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July 18, 2016

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

Re: Comments on Draft Guidance Documents for Industry Regarding Compounding Under the Federal Food, Drug, and Cosmetic Act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

The Pew Charitable Trusts is pleased to offer comments on three draft guidance documents issued by the Food and Drug Administration (FDA) in April 2016 relating to compounding under the Federal Food, Drug, and Cosmetic Act (FDCA). Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including compounding.

Pew supports the FDA's actions to implement Title I of the Drug Quality and Security Act of 2013 (DQSA), including the three draft guidance documents discussed here: *Prescription Requirement Under Section 503A of the Federal Food, Drug and Cosmetic Act*; *Hospital and Health System Compounding Under the Federal Food, Drug and Cosmetic Act*; and *Facility Guidance Under the Federal Food, Drug and Cosmetic Act*. While we suggest a number of specific revisions herein, in general the policies detailed in the draft guidance documents promote public health safeguards by affirming the clear oversight distinctions between traditional compounding, outsourcing facilities, and pharmaceutical manufacturing. We applaud the Agency's approach, which balances the needs of individuals for whom an approved or commercially available medication is not available and the health risks that compounded drugs can pose.

The DQSA: Patient Safety and Clear Accountability

To understand the balance struck in FDA's proposed guidance, it is helpful to recall the compromises embodied in the underlying statute, and the reasons those tradeoffs were made. The DQSA was negotiated and passed under the shadow of an unfolding tragedy. In 2012 and 2013, 751 patients were sickened and 64 died in a multistate outbreak of fungal meningitis associated with contaminated spinal injections manufactured by a single compounding pharmacy. These

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drugs were produced in large batches and shipped to twenty states across the country – production that was comparable to conventional pharmaceutical manufacturing. This was the most serious in a long history of adverse events that resulted from contaminated compounded medications. Congress reacted to the outbreak by reaffirming the original compounding statute – section 503A of the FDCA – that created a framework for pharmacists to produce individualized medicines for specific patients pursuant to a prescription without having to go through the FDA process for safety and effectiveness. At the same time, to capture compounding that is not specific to a particular patient but instead produces stock supplies of compounded drugs, Congress created a new regulatory category for "outsourcing facilities", which are defined in, and governed by, section 503B. This new category responds to the need of hospitals and other healthcare providers for larger-scale production of sterile drugs that are not otherwise available. The statute was clearly written to ensure that sterile drugs that were being produced without a prescription (often called "office stock" drugs) would be held to more robust quality standards to minimize the risk to patient safety.

Patient safety was not, however, the only goal. In addition to ensuring the availability of quality compounded drugs, an equally important Congressional goal was to ensure that there were clear lines of accountability. At the time of this fungal meningitis outbreak, the legal landscape for the oversight of drug compounding was fractured and confusing. The governing statute – section 503A of the FDCA – had been upheld by the appellate court in one circuit, struck down in another, and thus was of uncertain application everywhere else. As a result, there was a lack of clarity about what compounding activities were subject to federal oversight and what was subject to state regulation, and, therefore, about whether federal or state regulators were accountable if oversight was inadequate. As Congress negotiated the DQSA, substantial attention was paid not only to the quality standards that would apply, but to who would enforce those standards – that is, to use Senator Alexander's language, who would be "on the flagpole."[1]

This emphasis on accountability meant that Congress considered many options for drawing the lines between traditional pharmacy compounding, outsourcing, and conventional manufacturing, the statute that was ultimately passed drew very clear boundaries. The final statute does not require complicated formulas or judgment calls to determine which category an entity falls into; it draws bright lines. Entities that compound pursuant to prescriptions for individual patients are traditional pharmacies (assuming they otherwise meet the requirements of 503A), entities that

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[1] *See e.g.,* Sen. Lamar Alexander, "To Help Avoid Repeat of Deadly Meningitis Outbreak, Senate Sends Alexander Compounding Legislation to President," Press Release (Nov. 18, 2013), available at: http://www.alexander.senate.gov/public/index.cfm/2013/11/to-help-avoid-repeat-of-deadly-meningitis-outbreak-senate-sends-alexander-compounding-legislation-to-president.

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create stock supplies of compounded drugs are outsourcing facilities (assuming they otherwise meet the requirements of 503B), and entities that are neither (e.g. entities that do not obtain prescriptions and also do not register as outsourcing facilities) are treated under the statute as conventional manufacturers.

As FDA implements the DQSA, the agency is right to look not just at what policy enhances drug quality (and thus patient safety), but also at what policy best ensures that quality standards are enforced (and thus patient safety achieved) by keeping the lines of accountability clear so both the regulators and the regulated entities understand which standards apply.

- **Comments Regarding FDA's Draft Guidance: "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetics Act"**

Pew supports the clear line FDA draws in the draft guidance regarding the prescription requirement that applies to traditional pharmacies subject to section 503A. The draft guidance states that "unless a drug product is compounded in limited quantities before the receipt of a valid prescription order....the drug product must be compounded *after* the licensed pharmacist or licensed physician receives a valid prescription order for an individual patient." This requirement that a traditional pharmacy receive a valid prescription before dispensing a compounded drug supports patient safety and promotes clear accountability.

Congress created a new category of facility uniquely permitted to compound without a prescription for the purpose of providing office stock to hospitals, physician offices and other healthcare facilities. Outsourcing facilities producing stock supplies of compounded product must meet current good manufacturing practices (cGMP), the same quality standards applied to pharmaceutical manufacturers. These standards were developed to help ensure the proper production of batches of medicines that may not be immediately used. They are significantly more robust than those applied to traditional pharmacies, particularly in the areas of environmental monitoring, sterile gowning, cleaning, training, and testing. For example, cGMP requires validation of systems and processes to ensure that medicines meet consistent quality and safety standards. These standards also require the testing of a drug's starting ingredients, whereas traditional pharmacy compounding standards do not. Outsourcing facilities, unlike traditional pharmacies, are subject to FDA inspections and must report adverse events related to their products. The prescription requirement helps ensure that compounders that produce stock supplies of product adhere to quality standards suitable for that activity.

The prescription requirement also functions as a key incentive for outsourcing facilities to register with the FDA and to comply with more the robust and appropriate quality standards. If traditional pharmacies are permitted to produce and dispense compounded medications without valid prescriptions, and under less stringent quality standards, patient safety will be undermined because compounders will have no incentive to submit to the more rigorous standards that apply to outsourcing facilities. The new outsourcing facility sector is in a nascent phase of

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development -- 66 outsourcing facilities are currently registered with the FDA. As 503B business models emerge, guidance that clearly prohibits entities that do not invest in higher quality standards from competing for office stock orders with those that do supports the viability of this sector as well as patient safety.

In addition to helping to ensure that medicines compounded for office stock are produced under appropriate quality standards, the prescription requirement creates a clear line for enforcement purposes. As Congress required, FDA has set forth a well-defined boundary separating traditional compounders from outsourcing facilities and conventional manufacturers: the prescription. FDA's proposed guidance makes clear that entities that do not receive prescriptions before compounding (or, in limited quantities, after compounding but before dispensing) do not fulfill the requirements of section 503A. Thus, the guidance sets the transparent expectation that entities compounding product in primarily state-regulated traditional pharmacies must ensure that they receive prescriptions before dispensing these products.

Congress recognized that there are times, based on a history of prescription orders for a particular compounded medication for individual patients, a pharmacist or physician will produce *a limited quantity* of compounded medication, in advance of receiving prescriptions. This is referred to as "anticipatory compounding." The draft guidance defines "limited quantity" as a 30-day supply of a particular compounded medication based on the number of valid prescriptions that have been received for individual patients in a 30-day period during the past year.

Pew supports FDA's recognition of the practical need for traditional pharmacies to compound medication, in limited quantities, in advance of receiving a prescription. We appreciate that the approach in the guidance requires compounders to ground the quantities they produce in anticipation of a prescription in data establishing a basis for the anticipated quantity of drugs. And we were pleased that FDA will require compounders to maintain records of this data. This evidence-based approach to establishing the quantity of drug a compounder anticipates needing to produce in a 30-day period helps ensure that those estimates are based on a realistic assessment of historical needs.

However, to ensure that patients receive safe and effective medications and to maintain the integrity of the regulatory framework that distinguishes traditional compounding from pharmaceutical manufacturing, the 30-day timeframe proposed in the draft guidance may not be the optimal limiting metric. For compounders already producing a significant volume, the 30-day limit would permit production at significant scale. Furthermore, regardless of a compounder's current volume, a 30-day timeframe will permit traditional compounders to continually grow the volume of a drug product compounded for anticipatory purposes. This could lead to a traditional

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pharmacy, operating under less stringent quality standards, to operate at a scale that is more akin to commercial drug manufacturers and that could not be fairly characterized as the "limited quantity" Congress intended.

Additionally, FDA should make it clear in the guidance that any policy that permits drug products to be compounded in advance of dispensing must be coupled with strong requirements for compliance with beyond-use-dates (BUDs) that ensure the quality and safety of these products. Thus, the 30-day supply limit would not operate as an exception to BUD restrictions.

Comments Regarding FDA's Draft Guidance: Hospital and Health Care System Compounding Under the Federal Food, Drug and Cosmetic Act

Pew supports FDA's policy that the prescription requirement applies to all traditional compounding wherever it occurs. We also agree with FDA's recognition that hospital and health care system pharmacies operate in a manner that does not fit cleanly into the statutory provisions governing compounding for either other pharmacies or for physicians, and thus necessitate a different procedure for fulfilling the prescription requirement.

While all pharmacies have a responsibility for the patients they serve, we recognize the unique circumstances that apply when the entity compounding a drug and administering it are one and the same. In both physician and hospital settings we recognize that because the compounder is producing drugs for use with their own patients, the prescription requirement is fulfilled by making a notation in the patient's chart when the product is administered.

The draft guidance indicates that the FDA will exercise enforcement discretion if the hospital or health care system distributes compounded drug products without first receiving prescriptions or orders as long as three criteria are met:

- 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 with a 1 mile radius of the compounding pharmacy;
- The drug products are only administered to patients within the healthcare facilities pursuit to a specific patient order; and
- The drug products are compounded in accordance with all other provision of section 503A.

These criteria help ensure that a hospital pharmacy is compounding only for the hospital's own patients, and not selling compounded drugs to a separate care provider as a non-hospital-based compounder would.

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We generally agree that a clear, short geographic distance metric, such as the 1-mile radius proposed, balances the operational needs of hospitals and health care systems with the need for clear enforcement of the prescription requirement for traditional compounding. Establishing a clear, short radius will generally help prevent products compounded under the less stringent quality standards governing traditional pharmacy from being widely distributed. This radius requirement complements, but should not supplant, the requirement that there be other indicia – such as ownership and control – that the compounder and the care provider share responsibility for the patient.

While we support a short and clear geographic limitation on distributing compounded drugs without a prescription for hospitals and health systems, we recognize that for a number of these facilities, such a limitation could pose inefficiencies. For example where a hospital operates two inpatient facilities within a town, centering the compounding facilities in just one location may permit investment and specialization in that single facility that would not be possible if each inpatient facility were required to host separate compounding capability. We suggest that FDA develop an exception process for facilities meeting criteria designed to protect patient safety, wherein they could request an increase in the distance metric. The exception process would need to be designed to permit the exceptions like the example described above, but not too broadly so as to allow hospital pharmacies to serve as outsourcers for loosely affiliated physician practices.

Because outsourcing facilities produce standardized supplies of compounded drugs under more robust quality standards than traditional pharmacies, including those in hospitals and health care systems, we suggest that the Agency specify that to best protect their patients, hospitals and health systems should whenever possible obtain stock supplies of compounded product needed in larger volumes from outsourcing facilities.

Comments Regarding FDA's Draft Guidance: Facility Guidance Under the Federal Food, Drug and Cosmetic Act

Pew supports the FDA's draft guidance clarifying that traditional compounding, governed by Section 503A, and outsourcing, governed under Section 503B, should not take place in the same geographic location or address, even if these activities are conducted in separate buildings or suites. These activities are subject to significantly different quality standards and other requirements and co-locating them could compromise FDA's ability to ensure that quality standards are being met. Separating 503A and 503B facilities is important to ensuring clear accountability for quality compounding within facilities.

In implementing this provision, however, to avoid discouraging 503B registration, FDA should consider how hospital-based compounding operations that choose to register as 503B outsourcing facilities (e.g. to supply the needs of affiliated clinics outside of the 1-mile radius)

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might nevertheless be able to conduct the compounding activities that typically take place in patient wards.

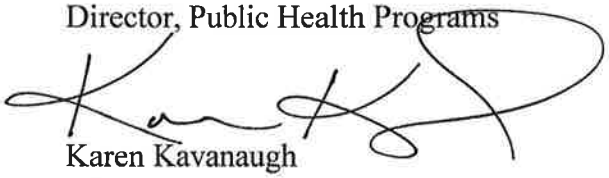
FDA has also proposed to permit 503B facilities to be co-located with conventional manufacturing facilities. We recognize that this proposal does not present the same concerns as co-locating 503A and 503B facilities because both 503B and conventional manufacturing facilities are subject to cGMP and inspected by FDA. However, in permitting co-location of 503B and conventional manufacturing facilities, FDA should take steps to ensure that companies seeking to produce new formulations of their approved products continue to conduct relevant studies and modify their applications rather than circumvent the approval process by producing the new formulation as a 503B. We are optimistic that the limitations on compounded drugs produced by 503B outsourcing facilities, such as the prohibition on wholesaler distribution and unavailability of exclusivity for formulations not the subject of an approved application, would be sufficient to discourage companies from circumventing the approval process. However, we recommend that FDA monitor to ensure that the co-location policy it proposes does not undermine the approval process.

* * *

Thank you for your efforts to protect patients through robust implementation of the DQSA, and for your consideration of these comments.

Sincerely,

Elizabeth Jungman
Director, Public Health Programs



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