TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

| Type of recordkeeping | Number of recordkeepers | Number of records per recordkeeper | Total annual records | Average burden per recordkeeping (hours) | Total hours |
|---|---|---|---|---|---|
| Records of adverse events, including records of efforts to obtain the data elements for each adverse event report | 50 | 1 | 50 | 16 | 800 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

## III. Comments

Interested persons may submit either electronic comments regarding this document to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments can be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

## IV. Electronic Access

Persons with access to the Internet may obtain the document at either *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.regulations.gov.*

Dated: February 11, 2015.

**Leslie Kux,**

*Associate Commissioner for Policy.*

[FR Doc. 2015–03419 Filed 2–18–15; 8:45 am]

**BILLING CODE 4164–01–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2014–N–1459]**

### Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the States and the Food and Drug Administration; New Proposed Draft; 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 for public comment of a draft standard memorandum of understanding (MOU) entitled ''Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert State] and the U.S. Food and Drug Administration.'' The draft standard MOU describes the responsibilities of the State that chooses to sign the MOU in investigating and responding to complaints related to compounded human drug products distributed outside the State and in addressing the interstate distribution of inordinate amounts of compounded human drug products.

FDA is also announcing the withdrawal of an earlier draft standard MOU entitled ''Memorandum of Understanding on Interstate Distribution of Compounded Drug Products,'' which was issued in January 1999. The January 1999 draft standard MOU is superseded by the new draft standard MOU.

**DATES:** FDA is withdrawing its draft standard MOU that published on January 21, 1999 (64 FR 3301), as of February 19, 2015. Submit either electronic or written comments on the new draft standard MOU by June 19, 2015. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by June 19, 2015 (see the ''Paperwork Reduction Act of 1995'' section of this document).

**ADDRESSES:** Submit written requests for single copies of the MOU to Edisa Gozun, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Suite 5100, Silver Spring, MD 20993–0002. Send one self-addressed label to assist that office in processing your request. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the new draft standard MOU.

Submit electronic comments on the new draft standard MOU or on the collection of information to *http://www.regulations.gov.* Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Edisa Gozun, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Suite 5100, Silver Spring, MD 20993–0002, 301–796–3110.

**SUPPLEMENTARY INFORMATION:**

## I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (the 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 compounded 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 (see section 503A(b)(3)(B)(i) and (b)(3)(B)(ii) of the FD&C Act).

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).

## 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 provisions in section 503A,[1] the draft standard MOU was never 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 is implementing section 503A, including the provisions on the MOU. By this notice, FDA is withdrawing the 1999 draft standard MOU, and the new draft standard MOU made available today supersedes that draft standard MOU.

## III. New 503A Guidance

Immediately after the enactment of the DQSA, in December 2013, the Agency published 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) announcing the availability of the draft guidance). That draft guidance described FDA's proposed policy with regard to specific provisions of section 503A of the FD&C Act that require rulemaking or other action by FDA, such as the MOU provisions. Thirty-one commenters on the 2013 draft 503A guidance offered FDA their views on the MOU provisions of section 503A. FDA considered these comments in developing the new draft standard MOU. The final 503A guidance, published July 2, 2014 (see 79 FR 37742 announcing the availability of the final 503A guidance), states that FDA does not intend to enforce the 5 percent limit on distribution of compounded drug products out of the State in which they are compounded until after FDA has finalized an MOU and made it available to the States for their consideration and signature. After considering any comments on the new draft standard MOU submitted to this docket, FDA intends to finalize the standard MOU and make it available for signature by individual States. FDA will determine at the time of publication of the final MOU how long it will allow States to consider whether to sign the MOU before FDA begins to enforce the 5 percent limit in those States that have not signed an MOU.

## IV. New Draft Standard MOU

FDA has now developed a new draft standard MOU on which it is soliciting public comment. FDA has consulted with NABP in developing this new draft standard MOU. FDA also considered the comments submitted in 1999 on the previous draft standard MOU, as well as comments on the MOU provisions it received in connection with the published 2013 draft 503A guidance. Key provisions of the new draft standard MOU are summarized and discussed in this section of the document and, where appropriate, compared to the provisions in the 1999 draft standard MOU.

### *A. Investigation of Complaints*

The new draft standard MOU provides that States that enter into the MOU will agree to:

- Investigate complaints relating to human drug products compounded in the State and distributed outside the State, including complaints about adverse drug experiences or certain product quality issues to, among other things, determine whether there is a potential public health risk or safety concern, and confirm that any risk or safety concern is adequately contained;
- As appropriate, take action to ensure that the relevant compounding pharmacy, pharmacist, or physician determines the root cause of the problem and eliminates any public health risk identified in relation to the complaint;
- Notify FDA within 72 hours of any complaints relating to a compounded human drug product distributed outside the State involving a potential public health risk or immediate safety concern, such as a report of a serious adverse drug experience or serious product quality issue, the State's initial assessment of the validity of the complaint, and any actions the State has taken or plans to take to address such complaints;
- Provide FDA with certain information about the complaint, including the following:
  - Name and contact information of the complainant;
  - name and address of the pharmacist/pharmacy/physician that is the subject of the complaint;
  - a description of the complaint, including a description of any compounded drug product that is the subject of the complaint;
  - the State's initial assessment of the validity of the complaint relating to a compounded human drug product distributed outside the State; and
  - a description and date of any actions the State has taken to address the complaint; and
- Maintain records of the complaints it receives, the investigation of each complaint, and any response to or action taken as a result of a complaint, beginning when the State receives notice of the complaint. The draft standard MOU says that the State agrees to maintain these records for at least 3 years, beginning on the date of final action or the date of a decision that the complaint requires no action.

The new draft standard MOU, as compared to the 1999 draft standard MOU, clarifies that the types of complaints of compounded human drug products that should be investigated include *any* adverse drug experience (not just *serious* adverse drug experiences, which were identified as an example of the types of complaints to be investigated in the 1999 draft standard MOU) and product quality issues that, if left uncorrected, could lead to potential public health risks or safety concerns. Even nonserious 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 product contamination from inadequate sterile practices at the compounding pharmacy. If the pharmacy has inadequate sterile practices, other more serious contamination could result in serious adverse events.

FDA is clarifying that the complaints that States agree to investigate under the MOU are only those complaints that are made about compounded human drug products distributed outside the State. In contrast to the 1999 draft standard MOU, the new draft standard MOU does not contain a provision that would require the States entering into the MOU with FDA to agree to investigate alleged violations of the FD&C Act. Upon further reflection, FDA has tentatively concluded that it would be more appropriate for FDA to determine whether a particular action is a violation of Federal law. Of course, if any State identifies a potential violation of Federal law, it is encouraged to report it to FDA.

Furthermore, the new draft standard MOU does not include specific directions to the States relating to how to conduct their investigation of

[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).

complaints. Rather, as recommended by comments previously submitted on the 1999 draft standard MOU, the details of such investigations are left to the States' discretion.

States signing the new standard MOU would agree to notify FDA about certain complaints and provide FDA with certain information about the complaint so FDA could investigate the complaint itself, or take other appropriate action.[2]

*B. Inordinate Amounts*

The new draft standard MOU provides that States that enter into the MOU will agree to:

- Review compounding records during inspections of compounding pharmacies to identify whether the compounding pharmacy, or the compounding pharmacist or physician, is distributing inordinate amounts of compounded human drug products interstate;
- Notify FDA if the State identifies any pharmacy, pharmacist, or physician within its jurisdiction that has distributed inordinate amounts of compounded human drug products interstate;
- Take action regarding any pharmacy, pharmacist, or physician that distributes inordinate amounts of compounded human drug products interstate; and
- Provide FDA with certain information, including the following:
  - The name and address of the pharmacy/pharmacist/physician;
  - a description of the evidence indicating that the pharmacy/pharmacist/physician has distributed inordinate amounts of compounded human drug products interstate, including a description of any compounded drug product that was distributed in inordinate amounts; and
  - a description and date of any actions the State has taken to address the distribution of inordinate amounts of compounded human drug product interstate.

In the new draft standard MOU, a pharmacist, pharmacy, or physician is considered to have distributed an inordinate amount of compounded human drug products interstate if 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 by such pharmacist, pharmacy, or physician during that calendar month. FDA does not intend to include in the consideration of inordinate amounts those prescriptions dispensed to a patient (or patient's agent), where the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patient (or the patient's agent) at the facility in which the drug was compounded.[3] This concept would be called the 30 percent limit.

The 1999 draft standard MOU defined ''inordinate amounts'' as the number of compounded prescriptions dispensed or distributed interstate annually by a pharmacy or physician that is equal to or greater than 20 percent of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician; or the number of compounded prescriptions dispensed or distributed interstate annually by a pharmacy or physician that is less than 20 percent of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician, but prescriptions for one or more individual compounded drug products (including various strengths of the same active ingredient) dispensed or distributed interstate constitute more than 5 percent of the total number of prescriptions dispensed or distributed. The 1999 draft standard MOU also included an exclusion from calculations to determine inordinate amounts for ''local'' interstate distribution to patients within 50 miles of the compounding pharmacy, and for interstate distribution in response to a public health emergency or catastrophic event.

Many comments on the 1999 draft standard MOU opposed the percentage limits it contained, and some comments on the 2013 draft 503A guidance opposed any definition of inordinate amounts that would significantly restrict interstate distributions under section 503A of the FD&C Act. Other comments suggested not defining ''inordinate amounts,'' leaving the definition up to the States, or defining the term as ''the amount that would be considered conventional manufacturing.'' FDA is proposing the 30 percent limit as the definition of ''inordinate amounts'' for the following reasons.

Section 503A of the FD&C Act reflects Congress' recognition that human drug compounding may be appropriate when it is based on receiving a valid prescription or notation for an identified individual patient. However, drug products compounded under this section of the FD&C Act are not required to demonstrate that they are safe or effective, bear adequate directions for use, or conform to CGMP. Congress, therefore, imposed strict limits on the distribution of drug products compounded under this section 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. Although other provisions of the FD&C Act apply to state-licensed pharmacies and physicians that may qualify for the exemptions under section 503A of the FD&C Act (*e.g.,* the adulteration provisions for making drugs under insanitary conditions), and although FDA may take action in appropriate cases against compounders that violate these provisions or that operate outside of the conditions in section 503A, Congress recognized that these compounders are primarily overseen by the States. If a substantial proportion of a compounder's drugs are distributed outside a State's borders, adequate regulation of those drugs poses significant challenges to State regulators. States face logistical, regulatory, and financial challenges inspecting compounders located outside of their jurisdiction. In addition, particularly if a compounder distributes drugs to multiple States, it can be very difficult to gather the scattered information about possible adverse events associated with those drugs, 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) of the FD&C Act limits the distribution of compounded human drug products outside of the State in which they are compounded under section 503A(a) 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 human drug products interstate and provides for appropriate

[2] FDA is currently considering whether to propose regulations or issue guidance documents to further its implementation of section 503A(b)(3)(B) of the FD&C Act. Notice of any such action will be provided in the **Federal Register**.

[3] Drugs that a patient takes across state lines in this manner are distributed interstate. However, for reasons explained in this notice, FDA's draft standard MOU does not count them toward the limit on distributing inordinate amounts of compounded drug products interstate.

investigation by a State agency of complaints relating to compounded human drug products distributed outside such State. Implementation of this provision requires FDA to determine whether a limit higher than 5 percent would be appropriate, provided the States make certain agreements: A State agrees to appropriately investigate complaints relating to compounded human drug products distributed out of the State and agrees to address the distribution of amounts that would be inordinate.

FDA tentatively concludes that if a State agrees to meet the conditions set forth in this MOU, distribution interstate up to the 30 percent limit would not be inordinate. This conclusion is based on FDA's expectation that States signing the MOU would appropriately investigate complaints about compounded human drug products distributed out of State, and address compounders distributing an inordinate amount of compounded drug products out of the state in which they are compounded. FDA's current view is that its proposed limit would appropriately balance the benefits of access to compounded human drug products with the need to protect the public health and the drug approval system. We do not believe that an additional limit is necessary for the distribution of an individual compounded drug product such as that contained in the 1999 draft standard MOU.

In developing the new draft standard MOU, we considered that patients can now obtain compounded human drug products from outsourcing facilities,[4] which are not subject to volume restrictions on interstate distribution. This could mitigate the access concerns noted in some comments FDA received on the definition of ''inordinate amounts'' in the 1999 draft standard MOU, and in more recent comments expressing concerns about access if ''inordinate amounts'' is defined restrictively or the 5 percent limit is enforced.

It is appropriate to provide a bright line test for when compounding pharmacies located in States that sign the MOU cross the line to conventional manufacturing that should be subject to all of the requirements of the FD&C Act, including the new drug approval and CGMP requirements. Congress provided such a bright line test, the 5 percent limit, for compounders located in States that do not sign the MOU.

Some commenters in response to the 1999 draft MOU and the 2013 draft 503A guidance were concerned with limitations on interstate distribution of compounded human drug products to contiguous States. In the 1999 draft MOU, the calculation of ''inordinate amounts'' excluded compounded human drug products that were distributed interstate but within 50 miles of the pharmacy or physician's office. After considering the provision in the 1999 draft MOU and the comments, FDA believes that the 30 percent limit on inordinate amounts provided in this new draft standard MOU is high enough that special calculations to address interstate distribution between contiguous States or over short distances are not needed. Moreover, the new draft standard MOU includes consideration of inordinate amounts of prescriptions dispensed to a patient (or patient's agent), if the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patient (or patient's agent) at the facility in which the drug was compounded. We also do not intend to count as part of the 5 percent limit on distribution out of the State prescriptions dispensed to a patient (or patient's agent), if the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patient (or patient's agent) at the facility in which the drug was compounded. We believe this treatment of these transactions where there are direct relationships among the patient, the prescriber, and the pharmacist or physician compounding the drug is consistent with section 503A of the FD&C Act.

Finally, the new draft standard MOU does not exclude from the calculation of ''inordinate amounts'' interstate distributions in response to a public health emergency or catastrophic event. We believe the 30 percent limit affords adequate opportunity for interstate distributions and note that outsourcing facilities may be able to compound drugs in an emergency and drugs on FDA's drug shortage list, further mitigating access concerns.

### *C. Definitions*

The Appendix to the new draft standard MOU defines key terms used in the MOU, including ''adverse drug experience,'' ''serious adverse drug experience,'' ''product quality issue,'' ''serious product quality issue,'' and ''distribution.'' The definitions of ''adverse drug experience,'' ''serious adverse drug experience,'' ''product quality issue,'' and ''serious product quality issue'' are taken from relevant sections of FDA's regulations (see 21 CFR 310.305 and 314.81). For purposes of the new draft standard MOU, a ''distribution'' occurs when a compounded human drug product leaves the facility in which the drug was compounded. Distribution includes delivery or shipment to a physician's office, hospital, or other health care setting for administration and dispensing to an agent of a patient or to a patient for his or her own use. However, the definition notes that, to qualify for the exemptions under section 503A of the FD&C Act, a compounder must obtain a prescription for an individually identified patient (section 503A(a)), and the draft standard MOU would not alter this condition. Interstate distributions of compounded drug products would count toward the 30 percent limit whether or not the compounded drug products satisfied the prescription condition, or other conditions, in section 503A of the FD&C Act.

Some comments on the 2013 draft 503A guidance state that provisions in the standard MOU relating to drug distribution should not apply to dispensed drugs. Although the comments do not share a single definition of dispensing, or offer a detailed definition, they generally take the position that a drug is dispensed when it is provided pursuant to a prescription or doctor's order, and that dispensing is not a form of distribution. We have not adopted this approach, and propose a definition of distribution that we believe is consistent with the text and purpose of section 503A of the FD&C Act. Under our draft standard MOU, a distribution occurs when a compounded drug leaves the facility where it was made, regardless of whether the drug is also deemed to be dispensed.

Section 503A(b)(3)(B) of the FD&C Act directs FDA to include provisions in the MOU regarding the distribution of compounded drugs. The section does not define distribution to exclude dispensing, which Congress has done elsewhere when that was its intention.[5]

[4] The DQSA adds new section 503B to the FD&C Act (21 U.S.C. 353b). Under section 503B(b) of the FD&C Act, a compounder may elect to become an outsourcing facility by registering with FDA. Products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act and the requirement to label products with adequate directions for use under section 502(f)(1) of the FD&C Act if the requirements in section 503B are met. Outsourcing facilities will be inspected by FDA and must comply with other provisions of the FD&C Act, such as CGMP requirements.

[5] In different contexts, where it would further a regulatory purpose, Congress and the Agency have specifically defined distribute to exclude

Continued

Our proposed definition implements the purpose of section 503A(b)(3)(B) of the FD&C Act, which is to limit and regulate compounded drugs that are sent out of the state in which they are made.[6] Our definition is also consistent with the ordinary meaning of distribute; it is natural to say that an entity compounding under section 503A of the FD&C Act distributes the drugs it makes to patients and health care providers, just as the manufacturers of other regulated articles are said to distribute their products to their customers. The definition proposed by comments, on the other hand, would write an exclusion for dispensing into the statute where Congress did not. It would also mean that drug products compounded under section 503A of the FD&C Act are excluded from the MOU and the 5 percent limit, because, in order 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 section IV.B of this document, we believe this would achieve the opposite of what Congress intended.

In support of their alternative approach, commenters note that in section 503A(b)(3)(B)(ii) of the FD&C Act, Congress directed FDA to calculate the quantity of ''prescription orders dispensed and distributed'' when the Agency applies the 5 percent limit to compounders in states that do not sign the MOU. This language, however, supports FDA's proposed approach, because it makes clear that Congress understood the word distribute in this section to refer to filling prescription orders; otherwise it would not have directed the Agency to count the number of prescription orders that pharmacists and prescribers ''distributed.'' Nor is there anything to suggest that Congress understood distributed and dispensed to be mutually exclusive categories rather than overlapping categories. Given the statutory text and purpose, we believe that Congress referred to drugs dispensed or distributed in section 503A(b)(3)(B) of the FD&C Act to make clear that the Agency must not limit its calculation of total prescription orders to compounded drugs that the pharmacy or prescriber makes, but also include any other prescription orders, such as conventionally manufactured drugs, for which the pharmacist or prescriber serves solely as the dispenser.

## V. Other Issues

### *A. Development of a Standard MOU*

A number of commenters on both the 1999 draft MOU and on the 2013 draft 503A guidance suggested that FDA specifically 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 interstate distribution from compounders seeking to qualify for the exemptions under section 503A of the FD&C Act. This would be confusing to the health care community, as well as regulators.

### *B. Exemptions From the Interstate Distribution Provisions*

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

Congress did not exempt any particular drug products or compounding entities from the 5 percent limit. Furthermore, FDA believes that the 5 percent limit and the MOU limit on inordinate amount provisions are important to distinguish pharmacy compounding from conventional manufacturing in the guise of compounding, and to protect consumers and the integrity of the drug approval process. 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 human drug compounding 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 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 manufacturers and provided that only if they 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 on the interstate distribution of compounded human drug products, 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.

### *C. Information Sharing Between States and FDA*

Several commenters on the 1999 draft MOU proposed that signatories to the MOU would agree to share information on a variety of subjects. The new draft standard MOU provides that States will agree to notify FDA of any complaint relating to a compounded human drug product distributed outside the State involving a potential public health risk or immediate safety concern, such as a report of a serious adverse drug experience or serious product quality issue, and provide information about those events and issues. The new draft standard MOU also provides that States will notify FDA if they identify a pharmacist, pharmacy, or physician within their jurisdiction that has distributed inordinate amounts of compounded human drug products interstate. In addition, FDA regularly posts on its compounding Web site 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.

dispensing. See, for example, section 581(5) of the FD&C Act, which applies to Title II of the DQSA, and 21 CFR 208.3, which applies to 21 CFR part 208 of our regulations. Section 503A of the FD&C Act does not contain a similar definition, or 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 compounded drugs, and the reasons for defining distribution to exclude dispensing in Title II of the DQSA or part 208 do not apply.

[6] See discussion of the purposes of section 503A of the FD&C Act in section IV.B, supra.

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

In the 2013 draft 503A guidance, FDA stated that it does not intend to enforce the 5 percent limit on distribution of compounded 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 commenters on the 2013 draft 503A guidance said this period was too short, but did not recommend a specific alternative. A few commenters 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.[7] The Agency proposes 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 invites public comment on whether this is the appropriate timeframe. FDA will announce at the time it publishes the final standard MOU and makes it available for signature when it intends to begin enforcing the 5 percent limit in States that do not sign.

**VI. Paperwork Reduction Act**

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. ''Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)), requires Federal Agencies to provide a 60-day notice in the **Federal Register** for each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Section 503A of the FD&C Act describes, among other things, the circumstances under which certain human drug products compounded by a licensed pharmacist or licensed physician are exempt from certain sections of the FD&C Act. One of the conditions to qualify for the exemptions listed in section 503A of the FD&C Act is that: (1) The human drug product is compounded in a State that has entered into an MOU with FDA that addresses the distribution of inordinate amounts of compounded human drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded human drug products distributed outside such a State; or (2) if the human 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 human drug products out of the State in which they are compounded, more than 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (see section 503A(b)(3)(B)(i) and (b)(3)(B)(ii).

Section 503A(b)(3) directs FDA, in consultation with the NABP, to develop a standard MOU for use by states in complying with the provisions concerning the interstate distribution of inordinate amounts of compounded human drug products interstate and appropriate investigation by a State agency of complaints relating to compounded human drug products distributed outside such State.

The new draft standard MOU contains the information collections that must be approved by OMB under the PRA. These information collections are described in this section of the document. For purposes of this analysis, FDA assumes that 25 States will sign the standard MOU with FDA.

Under section III.a. of the new draft standard MOU, the State will notify FDA by email at *StateMOU@fda.hhs.gov* within 72 hours of receiving any complaint relating to a compounded human drug product distributed outside the State involving a potential public health risk or immediate safety concern, such as a report of a serious adverse drug experience or serious product quality issue. The notification will include the following information: (1) The name and contact information of the complainant, in the case of a complaint; (2) the name and address of the pharmacist, pharmacy, and/or physician that is the subject of the complaint; (3) a description of the complaint, including a description of any compounded drug product that is the subject of the complaint; (4) the State's initial assessment of the validity of the complaint relating to a compounded human drug product distributed outside the State; and (5) a description and date of any actions the State has taken to address the complaint. In addition, the States will maintain records of the complaints they receive, the investigation of each complaint, and any response to or action taken as a result of a complaint, beginning when the State receives notice of the complaint. The States will maintain these records for at least 3 years, beginning on the date of final action or the date of a decision that the complaint requires no action.

Based on our knowledge of State regulation of compounding practices and related complaints, we estimate that annually a total of approximately 25 States (''no. of respondents'' in table 1, row 1) will notify FDA within 72 hours of receiving any complaint relating to a compounded human drug product distributed outside the State involving a potential public health risk or immediate safety concern. We estimate that each State will notify FDA annually of approximately 3 complaints it receives (''no. of responses per respondent'' in table 1, row 1), for a total of 75 notifications of complaints sent to FDA (''total annual responses'' in table 1, row 1). We estimate that preparing and submitting this information to us as described in the MOU will take approximately 0.5 hours per response (''average burden per response'' in table 1, row 1), for a total of 37.5 hours (''total hours'' in table 1, row 1).

We also estimate that a total of approximately 25 States (''no. of recordkeepers'' in table 2) will prepare and maintain records for 3 years of the complaints they receive, investigations of complaints, and on any State action

[7] ''[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, see note 2.)

taken or replies to complaints. We estimate that each State will receive approximately 3 complaints annually and will prepare and maintain approximately 5 records per each complaint the State receives, for a total of 15 records per State (''no. of records per recordkeeper'' in table 2), and a total of 375 records annually across all States (''total annual records'' in table 2). We further estimate that preparing and maintaining these records will take approximately 1 hour per record (''average burden per recordkeeping (in hours)'' in table 2), for a total of 375 hours (''total hours'' in table 2).

Under section III.a. of the new draft standard MOU, investigations performed by the State under this MOU will ensure that (1) the root cause of the problem that is the subject of the complaint is determined, (2) any risk or safety concern associated with the compounded human drug product is adequately contained (*i.e.,* there is no ongoing risk to the public), and (3) sufficient corrective action has been taken to eliminate any future public health risk.

Under section III.b of the new draft standard MOU, the States will notify FDA by email at *StateMOU@fda.hhs.gov* within 7 days of determining that a pharmacist, pharmacy, or physician within their jurisdiction has distributed inordinate amounts of compounded human drug products interstate, as described in the MOU. The notification should include the following information: (1) The name and address of the pharmacist/pharmacy/physician; (2) a description of the evidence indicating that the pharmacist/pharmacy/physician has distributed inordinate amounts of compounded human drug products interstate, including a description of any compounded drug product that was distributed in inordinate amounts; and (3) a description and date of any actions the State has taken to address the distribution of inordinate amounts of compounded human drug products interstate.

We estimate that annually a total of approximately 25 States (''no. of respondents'' in table 1, row 2) will notify FDA of their determination that a pharmacist, pharmacy, or physician has distributed inordinate amounts of compounded human drug products interstate. We estimate that each State will notify FDA annually of approximately 2 determinations it makes (''no. of responses per respondent'' in table 1, row 2), for a total of 50 determinations (''total annual responses'' in table 1, row 2). We estimate that preparing and submitting this information to FDA as described in the MOU will take approximately 0.5 hours per response (''average burden per response'' in table 1, row 2), for a total of 25 hours (''total hours'' in table 1, row 2).

Under section V of the current draft standard MOU, a State may designate a new liaison to the MOU by notifying FDA's administrative liaison in writing. If a State's liaison becomes unavailable to fulfill its functions under the MOU, the State will name a new liaison within 2 weeks and notify FDA.

We estimate that annually a total of approximately 13 States (''no. of respondents'' in table 1, row 3) will notify FDA of a new liaison to the MOU. We estimate that each State will submit to FDA annually approximately 1 notification of a new liaison (''no. of responses per respondent'' in table 1, row 3), for a total of 13 notifications of a new liaison (''total annual responses'' in table 1, row 3). We estimate that preparing and submitting each notification as described in the MOU will take approximately 0.2 hours per response (''average burden per response'' in table 1, row 3), for a total of 2.6 hours (''total hours'' in table 1, row 3).

Under section VI of the new draft standard MOU, a State may terminate its participation in the MOU by submitting to FDA a 30-day notice of termination.

We estimate that annually a total of approximately 1 State (''no. of respondents'' in table 1, row 4) will notify FDA that it intends to terminate its participation in the MOU. We estimate that this State will submit to FDA annually approximately 1 notification of termination (''no. of responses per respondent'' in table 1, row 4), for a total of 1 notification (''total annual responses'' in table 1, row 4). We estimate that preparing and submitting the notification as described in the MOU will take approximately 0.2 hours per notification (''average burden per response'' in table 1, row 4), for a total of 0.2 hours (''total hours'' in table 1, row 4).

Under section VI of the new draft standard MOU, if a State does not adhere to the provisions of the MOU, FDA may post a 30-day notice of termination on its Web site. As a result of this action by FDA, the State will notify all pharmacists, pharmacies, and physicians within the State of the termination and advise them that compounded human drug products may be distributed (or caused to be distributed) out of the State only in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by the pharmacist, pharmacy, or physician.

We estimate that annually a total of approximately 1 State (''no. of respondents'' in table 3) will submit 1 notification of termination as described in the MOU (''no. of disclosures per respondent'' in table 3) to the pharmacists, pharmacies, and physicians in its State for a total of 1 notification of termination (''total annual disclosures'' in table 3). We estimate that preparing and submitting each notification will take approximately 1 hour per notification (''average burden per disclosure (in hours)'' in table 3), for a total of 1 hour (''total hours'' in table 3).

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]

| Compounding MOU between FDA and States | Number of respondents | Number o esponses per respondent | Total annual responses | Average burden per response | Total hours |
|---|---|---|---|---|---|
| State notifies FDA of compounding complaints it receives | 25 | 3 | 75 | 0.5 | 37.5 |
| State notifies FDA of the distribution of inordinate amounts of compounded drug products | 25 | 2 | 50 | 0.5 | 25 |
| State notifies FDA of a new liaison to the MOU | 13 | 1 | 13 | 0.2 | 2.6 |
| State notifies FDA of its intent to terminate participation in the MOU | 1 | 1 | 1 | 0.2 | 0.2 |
| Total | 64 | 7 | 139 | N/A | 65.3 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

| Compounding MOU between FDA and States | Number of recordkeepers | Number of records per recordkeeper | Total annual records | Average burden per recordkeeping (in Hours) | Total Hours |
|---|---|---|---|---|---|
| State recordkeeping for 3 years of compounding complaints | 25 | 15 | 375 | 1 | 375 |
| Total | 25 | 15 | 375 | 1 | 375 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 3—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN [1]

| Compounding MOU between FDA and States | Number of respondents | Number of disclosures per respondent | Total annual disclosures | Average burden per disclosure (in Hours) | Total hours |
|---|---|---|---|---|---|
| State notification to pharmacists, pharmacies, and physicians that its participation in the MOU has been terminated by FDA | 1 | 1 | 1 | 1 | 1 |
| Total | 1 | 1 | 1 | 1 | 1 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

## VII. Request for Comments

FDA invites comments from interested persons on the new draft standard MOU that would establish an agreement between the signatory States and FDA regarding the appropriate investigation by such States of complaints relating to compounded human drug products distributed outside the State, and the distribution of inordinate amounts of compounded human drug products interstate. The Agency is providing a 120-day comment period.

After considering any comments on the new draft standard MOU submitted to this docket, FDA intends to finalize the standard MOU and make it available for signature by individual States. FDA will determine at the time of publication of the final MOU how long it will allow States to consider whether to sign the MOU before FDA begins to enforce the 5 percent limit in those States that have not signed an MOU.

Interested persons may submit either electronic comments regarding this document to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

## VIII. Electronic Access

Persons with access to the Internet may obtain the draft standard MOU at *http://www.regulations.gov.*

Dated: February 12, 2015.

**Leslie Kux,**

*Associate Commissioner for Policy.*

[FR Doc. 2015–03420 Filed 2–18–15; 8:45 am]

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2014–D–1525]**

### Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application; Draft Guidance for Industry; Availability

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is announcing the availability of a draft guidance for industry entitled ''Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.'' This draft guidance describes the conditions under which FDA does not intend to take action against a state-licensed pharmacy, a Federal facility, or outsourcing facility that mixes, dilutes, or repackages certain biological products without obtaining an approved biologics license application (BLA).

**DATES:** Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by May 20, 2015.

**ADDRESSES:** Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2201, Silver Spring, MD 20993–0002; or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 71, Rm. 3128, 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 guidance document.

Submit electronic comments on the guidance to *http://www.regulations.gov.* Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Leah Christl, Center for Drugs Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6426, Silver Spring, MD 20903, 301–796–0869; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903