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ONE HUNDRED FIFTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115

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MEMORANDUM

January 28, 2018

To: Subcommittee on Health Democratic Members and Staff

Fr: Committee on Energy and Commerce Democratic Staff

Re: Hearing on "Examining Implementation of the Compounding Quality Act"

On **Tuesday, January 30, 2018, at 11:00 a.m. in room 2123 of the Rayburn House Office Building**, the Subcommittee on Health will hold a hearing entitled "Examining Implementation of the Compounding Quality Act."

I. BACKGROUND

Traditional drug compounding involves the mixing, combining, or altering of Food and Drug Administration (FDA) approved medications by pharmacists to fulfill the special needs of individual patients, such as individuals with specific allergies or seniors or young children who cannot tolerate FDA-approved dosage forms.[1] Compounded drugs may include either nonsterile products, such as topical creams, or sterile products, such as injectable and ophthalmic products.

Compounded drugs are not reviewed by FDA for safety, efficacy, or quality before they are marketed. In fact, most compounding pharmacies are overseen by the states. The level of oversight varies substantially among the states including in regard to inspections frequency and quality practice and prescription requirements.[2] Over the years, particularly in those years prior

[1] Food and Drug Administration, *Compounding and the FDA: Questions and Answers* (Nov. 2017) (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm).

[2] The Pew Charitable Trusts, *National Assessment of State Oversight of Sterile Drug Compounding* (Feb. 2016) (http://www.pewtrusts.org/~/media/assets/2016/02/national_assessment_of_state_oversight_of_sterile_drug_compounding.pdf).

to passage of the Drug Quality Security Act, the number and size of entities engaged in drug compounding has increased, raising concerns about certain entities manufacturing under the guise of compounding.[3]

In 1997, Congress included several new provisions regulating the practice of pharmacy compounding in the Food and Drug Administration Modernization Act (FDAMA).[4] Section 503A of the law at that time exempted compounded drugs from the other requirements of the Federal Food, Drug, and Cosmetic Act (FDCA)[5], so long as the pharmacy was licensed in a state, made the drug pursuant to a valid prescription for an individual patient, limited interstate shipments to no more than five percent of its business, and did not engage in advertising or promotion.[6] Section 503A also stated that compounders may not "compound regularly or in inordinate amounts…any drug products that are essentially copies of a commercially available drug product."[7]

Immediately upon the law taking effect, compounding pharmacies challenged the advertising and promotion restrictions in Section 503A in federal court.[8] The Ninth Circuit Court found that Section 503A's ban on advertising and promotion was an unconstitutional limit on free speech. It also found that the unconstitutional provisions could not be severed from Section 503A and that the entire section was therefore void.[9] Subsequently, the Supreme Court agreed that the advertising and promotion ban was unconstitutional, but did not comment on the 9th Circuit ruling that the unconstitutional provisions could not be severed from Section 503A and that the entire section was therefore void.[10]

In 2008 a federal appellate court ruled in favor of FDA's interpretation that compounded drugs were "new drugs" subject to FDCA's drug approval, adulteration, and misbranding requirements,[11] however, the court also held that Section 503A was severable, effectively

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[3] U.S. Pharmacist, *Regulatory and Safety Issues in Compounding* (Oct. 1, 2015) (https://www.uspharmacist.com/ce/regulatory-and-safety-issues-in-compounding).

[4] Pub. L. No.105-115 (1997).

[5] Pub. L. No. 75-717 (1938).

[6] Pub. L. No. 105-115, section 503(A) (1997).

[7] *Id.*

[8] *Western States Medical Center, et al. v. Donna E. Shalala and Jane E. Henney*, 69 F. Supp. 2d 1288 (C.D. Nev. 1999).

[9] *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

[10] Congressional Research Service, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis* (R40503) (Oct. 17, 2012) (http://www.crs.gov/Reports/R40503?source=search&guid=32da9be974bc4a9c87c0286fae00f000&index=0).

[11] *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

reinstating Section 503A within the court's jurisdiction –Texas, Louisiana, and Mississippi.[12] The remainder of the country continued to be subject to FDA's 2002 Compliance Guide rather than Section 503A.

II. ENACTMENT OF THE COMPOUNDING QUALITY ACT

One of the most serious outbreaks associated with compounded drug products occurred in 2012, when the interstate distribution of contaminated compounded drug products led to a fungal meningitis outbreak in 20 states resulting in 753 cases of infection and 64 deaths.[13] An estimated 14,000 patients received injections from the contaminated drug products.[14] The compounding pharmacy responsible for the outbreak, the New England Compounding Center (NECC), had been the focus of previous complaints and was investigated by both FDA and the Massachusetts state board of pharmacy. However, NECC was allowed to continue operations.[15] This event prompted Congress to act and provide FDA and the compounding pharmacy industry with more clarity as to the agency's authority over compounding pharmacies. The Energy and Commerce Committee, Subcommittee on Oversight and Investigations held a hearing on the fungal meningitis outbreak on April 16, 2013. The Committee also held two hearings on the issue of compounding in the Health Subcommittee on May 23, 2013 and July 16, 2013.

On November 27, 2013, the Compounding Quality Act (CQA) of the Drug Quality Security Act was signed into law. CQA made two key revisions to FDCA: removing the advertising provisions that had been ruled unconstitutional thereby clarifying FDA's authority over traditional compounding pharmacies under section 503A and creating a new category of drug compounders called outsourcing facilities under a new section 503B.

A. Section 503A

Under section 503A, compounded drug products that are compounded by a licensed pharmacist in a state-licensed pharmacy or a federal facility, or a licensed physician, can be exempt from certain requirements under the law such as a new drug approval, labeling with adequate directions for use, and compliance with current Good Manufacturing Practices (cGMP). In order to be exempt, the product must be for an identified patient based on the receipt of a valid prescription, or in limited quantities before the receipt of a prescription if it is based on a history of valid prescription orders "generated solely with an established relationship" between the provider and patient. A drug product may be compounded if it has not been identified by FDA

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[12] *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383, 401 (5th Cir. 2008).

[13] Centers for Disease Control and Prevention, *Multistate Outbreak of Fungal Meningitis and Other Infections* (Oct. 30, 2015) (https://www.cdc.gov/hai/outbreaks/meningitis.html).

[14] Food and Drug Administration, *FDA's Human Drug Compounding Progress Report: Three Years after Enactment of the Drug Quality and Security Act* (Jan. 2017) (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM536549.pdf).

[15] U.S. Pharmacist, *Regulatory and Safety Issues in Compounding* (Oct. 1, 2015) (https://www.uspharmacist.com/ce/regulatory-and-safety-issues-in-compounding).

as "demonstrating difficulties for compounding that demonstrate an adverse effect on the safety or effectiveness of the drug product" and is compounded in a state that has entered into a memorandum of understanding (MOU) with the Secretary addressing the "interstate distribution of inordinate amounts of compounded drug products interstate." If the pharmacy is not in such a state, the compounded drugs are limited to quantities not to exceed five percent of the total prescriptions dispensed or distributed by the pharmacy or physician.[16]

It is important to note that under section 503A compounding pharmacies are not required to register with FDA, report adverse events to FDA, or report the types of drugs being compounded. FDA does, however, have authority to inspect such pharmacies.

B. Section 503B

CQA also established a new category of compounding pharmacies called "outsourcing facilities" under Section 503B of FDCA. An outsourcing facility is defined as a facility at one geographic location or address that compounds sterile drugs, voluntarily registers as an outsourcing facility, and complies with the new requirements of Section 503B.[17] Outsourcing facilities are exempt from the new drug approval, labeling of drugs with adequate directions for use, and track and trace requirements if the following requirements are met: registers with FDA annually; submits a semi-annual report identifying the drugs compounded, including the active ingredient and its source, National Drug code numbers, among other information; is subject to risk-based inspections; submits adverse event reports; complies with new labeling requirements; and pays an annual $15,000 fee. Outsourcing facilities are also required to comply with cGMPs, compound under the supervision of a licensed pharmacist or physician, and can only utilize drug substances from an approved bulk ingredients list. Outsourcing facilities are not required to obtain a patient-specific prescription.

III. FDA IMPLEMENTATION OF CQA

Since CQA's enactment, FDA has issued 24 draft and final guidances and released four proposed and final regulations implementing CQA and outlining more specifically the requirements under Sections 503A and 503B.[18,19] In addition, the agency released a draft MOU that outlined the threshold for interstate distribution of compounded drugs under Section 503A. The recently released 2018 Compounding Policy Priorities Plan provides an update regarding upcoming revisions and finalizations of guidances, as well as the MOU and Sections 503A and

[16] Section 503A(b)(3).

[17] Section 503B(d)(4)(A).

[18] Food and Drug Administration, *Compounding* (Jan. 2018) (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm452240.htm).

[19] Food and Drug Administration, *Regulatory Policy Information* (Jan. 2018) (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm).

503B bulks lists.[20] FDA has conducted over 480 inspections of compounding pharmacies, overseen 125 recalls, and issued over 160 warning letters regarding failure to comply with Sections 503A and 503B, including violations of new drug approval, cGMPs, and insanitary conditions.[21] As of January 5, 2018, there are 63 registered outsourcing facilities.[22]

While FDA has been working actively to implement CQA, there continues to be safety events associated with the use of compounded drug products. A recent analysis by Dr. Janet Woodcock, Director for the Center for Drug Evaluation and Research, and Julie Dohm, Agency Lead on Compounding, noted that, "Because the vast majority of compounding facilities do not report adverse events to the FDA, our records probably only include a small proportion of the adverse events that actually occur."[23] Examples of adverse events identified in the analysis include three infants receiving a compounded morphine sulfate preparation that was nearly 25 times stronger than indicated on the label; at least 43 patients experiencing diminished visual function, including blurred vision and loss of color perception from an intraocular injection of a steroid and anti-infective agent compounded by a Texas pharmacy; and a bacterial bloodstream infection impacting 15 patients and killing two in Texas as the result of contaminated infusions.[24]

Recent analyses of state perspectives on compounding have found that oversight and regulatory landscapes vary at the state level for compounding pharmacies, and there is a desire for greater guidance from FDA. For example, an analysis by the Pew Charitable Trusts found that only a quarter of states prioritize inspections for high-risk sterile compounding, and about half inspect pharmacies that perform sterile compounding annually.[25] Further, more than half of the states allow traditional pharmacies to compound without a patient prescription.[26] The Government Accountability Office (GAO) found that there is still an incomplete picture regarding drug compounding, noting:

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[20] Food and Drug Administration, *2018 Compounding Policy Priorities Plan* (Jan. 2018) (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm).

[21] Briefing by Food and Drug Administration, to House Committee on Energy and Commerce Staff (Dec. 1, 2017).

[22] Food and Drug Administration, *Registered Outsourcing Facilities* (Jan. 1, 2018) (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm).

[23] Janet Woodcock, M.D., and Julie Dohm, J.D., Ph.D., *Toward Better-Quality Compounded Drugs — An Update from the FDA*, New England Journal of Medicine (Dec. 28, 2017) (http://www.nejm.org/doi/full/10.1056/NEJMp1712905).

[24] *Id.*

[25] The Pew Charitable Trusts, *Reports Recommend Strong State Policies on Drug Compounding: A look at state regulation and oversight* (Feb. 23, 2016) (http://www.pewtrusts.org/en/research-and-analysis/analysis/2016/02/23/reports-recommend-strong-state-policies-on-drug-compounding).

[26] *Id.*

According to FDA officials, there is no good source for data on the extent of drug compounding and who is doing it except for data on outsourcing facilities. Although outsourcing facilities are required to provide FDA with a report of the drugs they compounded during the previous 6-month period, including the number of units they produced, aggregate data on the listed drugs were not available at the time of our review. According to FDA officials, not all outsourcing facilities provided these reports and the data provided were not yet collected and maintained in a standard format.[27]

IV. WITNESSES

Panel I

Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration

Panel II

Jenn Adams
Senior Vice President and President, Clinical Product Solutions
PharMEDium Services

Bruce A. Brod, M.D., FAAD
Chair, Congressional Policy Committee
American Academy of Dermatology Association

Nancy Dargan
Patient of New England Compounding Center

Shawn E. Hodges, PharmD
Pharmacist and Vice President
International Academy of Compounding Pharmacists

Elizabeth Jungman
Director, Public Health
The Pew Charitable Trusts

Jacob Olson, PharmD, R.Ph
President and CEO
Skywalk Pharmacy on behalf of National Community Pharmacists Association

[27] United States Government Accountability Office, *Drug Compounding: FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges* (GAO-17-64) (Nov. 2016) (https://www.gao.gov/assets/690/681096.pdf).

Molly Ventrelli
Vice President, Regulatory Affairs
Fresenius Kabi

George Williams, M.D.
President Elect
American Academy of Ophthalmology