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May 20, 2015

Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO 51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

Re: Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability (Docket No. FDA-2014-D-2138)

Dear Drs. Ostroff and Woodcock:

Public Citizen, a consumer advocacy organization with more than 350,000 members and supporters nationwide, submits the following comments on the draft guidance document titled "Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (the draft guidance).[1]

We generally support the contents of the draft guidance covering adverse event reporting for outsourcing facilities. However, we urge the Food and Drug Administration (FDA) to amend 21

[1] Food and Drug Administration. Adverse event reporting for outsourcing facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). February 2015.

CFR § 310.305 to require that outsourcing facilities report all serious adverse events or, at a minimum, all serious adverse events related to sterile injectable drugs.

As the draft guidance explains, Section 503B of the Food, Drug, and Cosmetic Act requires that outsourcing facilities submit adverse event reports "in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations."[2] That regulation, titled "Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications," requires that the manufacturer of a prescription drug that is marketed without an approved new drug application submit a report to the FDA within 15 days of learning of a "serious and unexpected" adverse drug experience for which there is a reasonable possibility that the drug caused the adverse experience.[3]

Regulation 310.305 defines a "serious" adverse drug experience as one that results in any of the following: death, a life-threatening adverse drug experience, new or prolonged inpatient hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or another important medical event that may jeopardize the patient and may require medical or surgical intervention.[4] This definition is relatively clear and easily applied to unapproved drugs produced in an outsourcing facility.

The regulation defines an "unexpected" adverse drug experience as an adverse drug experience "that is not listed in the current labeling for the drug product."[5] This definition is not easily applied to unapproved drugs, as such products lack uniform FDA-reviewed language, meaning products with the same active ingredient may list different adverse events in the labeling, or no adverse events at all.

The draft guidance "strongly recommends," but does not require, that outsourcing facilities report *all* serious adverse drug experiences associated with compounded drug products within 15 calendar days of receiving the initial report, regardless of whether these events may be considered "unexpected."[6] We agree that all serious adverse drug experiences should be reported, given the gravity of these events. However, this reporting should be required, rather than "strongly recommended."

As reporting of all serious adverse events is not currently required under regulation 310.305, we urge the FDA to amend this regulation. We note that regulation 310.305 was not created to address safety concerns related to sterile products compounded in outsourcing facilities. Instead, the regulation was created in the immediate aftermath of a series of adverse reactions, including

[2] *Ibid*.
[3] 21 C.F.R. § 310.305.
[4] *Ibid*.
[5] *Ibid*.
[6] Food and Drug Administration. Adverse event reporting for outsourcing facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). February 2015.

deaths, associated with a vitamin E product that was subsequently pulled from the market.[7] Drug production in outsourcing facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act raises a different set of concerns from those intended to be addressed originally by regulation 310.305. Specifically, Section 503B was passed in the aftermath of a large-scale infection outbreak linked to contaminated steroids illegally manufactured in a compounding pharmacy in 2012, and as such, it is focused on ensuring the quality and sterility of sterile injectable drugs.[8] Contamination and other quality problems can lead to many different adverse events, from those related to infection (e.g., fever, meningitis, or loss of vision [for eye injections]), as well as other adverse events that could relate to potential drug overdose or improperly labeled medication resulting from errors in the compounding process. Because these adverse events can manifest as a variety of different symptoms, some of which may not be included in the drug labeling, it would be appropriate for the FDA to amend regulation 310.305 to require reporting of all serious adverse events, or at a minimum all serious adverse events related to sterile injectable drugs produced by outsourcing facilities.

Thank you for the opportunity to comment on this important public health matter.

Sincerely,

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Public Citizen's Health Research Group

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[7] 51 FR 24476-01. July 3, 1986. The product, "E-Ferol," was toxic to small infants, yet was marketed to neonatal care centers without clinical testing or FDA approval, resulting in 38 reported infant deaths in 11 states. Balistreri WF, Farrell MK, Bove KE. Lessons from the E-Ferol tragedy. *Pediatrics.* 1986;78(3):503-506.
[8] Centers for Disease Control and Prevention. Multistate outbreak of fungal meningitis and other infections. October 23, 2013. http://www.cdc.gov/hai/outbreaks/meningitis.html. Accessed May 15, 2015.