July 18, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on Draft Guidances for Industry Regarding Compounding Under the Federal Food, Drug, and Cosmetic Act

Docket Nos. FDA-2016-D-0269 / FDA-2016-D-0271 / FDA-2016-D-0238

Dear Sir or Madam:

We, the undersigned, submit these comments on the three draft guidances issued by the Food and Drug Administration in April 2016 regarding compounding under the Federal Food, Drug, and Cosmetic Act (FDCA) in support of the Agency's efforts to safeguard patient safety through effective implementation of the statute's compounding provisions. We represent a range of stakeholders dedicated to safeguarding patient safety by ensuring patients have access to high quality, FDA-approved medicines and, where medically necessary, compounded medicines that are subject to appropriate safety standards and FDA oversight.

The Compounding Quality Act (CQA), which amended section FDCA 503A and added the new section 503B, was enacted to address gaps in regulatory oversight that precipitated a national meningitis outbreak linked to contaminated compounded drugs shipped across the country. This tragedy showed that, although access to medically necessary compounded drugs is important, this access cannot come at the expense of drug quality and patient safety. For this reason, Congress established in section 503B specific requirements that outsourcing facilities engaged in large-scale drug compounding must satisfy—such as complying with good manufacturing practices, being subject to FDA inspections, and reporting adverse events. It further affirmed, by retaining and amending section 503A, that traditional compounding pharmacies that do not meet these standards must prepare product only for individual patients upon receipt of, or in limited quantities in anticipation of, a prescription, thus ensuring that the traditional relationship between the compounder, the physician, and the patient is preserved.

The new statutory framework for outsourcing facilities has received a significant response: as of June 24, 2016, 66 outsourcing facilities have voluntarily submitted registration information with FDA to compound drugs in accordance with section 503B's requirements.[1] We applaud FDA's continued efforts to work with compounding pharmacies, outsourcing facilities, drug

[1] FDA, Facilities Registered As Human Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm.

manufacturers, professional medical associations, patient groups, and other stakeholders to implement and enforce the FDCA's provisions on drug compounding in a way that ensures access to high quality compounded medications while also protecting patient safety.

Despite the clear mandate of Congress and the considerable progress that has been made by FDA and industry in implementing the law's provisions, we see attempts to weaken the statutory requirements established by Congress by inserting loopholes, blurring the distinction between drug compounding conducted under section 503A and section 503B, and undermining the premarket approval requirement for new drugs. Moreover, despite the tragedy caused by the New England Compounding Center, poor compounding practices continue to occur. As FDA noted in its "Justification of Estimates for Appropriation Committees" for FY2017, the Agency "continues to identify serious problems at facilities that are making drugs expected or intended to be sterile," such as:

- the use of non-sterile drinking water dispensed from a top-loaded bottled water dispenser to make injectable drug products;
- dog beds, dog feces, and dog hairs within a compounding facility, including in close proximity to the compounding room;
- compounding of sterile drugs by personnel with exposed skin, which sheds particles and bacteria;
- use of coffee filters to filter particulates;
- toaster ovens used for sterilization;
- a kitchen dishwasher and detergent used to clean sterile compounding equipment and utensils;
- dead insects in ceilings; and
- renovations conducted next to sterile compounding operations without taking precautions to prevent contamination of the sterile products.

These observations show that much work still needs to be done to minimize the risks associated with compounding drugs, whether by traditional pharmacies or by outsourcing facilities, so that patients can use compounded drugs of the quality and safety that they deserve. We view FDA's recently issued three draft guidances as a step in this direction.

Our specific comments on each of the three draft guidances are offered below.

I. Comments on "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act"[2]

A. Compounding After Receipt of a Valid Prescription Order

We support FDA's interpretation of section 503A as requiring a drug product to "be compounded *after* the licensed pharmacist or licensed physician receives a valid prescription order for an individual patient."[3] This policy is consistent with section 503A's prescription requirement, which refers to a drug that "is compounded for an identified individual patient *based on the receipt of* a valid prescription order or notation."[4] The language "based on the receipt of a valid prescription order or notation" necessitates that a prescription be provided to serve as the impetus for a drug's compounding.

In addition to being grounded in statutory text, this policy supports a number of critical public health objectives. We agree with FDA's statement in the draft guidance that "[c]ompounded drug products can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product."[5] But, as the draft guidance also recognizes, compounded drugs "pose a higher risk to patients than FDA-approved drugs" do because compounded drugs "have not undergone FDA premarket review for safety, effectiveness, and quality."[6] The quality standards applied to pharmacies are appropriate for traditional practice on an individual patient basis but not for operations at a larger scale where more patients are exposed.

Indeed, the prescription requirement strikes a balance between, on the one hand, an individual patient's need for a customized formulation (e.g., because of an allergy or due to the lack of a pediatric formulation) and, on the other hand, the risks associated with the administration of unapproved drugs. Because of these concerns, compounding is appropriate only for patient-specific prescriptions that are written when a particular medical need arises. Permitting traditional compounding on a larger scale comes at the risk of drug quality and patient safety, as well as eroding both FDA's premarket approval process for new drugs and the distinction between traditional compounding (under section 503A) and outsourcing facilities (under section 503B).

B. Anticipatory Compounding

In keeping with the statutory text and its underlying public safety principles, we appreciate FDA's explanation in the draft guidance that section 503A permits anticipatory compounding

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[2] 81 Fed. Reg. 22617 (Apr. 18, 2016); FDA, Guidance for Industry – Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act (Apr. 2016) ("Prescription Requirement Draft Guidance").

[3] Prescription Requirement Draft Guidance at Lines 295-296 (emphasis added).

[4] FDCA § 503A(a) (emphasis added).

[5] Prescription Requirement Draft Guidance at Lines 76-77.

[6] *Id.* at Lines 120-122.

only "in limited quantities, based on an expectation that the licensed pharmacist or licensed physician will receive a patient-specific prescription for the particular drug product, written for a patient or by a prescriber with whom the compounder has a relationship."[7] Although anticipatory compounding occurs prior to receipt of a patient-specific prescription, the compounding is nevertheless tied to section 503A's prescription requirement, as made clear by the parameters set forth in the statutory provision[8] and echoed in FDA's draft guidance.

We agree with FDA's interpretation of section 503A's requirement for a "valid prescription order," including a contemporaneous notation documenting a prescriber's determination that a compounded drug is necessary for an identified patient in cases where it is not obvious that a prescription is for a compounded drug product. Critical to this policy, however, is an understanding that a notation in a patient's chart satisfies the statute's prescription requirement *only* when it is made in an inpatient setting or by a health care provider performing the compounding for his or her own patient. We share FDA's assessment that a notation it would not be appropriate in the context of a compounded drug obtained from a pharmacy or from the office stock of a health care provider that did not perform the compounding him- or herself. Similarly, we support FDA's position that a prescription must identify the specific patient for whom the drug has been prescribed and cannot be written for the prescriber him- or herself unless the prescriber is also the patient needing the compounded medicine. We also strongly support that copies of these notated, patient specific prescriptions are records that must be maintained and that FDA has the right to access during any inspections or investigation of 503A pharmacies. This approach helps ensure full compliance with section 503A's prescription requirement, which would be rendered meaningless by a loophole such as this.

We note that the draft guidance includes a statement that FDA will exercise enforcement discretion for anticipatory compounding if a pharmacy prepares no more than the quantity it expects to dispense pursuant to patient-specific prescriptions in a 30-day period, based on a 30-day period in the previous year. Because this approach means that some compounded formulations may not be dispensed to a patient for as many as 30 days, we urge FDA to ensure that these drugs comply with beyond-use-dates that are strict enough to maintain the quality and safety of these products for patient use.

In addition, we believe that the anticipatory compounding policy set forth in the draft guidance does not go far enough to ensure that anticipatory compounding occurs only in "limited quantities" as the statute requires. Prior to passage of the CQA, FDA and public health advocates routinely lamented that there were many entities operating under the guise of compounding pharmacies that were in reality performing drug compounding activities on the scale of a commercial drug manufacturers in violation of section 503A's requirement that such compounding be done only in limited quantities.[9] Permitting such entities to now base their

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[7] *Id.* at Lines 316-319.

[8] *See* FDCA § 503A(a)(2).

[9] *See, e.g., Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing before the Senate Committee on Health, Education, Labor, and Pensions*, 108th Cong. (2003) (statement of Steven K. Galston, Acting Director, (continued...)

anticipatory compounding inventories on past volume rewards them for their previous non-compliance and permits them to continue to distribute compounded drug products at a scale that exceeds the limited quantities permitted under 503A. We therefore encourage FDA to consider a two-pronged approach that would permit anticipatory compounding supplies to be prepared for the lesser of (i) the quantity to be dispensed in a 30-day period, based on a 30-day period in the previous year, and (ii) a fixed number of doses, if determined by FDA to be appropriate for a particular product type or dosage form (e.g., 500 units regardless of compounding history)—taking into consideration potential patient safety risks and consistent with the statute's limited quantities restriction.

C. Office Stock

We support FDA's policy in the draft guidance that compounded drug products kept as "office stock" by hospitals, clinics, and health care practitioners should be obtained from outsourcing facilities registered under section 503B of the FDCA. This approach recognizes the important distinction between anticipatory compounding—which is performed based on a history of prescription orders for an individual patient—and office stock, which is "kept . . . to administer to patients who present with an immediate need for a compounded drug product."[10] Allowing office stock to be sourced from traditional compounders, which would ordinarily comprise a much larger volume than anticipatory compounding, cause the limitations Congress placed on anticipatory compounding in section 503A(a)(2) to be subsumed entirely. Instead of conducting anticipatory compounding only in "limited quantities" and subjecting themselves to the statutory criteria, traditional compounders would have an incentive to prepare drugs only for use as office stock without the need to comply with GMP, thus disrupting the balance struck in section 503A between the risks of administering unapproved drugs and the medical needs of individual patients. Outsourcing facilities would, in turn, be discouraged from undertaking the investment necessary to satisfy section 503B's requirements, as traditional pharmacies would be permitted to engage in the same large-scale compounding operations without being subject to the same restrictions and degree of FDA oversight.

Such an outcome would contravene the intent of Congress when it added a new section 503B to the FDCA. During the floor debate over the pending legislation, Representative Henry Waxman explained that FDA "face[d] a pharmacy compounding industry that had dramatically changed," and the bill would "give hospitals and doctors the ability to access a source of compounded medicines that are made in a facility that is subject to stringent FDA quality standards and oversight."[11] Consistent with what Congress intended, FDA's approach in the draft guidance with respect to office stock protects patient safety. The steps required of registered outsourcing facilities—including compliance with good manufacturing practices, being subject to FDA inspections, and certain adverse event reporting requirements—helps mitigate the quality and safety risks that can be associated with compounded drugs.

CDER, FDA) (noting that FDA had for years "seen abuses, such as large-scale drug manufacturing under the guise of pharmacy compounding").

[10] Prescription Requirement Draft Guidance at Lines 373-375.

[11] 159 Cong. Rec. H5946, H5961 (daily ed. Sept. 28, 2013).

We also appreciate FDA's reminder that, even if office stock is necessary in certain circumstances, the FDCA's restrictions on compounding drugs that are essentially copies of commercially available or FDA-approved drugs remain in effect.[12] Permitting office stock to consist of such copies would seriously undermine FDA's premarket approval process (and framework of postmarket requirements), as compounders could produce these copies without undertaking any of the necessary investment and without being subject to the same rigorous regulatory requirements to demonstrate safety and effectiveness that apply to pharmaceutical manufacturers.

II. Comments on "Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act"[13]

In this draft guidance, FDA states, "Hospital and health systems may also compound drugs and distribute them within the hospital or health system before the receipt of a patient-specific prescription. The hospital or health system then holds the drug products until a patient presents with a need for the drug, for example in an operating room . . . or in emergency departments."[14] We ask that the Agency extend its analysis of anticipatory compounding and office stock, as discussed in the previous section, to this draft guidance (e.g., by cross-reference or directly incorporating the text). The same distinctions between anticipatory compounding and office stock—and, for that matter, section 503A and section 503B—also apply in the hospital and health system context. Specifically, we believe the draft guidance should specify that any compounded drug held by a hospital or health system "until a patient presents with a need for the drug" should be obtained from a section 503B outsourcing facility. Such a compounded formulation implicates the same considerations, regardless of whether that patient is in a physician's office or in an operating room. The legislative history for section 503B cited in the previous section, which referenced both hospitals and doctors, also supports this approach.

The draft guidance also indicates that FDA will exercise enforcement discretion if a hospital pharmacy distributes compounded drug products without first receiving a patient-specific prescription as long as three criteria are satisfied: (1) the drug products are distributed only to healthcare facilities "that are owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located within a 1 mile radius of the compounding pharmacy"; (2) the compounded formulations are administered to patients within the healthcare facilities pursuant to a patient-specific prescription or order; and (3) the compounding is done pursuant to the FDCA and FDA regulations.[15]

We support this policy and, in particular, agree with the Agency's adoption of a one-mile radius as a limitation on the cases in which it will exercise enforcement discretion. Such compounding

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[12] *See* Prescription Requirement Draft Guidance at fn. 3.

[13] 81 Fed. Reg. 22610 (Apr. 18, 2016); FDA, Guidance for Industry – Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act (Apr. 2016) ("Hospital and Health System Compounding Draft Guidance").

[14] Hospital and Health System Compounding Draft Guidance at Lines 93-97.

[15] *Id.* at Lines 209-220.

activities constitute a violation of the FDCA, but FDA's transparency regarding its policy achieves a compromise between enforcement of section 503A and facilitating hospital and health system operations. Establishing this radius helps prevent compounded formulations from being exposed to extended shipment conditions, which may cause a degradation in the compounded drug's quality (e.g., a proliferation of microbial contaminants to harmful levels that would endanger patient safety). Moreover, given the increasingly complex hospital and health system networks that stretch across the country, the one-mile radius will generally ensure that a hospital pharmacy's transfer of compounded drugs will not cross state lines. As described in a report prepared by Pew,[16] state-by-state quality requirements and enforcement systems for pharmacies vary, and shipment of compounded formulations from one state to another further complicates individual state oversight and exposes patients to risks that are difficult to manage. Setting a specific radius increases predictability for hospitals and health systems on enforcement risks, which in turn allows them to focus on patient care.

We do not expect that this geographic limitation will pose significant challenges for the relevant institutions, even in most rural parts of the country. To address any challenges that do arise, we believe FDA could create a formal exception process, whereby a limited number of institutions, meeting pre-defined criteria designed to protect patient safety, could request that FDA expand its enforcement discretion beyond the one-mile radius limitation. Generally, however, hospitals settings that do not meet the requirements for FDA's enforcement discretion policy should procure their office stocks from 503B outsourcing facilities, which are required to comply with GMP take other measures to protect patient safety.

III. Comments on "Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act"[17]

We support FDA's interpretation of section 503B's definition of "outsourcing facility" ("a facility *at one geographic location or address* that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of this section"[18]) as referring to "a business or other entity under one management, direct or indirect, engaged in human drug compounding" that includes "all activities, equipment, appurtenances, and materials . . . if they are related to human drug compounding under the supervision of the facility's management at the same street address, or in the same building, or in buildings located in close proximity to one another."[19] Construing the provision in this way clarifies the FDCA's standard in practical terms while also remaining consistent with the public health objectives underlying section 503B.

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[16] The Pew Charitable Trusts, *National Assessment of State Oversight of Sterile Drug Compounding* (Feb. 2016).

[17] 81 Fed. Reg. 22611 (Apr. 18, 2016); FDA, Guidance for Industry – Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Apr. 2016) ("Facility Definition Draft Guidance").

[18] FDCA § 503B(d)(4)(A) (emphasis added).

[19] Facility Definition Draft Guidance at Lines 95-100.

In particular, we agree with FDA's view that "[t]o be eligible for the exemptions in section 503B(a), a drug product must be compounded in an outsourcing facility in which drugs are compounded only in accordance with section 503B."[20] As the draft guidance recognizes, compounding under section 503A and 503B should not take place in the same geographic location or address for practical reasons, even if it were conducted in separate suites or separate buildings. The draft guidance's policy prevents the commingling of products compounded under two different statutory frameworks with different quality standards and also maintains transparency about the source of a compounded drug. Housing both a traditional pharmacy and an outsourcing facility at the same location or address could easily result in confusion about whether a particular drug was compounded in accordance with section 503B's more rigorous requirements. Such an outcome would contradict the intent of Congress, as articulated by Senator Barbara Mikulski, to "ensure that patients have better information about compounded drugs"[21] and, as articulated by Senator Pat Roberts that "patients have a right to know when they are receiving a product that is not FDA-approved and the risk that may come with using it."[22]

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We understand that there have been growing pains as traditional compounding pharmacies, outsourcing facilities and providers have had to adjust their practices to account for this important patient safety law. However, we must not lose sight of the goal and permit another tragedy to unfold. Congress enacted the reforms in the CQA in the wake of the meningitis outbreak but also in response to incidents of bacterial infections, blindness and other injuries caused by subpar compounded drugs dating back years. While CQA will take time and resources for stakeholders to implement, in the name of patient safety, FDA should be supported, not blocked, in its ongoing efforts to enforce sections 503A and 503B of the FDCA. Thank you for your consideration of these comments. We would welcome the opportunity to discuss these comments further.

Sincerely,

American Public Health Association (APHA)
Biotechnology Innovation Organization (BIO)
Generic Pharmaceutical Association (GPhA)
Pew Charitable Trusts
Pharmaceutical Research and Manufacturers of America (PhRMA)
Trust for America's Health (TFAH)

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[20] *Id.* at Lines 118-120.

[21] 159 Cong. Rec. S8027, S8028 (Nov. 14, 2013).

[22] Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak: Hearing before the Senate Committee on Health, Education, Labor, and Pensions, 112th Cong. (2012).


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