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Department of Health and Human Services
WO 2200
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Janet Woodcock, M.D.
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10903 New Hampshire Avenue
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance Documents on the Prescription Requirement Under Section 503A (Docket No. FDA-2016-D-0269); Facility Definition Under Section 503B (Docket No. FDA-2016-D-0238)

Dear Drs. Califf and Woodcock:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, submits these comments regarding the Food and Drug Administration (FDA) draft guidance documents on the prescription requirement under Section 503A of the federal Food, Drug, and Cosmetic Act (FDCA) and the facility definition under Section 503B of the FDCA.

In general, we support the policies expressed in both draft guidance documents. They serve to clarify the line between traditional pharmacy compounding activities (carried out by a state-licensed pharmacy that qualifies for the exemptions described in Section 503A of the FDCA) and drug manufacturing activities (carried out either by a traditional drug manufacturer in compliance with the new drug approval and other applicable requirements of the FDCA or by an

outsourcing facility in compliance with Section 503B and other applicable requirements of the FDCA).

Compounded drug products have traditionally served an important role in treating patients with individualized clinical needs that cannot be met by FDA-approved drugs. However, compounded drugs also carry increased risks for patients, as these drugs are not FDA-approved with appropriate safety and efficacy testing, not labeled with adequate directions for use, and not made in accordance with current good manufacturing practices (cGMP) standards. Such risks became abundantly clear in 2012, when contaminated injectable drugs produced by the New England Compounding Center in Massachusetts led to more than 750 cases of fungal infection across the country, including 64 that resulted in death.[1] This was not an isolated outbreak: Compounded drugs have been linked to hundreds of additional adverse events, including more than two dozen deaths, since 2001.[2]

The FDA's proposed draft guidances appropriately aim to minimize these risks by drawing a clear line between traditional pharmacy compounding activities and larger-scale drug manufacturing activities.[3]

1. Prescription Requirement Under Section 503A

Public Citizen supports the policies expressed in the FDA's draft guidance "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act" (Prescription Guidance).[4] In particular, we strongly agree with the FDA's explanation that Section 503A's prescription requirement effectively prohibits compounding pharmacies regulated under Section 503A from distributing drugs to health care practitioners for use as "office stock." In addition, we also agree with the agency's plans regarding implementation of anticipatory compounding restrictions contained in Section 503A.

The Prescription Guidance outlines important limits on the scope of activity that can qualify for the traditional compounding exemption under Section 503A. The most important of these is the requirement that compounded drugs be held at the pharmacy pending receipt of a patient-specific prescription. This requirement appropriately prevents compounding pharmacies from selling drugs to health care practitioners as "office stock" intended for use in as-yet-unidentified patients. As such, the requirement helps to draw a clear line between traditional compounding,

[1] Centers for Disease Control and Prevention. Multistate outbreak of fungal meningitis and other infections. October 30, 2015. www.cdc.gov/HAI/outbreaks/meningitis.html. Accessed July 5, 2016.
[2] The Pew Charitable Trusts. U.S. illnesses and deaths associated with compounded medications or repackaged medications. 2001-present. October 14, 2015. www.pewtrusts.org/en/multimedia/data-visualizations/2014/us-illnesses-and-deaths-associated-with-compounded-medications. Accessed July 5, 2016.
[3] We note that outsourcing facilities, while required to comply with cGMP, are exempt from new drug approval and labeling requirements, meaning drugs produced in such facilities also may carry greater risks for patients than do traditionally manufactured, FDA-approved drugs.
[4] Food and Drug Administration. Prescription requirement under Section 503A of the federal Food, Drug, and Cosmetic Act (draft guidance). April 2016. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf. Accessed July 5, 2016.

which involves the tailoring of medications for identified individual patients, and drug manufacturing, which involves the mass production of drugs for patient populations. The requirement also helps ensure that compounded drugs held in stock in physicians' offices for potentially extended periods are manufactured under appropriately high standards, by requiring that any purchase of such stock from an outside supplier be obtained from a traditional manufacturer or outsourcing facility.[5]

Most importantly, Section 503A's prescription requirement provides a key incentive for facilities engaged in drug manufacturing to seek new drug approval or register as outsourcing facilities to legally produce drugs for office stock. While Public Citizen continues to believe that new drug approval provides superior patient protections compared with outsourcing facility registration, both marketing pathways require that manufacturing be carried out in compliance with cGMP, and all drugs that are mass-produced and sold in bulk to physicians should be required to meet this important set of federal quality standards.

Public Citizen also believes that the FDA's proposed policy requiring patient-specific prescriptions for compounded products can be implemented without significantly affecting patient care, as health care practitioners will continue to have options for obtaining standardized office stock, including substituting FDA-approved products in place of compounded products and relying on outsourcing facilities when FDA-approved products are unavailable.

We also generally support the policies in the Prescription Guidance that relate to anticipatory compounding (i.e., compounding in advance of receiving a patient-specific prescription) by traditional compounding pharmacies under Section 503A. By statute, such compounding may be carried out only in "limited quantities," and the guidance appropriately interprets this limitation to be a 30-day supply of a particular compounded product, which can be held for distribution while awaiting patient-specific prescriptions.[6] This is a clear and workable restriction on anticipatory compounding, and a reasonable interpretation of the "limited quantities" language employed by Section 503A.

However, we have some concerns that the FDA's proposed definition of a 30-day supply may raise enforcement challenges. Specifically, the proposed definition bases the amount of the

[5] While licensed physicians could still compound office stock in-house, the scope of this activity is likely to remain limited, particularly as many physicians are not equipped to comply with Section 503A's other requirements, including meeting the standards of the United States Pharmacopoeia chapter on pharmacy compounding. Food and Drug Administration. Pharmacy compounding of human drug products under section 503A of the federal Food, Drug and Cosmetic Act (guidance). June 2016. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf. Accessed July 11, 2016. Also, as discussed below, the proposed guidance aims to limit such in-house anticipatory compounding to a 30-day supply. If enforced effectively, this would ordinarily result in stock being held for no longer than approximately 30 days. By contrast, office stock purchased in bulk without a patient-specific prescription could be held for much longer periods, increasing the potential for microbial growth and other quality concerns.

[6] Food and Drug Administration. Prescription requirement under Section 503A of the federal Food, Drug, and Cosmetic Act (draft guidance). April 2016. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf. Accessed July 5, 2016.

supply on "the number of valid prescriptions that the compounder has received for identified individual patients in a 30-day period over the past year that the compounder selected."[7] We understand this to mean that the compounder may select any 30-day period over the prior year as the baseline. If orders fluctuate dramatically over the year and the highest-volume period is selected, this could result in anticipatory compounding far exceeding actual orders for a 30-day period. In order to prevent this, we urge the FDA to implement an additional restriction that supplies be held for distribution for no more than 30 days. Such a requirement will help ensure that drugs are compounded in advance only in quantities clearly limited to a 30-day supply.

In addition, we would like to note that the 30-day supply restriction, standing alone, would be insufficient to draw a clear line between traditional compounding and drug manufacturing, as the quantity of drugs that can be produced and sold within any given 30-day period is essentially unlimited. Therefore it is critical that this restriction be applied in conjunction with the requirement that compounded drugs not be dispensed or distributed prior to the pharmacy's receipt of a patient-specific prescription. If the FDA reconsiders its interpretation of the individual prescription requirement of Section 503A, it should also reconsider its policy regarding the 30-day limited quantity restriction on anticipatory compounding.

In addition to supporting these policies, we suggest that the final guidance include additional language offering examples of scenarios under which health care practitioners and patients could access necessary compounded treatments under Section 503A, Section 503B, and other relevant provisions of the FDCA. The Prescription Guidance, in section II.A.2. ("Compounding, Generally"), describes a number of scenarios in which such access could be sought, including the following:

(1) "[A] prescriber writes a prescription for a compounded drug product, and the patient brings the prescription to a pharmacy, where a licensed pharmacist fills the prescription."

(2) "In an inpatient setting, such as in a hospital, a prescriber may write an order for a compounded drug product on a patient's chart."

(3) "[A] physician may compound a drug in the office for administration to his or her patient after the patient presents at the physician's office with a clinical need for the compounded drug."

(4) "[A] pharmacist may compound a drug product before receipt of a prescription for an identified individual patient in anticipation of receiving such a prescription, based on knowledge of what prescriptions the pharmacist has historically been asked to fill. The pharmacist then provides the drug product to a patient or a prescriber upon receipt of a prescription."

[7] *Ibid.*

(5) "Sometimes, it is necessary for health care practitioners in hospitals, clinics, offices, or other settings to have certain compounded drug products on hand that they can administer to a patient who presents with an immediate need for the compounded drug product."[8]

Yet the Prescription Guidance fails to specify how compounded drugs could be obtained in each scenario under the FDA's proposed policies. For example, whereas the first scenario above seems to involve compounding activity clearly covered under the 503A exemption, the last scenario would seem to require practitioners to either obtain the compounded product from an outsourcing facility under 503B or compound and hold the product in stock within a hospital health system, an activity the FDA proposes to permit under its draft hospital and health system compounding guidance.[9]

Given the complexity of the proposed regulatory framework and the need for clear communication with a diverse group of interested stakeholders, a chart or listing of examples added to the Prescription Guidance would be useful in clarifying the FDA's intent with regard to the options available for practitioners and patients under these (and possibly additional) scenarios.

2. Facility Definition Under Section 503B

Public Citizen also supports the policies expressed in the FDA's draft guidance: "Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act."[10]

In particular, we support the FDA's clarification of the requirement that all drugs produced within an outsourcing facility located at a single geographic location or address comply with current good manufacturing practices (cGMP) in order for the facility to qualify for a statutory exemption under Section 503B.[11] Without such a rule, it would be easy for consumers and health care practitioners to be misled in the belief that all products produced at a single geographic location are manufactured under federally enforced cGMP standards. We note that drugs compounded under 503A are not required to bear specific statements in their labeling distinguishing them from products compounded under 503B. We also note that companies registered with the FDA under 503B are likely to widely advertise their FDA-regulated status as an indicator of product quality. It is therefore especially important that all products produced at such registered outsourcing facilities actually comply with applicable federal cGMP standards.

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[8] *Ibid.*
[9] Food and Drug Administration. Hospital and health system compounding under the federal Food, Drug, and Cosmetic Act. (draft guidance). Note: Public Citizen does not plan to submit comments on the draft hospital and health system compounding guidance.
[10] Food and Drug Administration. Facility definition under Section 503B of the federal Food, Drug, and Cosmetic Act (draft guidance). April 2016. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496288.pdf. Accessed July 5, 2016.
[11] *Ibid.*

We thank you for the opportunity to comment on these important public health matters.

Sincerely,

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