed (e.g., picked up by a patient) at the facility in which they were compounded during that same calendar year.

We received a number of comments on the 2015 draft standard MOU and the 2018 revised draft standard MOU stating that distributing and dispensing are mutually exclusive activities, such that if a drug product is distributed, it is not also dispensed, and vice versa. Some

comments asserted, in particular, that a compounded drug product should not be considered to be “distributed” when it is provided pursuant to a prescription. Other stakeholders, however, agreed with the inclusion of drug products provided pursuant to a prescription within the definition of “distribution” and maintained that this interpretation was important to protect the public health.

After considering these comments and the public health objectives of section 503A(b)(3)(B) of the FD&C Act, FDA considers that when a drug is picked up at the facility in which it was compounded, dispensing, but not distribution, occurs for purposes of 503A(b)(3)(B).

FDA believes that in-person dispensing, where the transaction between the compounder and the patient is completed at the facility in which the drug product was compounded, is appropriately overseen, primarily, by the State outside the context of the MOU, regardless of whether the compounded drug product subsequently leaves the State. Such an intrastate, local transaction generally indicates a close connection among the patient, compounder, and prescriber. By contrast, transactions by mail often have a less direct nexus among the patient, compounder, and prescriber than in-person pick-ups and would be considered “distribution.”

Drugs dispensed in-person that are later taken out of State will not contribute to reaching the threshold for inordinate amounts under the final MOU. Nor will complaints associated with compounded drug products dispensed this way and subsequently taken out of State be subject to the complaint investigation provisions of the final MOU. FDA expects that, in practice, the State in which the initial transaction occurred would handle such complaints. The State may, in its discretion, notify FDA of the complaint.

FDA is not persuaded by comments urging the Agency to interpret “distribution” and “dispensing” to be entirely separate activities for purposes of section 503A(b)(3)(B) of the

FD&C Act. These comments recommend using definitions for these terms used elsewhere in the FD&C Act and FDA regulations, and generally conclude that distribution does not include the transfer of a drug pursuant to a prescription.

The conditions in section 503A, including section 503A(b)(3)(B), must be interpreted consistent with the prescription requirement in section 503A(a) of the FD&C Act. If we were to interpret the word “distribution” to apply only if a drug is provided without a prescription, it would mean that drug products compounded under section 503A of the FD&C Act are excluded from regulation under the MOU and the 5 percent limit, because to qualify for the exemptions under section 503A, a compounder must obtain a valid prescription order for an individually identified patient. For the reasons stated previously in this document, we believe this would achieve the opposite of what Congress intended. A compounded drug product may be eligible for the exemptions under section 503A of the FD&C Act only if it is, among other things, “compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.”

Nor is there anything to suggest that Congress understood “distributed” and “dispensed” to be mutually exclusive categories rather than overlapping categories for purposes of section 503A. Section 503A(b)(3)(B) of the FD&C Act does not define “distribution” to exclude dispensing, which Congress has done elsewhere when that was its intention.³ The definition

³ In other (non-compounding) contexts, where it would further a regulatory purpose, Congress and the Agency have specifically defined “distribute” to exclude dispensing. See, for example, section 581(5) of the FD&C Act (21 U.S.C. 360eee(5)), which applies to Title II of the DQSA, and 21 CFR 208.3, which applies to 21 CFR part 208. Section 503A of the FD&C Act does not contain a similar definition, or a similar specific direction to exclude dispensing from the meaning of distribution. We also note that these definitions were adopted for provisions that focus on conventionally manufactured drug products, which assign different obligations to dispensers than to wholesalers, packagers, or other intermediaries in light of the different role that dispensers play with respect to product labeling and the drug distribution chain. In contrast, section 503A of the FD&C Act focuses on

proposed by comments would write an exclusion for dispensing, in its entirety, into the statute where Congress did not. Indeed, with respect to comments suggesting that drugs dispensed pursuant to prescriptions could not also be “distributed,” we note that, in section 503A(b)(3)(B), Congress specifically contemplated that prescription orders could be “distributed” when it directed the Agency to count the number of prescription orders that pharmacists and prescribers distributed.

IV. Other Issues

A. Authority of State Boards of Pharmacy or other Appropriate State Agencies

The 2018 revised draft standard MOU proposed that “States” would be the signatories of the MOU. In the final standard MOU, FDA clarifies the State party to the agreement, which is described as the “State Board of Pharmacy or other appropriate State agency.” FDA received comments expressing concerns that the State entity signing the MOU (e.g., the State Board of Pharmacy) may not have regulatory authority over physician compounding and could not agree to the MOU provisions regarding physicians as they appeared in the 2018 revised draft standard MOU. With regard to physician compounding, FDA has revised certain provisions from the 2018 revised draft standard MOU. Under the final standard MOU, a State Board of Pharmacy or other appropriate State agency would enter into the MOU on behalf of the State and agree to (1) notify FDA and the appropriate regulator of physicians within the State when it receives a complaint about adverse drug experiences or product quality issues associated with a human drug product compounded by a physician and distributed outside the State; and (2) if it becomes

compounded drugs, and the reasons for defining “distribution” to exclude dispensing in Title II of the DQSA or part 208 do not apply.

aware of a physician distributing any amount of compounded human drug products interstate, notify FDA and the appropriate regulator of physicians within the State.

B. Physician Compounding

It is FDA's understanding that physicians who compound drugs generally do so for their own patients, within their own professional practice, and provide them intrastate. FDA believes that, generally, physicians are not engaged in compounding that results in routine distribution of compounded drug products interstate.

Additionally, several comments advised that State Boards of Pharmacy do not oversee physician compounding and would not be able to agree to the provisions under the 2018 revised draft standard MOU with respect to oversight of physician compounding (collecting additional information to identify whether a physician compounder is distributing inordinate amounts of compounded drug products interstate, etc.). Accordingly, under the final standard MOU, State Boards of Pharmacy or other appropriate State agencies would agree to (1) notify FDA and the appropriate regulator of physicians within the State when they receive complaints about adverse drug experiences or product quality issues associated with a human drug product compounded by a physician and distributed outside the State; and (2) if they become aware of a physician distributing any amount of compounded human drug products interstate, notify FDA and the appropriate regulator of physicians within the State. The information provided to FDA will help inform Agency inspectional priorities with respect to physicians who compound human drug products and provide information to State regulators of physicians for appropriate action.

C. Development of a Standard MOU

A number of comments on the 1999 draft standard MOU, the 2013 draft 503A guidance, the 2015 draft standard MOU, and the 2018 revised draft MOU suggested that FDA negotiate

MOUs with individual States, rather than develop a standard MOU. Section 503A of the FD&C Act requires the Agency to develop a standard MOU for use by the States. Furthermore, it would be impractical to develop an individualized MOU with every State, and creating individualized MOUs would create a patchwork of regulation of distribution of compounded human drug products interstate by compounders seeking for their drug products to qualify for the exemptions under section 503A of the FD&C Act. This would be confusing to the healthcare community, as well as regulators.

D. Exemptions from the Provisions Related to Distribution of Inordinate Amounts of Compounded Human Drug Products Interstate

Some comments on the 2013 draft 503A guidance, the 2015 draft standard MOU, and the 2018 revised draft standard MOU requested that we consider exempting certain drug products or types of compounding entities from the threshold in the MOU and the 5 percent limit. For example, some comments recommended that we exempt nonsterile products.

American consumers rely on the FDA drug approval process to ensure that medications have been evaluated for safety and effectiveness before they are marketed in the United States. Drugs made by compounders, including those made at outsourcing facilities, are not FDA-approved. This means that they have not undergone premarket review of safety, effectiveness, or manufacturing quality. Therefore, when an FDA-approved drug is commercially available, FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug product unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product.

In section 503A of the FD&C Act, Congress enacted several conditions to differentiate compounders from conventional manufacturers and provided that only if the compounders meet those conditions can they qualify for the exemptions from the drug approval requirements in section 505 of the FD&C Act. One of those conditions relates to limitations and other measures to address distribution of compounded drug products interstate, and FDA intends to enforce those provisions to differentiate compounding that qualifies for the exemptions from conventional manufacturing in the guise of compounding that does not and will apply the conditions to all types of drugs and all categories of compounding.

E. Information Sharing Between the State Boards of Pharmacy or Other Appropriate State Agencies and FDA

The final standard MOU provides that State Boards of Pharmacy or other appropriate State agencies will agree to notify FDA of a complaint relating to a compounded human drug product distributed outside the State involving a serious adverse drug experience or serious product quality issue and provide information about those experiences and issues. The final standard MOU also provides that State Boards of Pharmacy or other appropriate State agencies will notify FDA if they identify a pharmacy that has distributed inordinate amounts of compounded human drug products interstate. In addition, State Boards of Pharmacy or other appropriate State agencies will notify FDA and the appropriate regulator of physicians within the State if the State entity becomes aware of a physician who is distributing any amount of compounded human drug products interstate, or if the State entity receives a complaint involving an adverse experience or product quality issue relating to a human drug product compounded by a physician and distributed outside the State.

FDA has entered into a cooperative agreement with NABP to establish an information sharing network that is intended to, in part, facilitate State information reporting to FDA by State Boards of Pharmacy or other appropriate State agencies that enter into the MOU with FDA addressing distribution of compounded drugs interstate.⁴ The goal of this information-sharing and research initiative is to improve the management and sharing of information available to State regulators and FDA regarding State-licensed compounders and the distribution of compounded human drug products interstate to support better and more targeted regulation and oversight of compounding activities to help reduce risk to patients. This information will be important to help States to focus their limited resources on compounders for which they have primary oversight responsibility that present the greatest risk. It will also facilitate FDA's ability to determine when additional Federal oversight is warranted, such as when a large-scale compounder distributes drug products to multiple States, potentially causing significant and widespread harm if its products are substandard. FDA expects that the information sharing network will be designated by FDA for purposes of the MOU to collect, assess, and allow review and sharing of information pursuant to the MOU. FDA regularly posts, on its compounding website, information about enforcement and other actions related to compounders that violate the FD&C Act, and it is obligated to share certain information with States under section 105 of the DQSA. In addition to these measures, FDA is taking steps to proactively share information with States about complaints that it receives regarding compounded drug products, consistent with Federal laws governing information disclosure.

*F. Enforcement of the 5 Percent Limit on Distribution of Compounded Human Drug Products
Out of the State in Which They Are Compounded*

⁴ See RFA-FD-19-025, available at <https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-19-025.html>.

In the 2013 draft 503A guidance, FDA stated that it does not intend to enforce the 5 percent limit on distribution of compounded human drug products outside of the State in which they are compounded until 90 days after FDA has finalized a standard MOU and made it available to the States for their consideration and signature. Most comments on the 2013 draft 503A guidance that raised this issue said this period was too short but did not recommend a specific alternative. A few comments recommended a different timeframe, one recommending 120 days and another recommending 365 days. The 1997 Senate Committee Report for the Food and Drug Administration Modernization Act suggests that a 180-day period for States to decide whether to sign might be appropriate.⁵ In the notice of availability for the 2018 revised draft standard MOU, consistent with the 2015 draft standard MOU, the Agency proposed a 180-day period after the final standard MOU is made available for signature before FDA will enforce the 5 percent limit in States that have not signed the MOU, and invited public comment on whether this was an appropriate timeframe. Some commenters on the 2018 revised draft standard MOU stated that more time may be necessary because some States may be required to enact new laws and promulgate new regulations before entering the MOU. Therefore, in response to these comments, FDA is providing a 365-day period for States to decide whether to sign the MOU before FDA intends to begin enforcing the 5 percent limit in States that do not sign. It is FDA's understanding that this extended timeframe corresponds to a full legislative cycle for most States and should, therefore, afford sufficient time for States to modify their laws and regulations, if necessary.

⁵ “[U]ntil the State . . . enters into a memorandum of understanding (MOU) with the Secretary or 180 days after the development of the standard MOU, whichever comes first, the [section 503A] exemption shall not apply if inordinate quantities of compounded products are distributed outside of the State in which the compounding pharmacy or physician is located.” (U.S. Senate Committee Report)

V. Paperwork Reduction Act of 1995

This MOU refers to previously approved collections of information. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information have been approved under OMB control number 0910-0800.

VI. Electronic Access

Persons with access to the internet may obtain the final standard MOU at either <https://www.fda.gov/drugs/human-drug-compounding/regulatory-policy-information>, <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, or <https://www.regulations.gov>.

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