March 20, 2018

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Gottlieb and Dr. Woodcock:

The undersigned[1] commend the Food and Drug Administration for its progress in implementing the Drug Quality and Security Act of 2013 (DQSA) and would like to offer our perspective as the agency continues its implementation. We are a diverse group of stakeholders from the public health, manufacturing, outsourcing facility, and pharmacy communities, whose goals align with the goals of the FDA to protect patients and ensure that compounded medications are made under appropriate quality standards.

**Background: The Drug Quality and Security Act Enactment**

In 2012, the nation suffered its worst known public health crisis associated with compounded drugs. In all, approximately 76 people died and 778 individuals in 20 states were stricken with meningitis or other infections[2]. While this was the largest outbreak of infections associated with compounded drugs, it is by no means the only time that compounded drugs harmed or killed patients. To be sure, compounded medicines remain an important clinical intervention for some patients, Congress enacted the DQSA in order to ensure that these drugs meet minimum standards to ensure drug quality.

A key component of the DQSA is its distinction between traditional compounders and the new category of outsourcing facilities governed by section 503B of the Food, Drug, and Cosmetic Act (FDCA). The category was created so regulators could mitigate the specific – and higher – risks associated with producing stock supplies of compounded drugs needed by hospitals and healthcare providers. Congress required these facilities to adhere to current Good Manufacturing Practices (cGMP)—rigorous requirements enforced by FDA for the appropriate manufacturing, processing, packing, and storage of pharmaceutical products.

To reduce the risks to patient safety, the statute was explicitly written to ensure that sterile drugs produced without a prescription would be held to more robust standards than medicines compounded pursuant to individual prescriptions. Furthermore, by distinguishing the two categories of compounders, the DQSA enhances accountability by making it clear - both for regulators and the regulated industry - whether any given compounder is primarily regulated by the federal or state government.

[1] The Compounding Quality Coalition, NACCHO and APHA
[2]Tennessean. "Meningitis Outbreak Trial: Potentially Deadly Bacteria Found in NECC Drugs" (October 2017). https://www.tennessean.com/story/news/2017/10/12/meningitis-trial-new-england-compounding-center/759459001/

Yet, despite the progress that has been made, including a robust FDA guidance assisting compounding facilities in identifying and correcting insanitary conditions as well as an increase in the agency's site visits and facility inspections, numerous other instances of patient injury and death have been associated with compounded drugs since the enactment of the DQSA, indicating the work that still needs to be done to keep patients safe. Examples of these recent adverse events include:

- 2017- In Texas, an injectable steroid antibiotic for administration in the eye caused patients to experience vision loss. FDA estimates that at least 43 patients were affected.[3]
- 2016- IV flush solutions produced in New York were not compounded under appropriate quality standards, resulting in contamination. They were also used past appropriate "beyond-use" dating. Subsequent fungal bloodstream infections killed two patients and sickened more - 17 patients were affected in total.[4]
- 2016- FDA alerted health care professionals of a voluntary recall of a compounded morphine sulfate injectable drug product after laboratory results indicated the product was 25 times stronger than labeled. Three infants who received the overly potent drug experienced serious adverse events.[5]
- 2015- FDA alerted health care professionals and patients of a voluntary recall of compounded multivitamin capsules containing high amounts of Vitamin D3. This product was distributed nationwide by a compounder.[6]
- 2013- Twenty-six patients experienced skin abscesses and other adverse events after receiving injections of methylprednisolone acetate from a TN compounder.[7]
- 2013- A compounder recalled all purportedly sterile drugs within expiry, and ceased making any sterile products, after 15 patients who had been injected with calcium gluconate dispensed by the compounder developed bacterial bloodstream infections, two of whom died.[8]

**DQSA Implementation Must Ensure Patients Have Access to High-Quality, Clinically Necessary Compounded Drugs**

The CQC agrees with the FDA that all stakeholders have a role to play in making the implementation of the DQSA a success[9]. To this end, implementation must enable patients to have access to high-quality, clinically necessary compounded drugs through the following:

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[3] U.S. Food and Drug Administration, "Compounded Triamicinolone and Moxifloxacin Product for Intravitreal Injection by Guardian Pharmacy Services: Alert to Health Professionals - Serious Adverse Events Reported," accessed Nov. 14, 2017, https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm569123.htm

[4] The Pew Charitable Trusts, "U.S. Illnesses and Deaths Associated with Compounded Medications or Repackaged Medications" (2017), http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/us-illnesses-and-deaths-associated-with-compounded-medications-or-repackaged-medications..

[5] Ibid.

[6] U.S. Food and Drug Administration, "FDA's Human Drug Compounding Progress Report" (Jan 2017), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.pdf.

[7] Ibid.

[8] Ibid. The Pew Charitable Trusts.

[9] The New England Journal of Medicine, "Toward Better-Quality Compounded Drugs—An Update from the FDA" (Dec 2017). http://www.nejm.org/doi/full/10.1056/NEJMp1712905#t=article

Ensure compounding is performed under appropriate standards wherever it occurs[10]

The foundation of the DQSA is a risk-based approach, ensuring that compounding takes place under quality standards appropriate to the level of risk of the drugs being produced. Current federal law, as amended by DQSA, will help prevent another tragedy – but only if compounding is performed in a way that is consistent with the law, and if FDA prioritizes the law's implementation and enforcement.

Regulators should ensure that physicians can acquire compounded drugs produced under the appropriate standards, unless physicians are able to produce drugs under those standards themselves. Similarly, if current Good Manufacturing Practices (cGMPs) are tailored to the needs of smaller-scale producers, any such revision must preserve outsourcing facilities as a reliably safe supply of sterile office stock product.

Ensure that patients who have a clinical need for a compounded drug have access to the highest-quality product

Compounded drugs benefit patients who have a medical need for a particular drug formulation that is not commercially available. It is important that these drugs are produced in full compliance with applicable standards and under conditions that guarantee potency, stability and freedom from contamination.

Encourage the implementation of an effective, robust "Section 503B" program

The DQSA established the outsourcing facility category to ensure hospitals, other health care facilities, physicians, and patients have access to a safe supply of high-quality, sterile drugs. This category provides for the compounding of drugs under rigorous standards different than those that apply to traditional compounders, including adherence to cGMPs. 503B outsourcing facilities can compound without patient-specific prescriptions, strongly differentiating 503B facilities from traditional compounders.[11] This distinction is integral to the DQSA because it incentivizes compounding facilities to register with FDA and ultimately make the investments necessary to bring their facilities into compliance with the standards under Section 503B. DQSA also clearly restricts the use of bulk ingredients for 503B compounding except when truly clinically necessary. This restriction must be enforced by FDA.

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[10] Such as the enforcement of the MOU provision of Section 503A(b)(3)(B)(i), which establishes an agreement between a State and the FDA regulating the distribution of inordinate amounts of compounded drug products. The MOU provision ensures that there are adequate protections and regulations in place, which makes states responsible for investigating complaints about compounded drugs made in the state and distributed outside of the state. This ensures that compounders shipping compounded drugs interstate are held to robust quality and safety standards. In their recently released "2018 Compounding Policy Priorities Plan", FDA stated that they intend to release a revised version of the current MOU, with language that would increase the amount considered to be "inordinate" from 30 to 50 percent of total drugs distributed interstate, as well as putting a mechanism in place that would require reporting obligations on compounders that distribute more than 50 percent across state lines.

[11] As we define the term, "traditional pharmacies" do not include pharmacies covered under FDA's hospital- and health system-specific guidance, "Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act", published in April 2016, which sets out a separate anticipatory compounding framework for those entities.

Preserve the traditional role of pharmacy practice consistent with the DQSA prescription requirement

A key distinction between Section 503A and Section 503B in the DQSA is the prescription requirement. While Section 503B allows for outsourcing facilities following cGMP standards to provide stock supplies of medications, Section 503A dictates that traditional compounders must obtain individual patient prescriptions to compound and dispense or distribute medications. Although limited quantities can be produced in advance of the receipt of a prescription in the case that a history for such prescriptions exists, a prescription must be received prior to distribution. The foundational aspect of a prescription requirement ensures the traditional practice of pharmacy is maintained, including the accountability of a patient care triad between a patient, a prescriber, and a pharmacist.

Protect the FDA approval process (innovator and generic pathways) by ensuring that commercially available drug products cannot be copied

Another key to protecting patients is safeguarding the FDA approval process for new drugs. Unlike compounded drugs, FDA approved drugs are supported by substantial evidence demonstrating safety and efficacy. To uphold patient safety, Congress sought to ensure that FDA-approved drugs would be used whenever possible, including in the preparation of compounded formulations. Compounders should not use an active pharmaceutical ingredient (API) from a bulk substance that is available through an FDA-approved medication unless doing so would produce a clinical difference for an identified patient. As Commissioner Gottlieb has stated, if there is "an FDA-approved product available that you can compound from, you have to compound from that product." [12] In addition, federal law prohibits the compounding of drugs that are essentially a copy of an FDA-approved medicine, unless FDA has placed that drug on the drug shortage list. It is critical that these provisions be fully implemented and enforced to avoid a disincentive for a drug maker to invest in new drug approvals and in the production of approved versions of drugs. While compounded drugs are an important option when approved drugs cannot meet a patient's clinical needs, only products that have been evaluated and proved through FDA's approval process meet the gold standard for safety and efficacy.

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The FDA's commitment to patient safety is evident in its efforts to implement and enforce the DQSA. The CQC believes this effort will create a clearer framework for compounded medicines, and protect the patients who rely on them. With that, we commend the FDA's leadership and would like to extend our help in ensuring this bipartisan, public-health focused initiative is successful. Please do not hesitate to contact Clay Alspach at clay.alspach@leavittpartners.com if the CQC can be of any assistance as the administration continues to develop this sector.

[12]Commissioner Gottlieb Testimony from E&C Hearing, "Examining Implementation of the Compounding Quality Act" (January 30, 2018).

Sincerely,

The Compounding Quality Coalition, National Association of County & City Health Officials, and The American Public Health Association