



The DQSA: Five Years In

Part One of Two

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November 27, 2018 marked five years since President Obama signed the Drug Quality and Security Act (DQSA) into law. The law addresses two distinct areas of drug oversight, but it was the combined concerns about the quality and reliability of the drug supply that enabled passage of the law:

- Title I, the Compounding Quality Act (CQA), primarily responded to an acute public health crisis that was caused by the distribution of contaminated steroidal injections, compounded without patient prescriptions, which had already claimed the lives of more than 60 Americans.
- Title II, the Drug Supply Chain Security Act (DSCSA), addressed the long-held desire for a federal drug tracking and tracing system to prevent a series of ills, especially the distribution of counterfeit drugs, but the particular timing was motivated by the pending onset of state-level drug-tracking requirements that the DSCSA ultimately preempted.

The core objective of both titles of the DQSA was to safeguard public health from future threats from dangerous drug products. The CQA, which is the subject of this report, was designed to accomplish several interrelated, but potentially competing, goals: (1) to crack down on dangerous practices in the compounding of drugs for human use, (2) to preserve the traditional role of state-licensed pharmacies compounding drugs for known patients and (3) to establish a federally regulated industry to supply health care providers with “office stock” of compounded sterile drugs. The DSCSA was intended to establish the parameters for a nationwide, interoperable drug product tracing system and will be addressed in an upcoming report.

In implementing the DQSA, the U.S. Food and Drug Administration (FDA) has made measureable progress since 2013, but it has also experienced implementation challenges. In addition to the concerns that the law was designed to meet, new public health and policy challenges have emerged. The affected industries have also confronted setbacks in accommodating the law’s new mandates, many of which require implementation steps by FDA.

This five-year milestone offers a valuable opportunity to assess the state of the law, what has transpired over the first five years since the law’s enactment and what is ahead by analyzing several key themes of the CQA.

THE IMPETUS FOR THE CQA

2012 Fungal meningitis outbreak:

- Three lots of contaminated drug product were distributed, totaling more than 17,000 vials of medication.
- In 20 different states, 753 patients were diagnosed with fungal infections.
- 76 patients died.

1. The marketplace for outsourced sterile drug preparation

What is it?

The CQA’s congressional sponsors characterized the fundamental bargain of the legislation as a market-based approach: if a compounding facility voluntarily registers with FDA under the new Section 503B added to the Food, Drug, and Cosmetic Act (FDCA), and agrees to meet current good manufacturing practices (cGMPs) and a host of other regulatory obligations thereunder, this “outsourcing facility” may engage in larger-scale production and unlimited interstate distribution without obtaining patient-specific orders or prescriptions as traditional compounding pharmacies must do. This fundamental bargain aimed to ensure that those compounded preparations that are needed at higher volumes—and thus pose greater public health risks—would be made under higher manufacturing standards and federal oversight. An open question for the law is whether the balance of benefits and requirements under Section 503B has

generated a robust and reliable supply of high-quality, clinically necessary preparations.

At the five-year mark, there are 73 registered outsourcing facilities, although dozens of other registrants have come and gone over the course of five years. In late 2017, FDA Commissioner Scott Gottlieb indicated that FDA was disappointed by the low uptake and had expected hundreds more of facilities to register. However, the CQA's registration fees and inspection schedules were built on assumptions of less than 100 registrants, and the regulatory impact assessments accompanying FDA's first several draft guidance documents estimated 50 registrants.¹ Moreover, the volume of registered outsourcing facilities is not necessarily a reliable proxy for the industry's overall ability to meet clinical demand.

What has happened?

One of the first critical questions of Section 503B's voluntary approach was "If you build it, will they come?". FDA had to work quickly to ensure that there were enough "rules of the road" for compounders to decide to enlist in a new regulatory category with significant entry costs. Within two months of enactment, FDA had issued draft guidance conveying the agency's tentative expectations for registering with FDA and reporting production—as required by statute—and also sent a letter to health care providers urging them to purchase from FDA-registered facilities. Twenty-two facilities registered within these first two months.²

A year after enactment, FDA had issued five draft and final guidance documents, and 57 facilities had enlisted.³ These guidance documents related to many of the key provisions of Section 503B, including the registration process, fees associated with registered facilities and reporting adverse events to the agency. Most significantly, the agency issued interim draft guidance outlining the agency's expectations for compliance with cGMPs, by far the most weighty—and costly—aspect of complying with Section 503B.

At the five-year mark, FDA has issued two final rules and one proposed rule. The agency has issued final policies relating to electronic product reporting, registering and co-locating facilities, repackaging drugs and biologics, copying FDA-approved drugs and an interim policy on using bulk drug substances.

1 See, e.g., Draft Guidance for Industry on Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and Cosmetic Act, 79 Fed. Reg. 37,743, 37,744 (July 2, 2014).

2 Cheryl A. Thompson, *Registrations of Compounding Outsourcing Facilities Trickle In*, 71 Am. J. Health-Sys. Pharmacy 350 (2014).

3 FDA, Regulatory Policy Information (Nov. 24, 2014), <https://web.archive.org/web/20150101193201/http://www.fda.gov:80/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm>; FDA, Registered Outsourcing Facilities (Dec. 5, 2014), <https://web.archive.org/web/20141215085405/http://www.fda.gov:80/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>.

WHAT DOES THE CQA DO EXACTLY?

Basic premise: All compounded drugs are “new drugs” subject to FDA requirements:

- **New Section 503B exempts compounded drugs from three requirements of the FDCA:**
 1. FDA premarket approval (§ 505)
 2. drug labeling with adequate directions for use (§ 502(f)(1))
 3. tracking and tracing requirements (§ 582).
- **If certain conditions are met:**
 - The drugs are compounded under a licensed pharmacist’s supervision, are labeled as compounded drugs, are not made using bulk substances (except under narrow circumstances, are not “essentially a copy” of an approved product and have not been withdrawn from the market.
 - The outsourcing facility registers with FDA annually, submits to risk-based inspections, pays all applicable fees, electronically reports all production to FDA biannually, reports adverse events and does not engage in wholesaling.
- **Section 503A, as amended, exempts compounded drugs from three requirements of the FDCA:**
 1. FDA premarket approval (§ 505)
 2. drug labeling with adequate directions for use (§ 502(f)(1))
 3. compliance with CGMPs (§ 501(a)(2)(B)).
- **If certain conditions are met:**
 - The drug is compounded by a licensed pharmacist or physician, and it is not dispensed before receipt of a valid prescription for an individual patient.
 - No more than 5 percent of prescriptions are being distributed across state lines, unless the state has entered into a Memorandum of Understanding with FDA.

What is ahead?

Although many significant rules of the 503B road remain outstanding or unclear, including six guidance documents that are still in draft form and several policies that have yet to be decided,⁴ the most pressing open questions revolve around the manufacturing standards to which outsourcers are bound. During the

development of the legislation, congressional drafters recognized that the regulatory cGMPs for conventional drug manufacturing would need to be tailored to the outsourcing model, which involves relatively smaller batches of production, frequently compounded from approved, finished drugs.⁵ FDA issued an interim draft guidance on cGMPs in 2014,

4 FDA has stated its intention to issue policy documents regarding (1) compounding supervision in outsourcing facilities; (2) compounding drugs or using bulk drug substances subject to a risk evaluation and mitigation strategy (REMS); (3) wholesaling restriction on an outsourcing facility’s compounded drugs; and (4) compounded drug product labeling. Center for Drug Evaluation and Research, Outsourcing Facility Information 6-8 (Sept. 2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM577334.pdf>.

5 See, e.g., S. 959, *Pharmaceutical Compounding Quality and Accountability Act*; S. 957, *Drug Supply Chain Security Act*, NLRB Nominations, Executive Session of the Subcomm. on Health, H. Comm. On Energy and Commerce, 113th Congr. (May 22, 2013) (statement of Al Franken, Senator, United States Senate, expressing his understanding that FDA will develop a new and different set of GMPs that address the different circumstances of compounding).

but in the more than four years since, it has not advanced beyond this stage. FDA is reportedly nearing completion of a revised **draft** guidance, expected by the end of 2018 or early 2019. However, the agency intends ultimately to issue final guidance, a proposed rule and a final rule amending FDA's regulations specifically to address cGMPs for outsourcing facilities.⁶ In the meantime, the agency has generally held outsourcing facilities to the draft standards on the basis that they convey only discretionary accommodations to the underlying statutory GMPs to which outsourcers are legally bound.

A little more than a year ago, in response to congressional pressure on a tangentially related compounding matter, Commissioner Gottlieb announced plans to issue a new policy—informally dubbed “503B Lite”—for smaller-scale compounding pharmacies willing to register with FDA.⁷ A few months later, before a House subcommittee, the Commissioner clarified his prior statements. Noting that there is inherent flexibility in cGMPs, he stated that FDA is working to “to apply [c]GMP requirements in a way that is tailored to the nature of the specific compounding operations conducted by outsourcing facilities, such as production in small batches,” rather than to create a stepped-down 503B Lite category.⁸ Until outsourcing facility cGMPs are finalized, it will be difficult to render a final verdict on whether this new sector is succeeding on the intentions of the CQA. It also remains unclear exactly what business relations will ultimately

predominate, between outsourcing facilities and providers on one hand, and between outsourcing facilities and manufacturers on the other.

2. Improved federal-state coordination and communication regarding drug compounding

What is it?

The CQA explicitly provides for enhanced communications between FDA and the states concerning traditional pharmacy compounding.⁹ The law also affirmed the traditional role of state-licensed pharmacies that are engaged in compounding, as well as their limitations under federal law. Specifically, the law struck Section 503A's prohibition on advertising that had previously been found unconstitutional, thereby removing any doubt about the validity of the remainder of Section 503A. That section of the FDCA provides that a drug compounded by a licensed pharmacist or physician pursuant to a prescription for an individual patient is nonetheless a “new drug” subject to regulation under the FDCA. If, however, it is compounded in accordance with all of Section 503A's conditions, the drug is exempt from federal requirements for premarket approval, adequate directions for use and preparation under cGMPs. To ensure that traditional pharmacy compounding complies with Section 503A and with the remainder of the FDCA, FDA must work closely with the states, which have greater knowledge of—and access to—these pharmacies.

⁶ These changes are expected to amend Parts 210 and 211 of Title 21 of the *Code of Federal Regulations*, although there has been discussion of creating a new part or subpart within the title.

⁷ Nate Raymond, Exclusive: FDA Plans New Compounding Pharmacy Policy, Agency Head Says, Reuters (Sept. 15, 2017), <https://www.reuters.com/article/us-usa-fda-pharmacies-exclusive/exclusive-fda-plans-new-compounding-pharmacy-policy-agency-head-says-idUSKCN1BQ2RV>.

⁸ *Examining Implementation of the Compounding Quality Act Before the Subcomm. on Health, H. Comm. On Energy and Commerce*, 115th Congr. (2018) (statement of Scott Gottlieb, Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services).

⁹ 21 U.S.C. § 353a-1.

What has happened?

FDA has stood firm on the centrality of Section 503A's prescription requirement in the face of considerable pushback from stakeholders that continue to promote an interpretation of the law that does not require patient-specific prescriptions. Shortly after the law's passage, FDA issued general guidance for traditional pharmacies concerning the exemptions under Section 503A, and it later issued more explicit guidance explaining the law's obligation that pharmacies obtain prescriptions **prior** to distributing product. In response, advocates sought congressional sign-on letters to FDA and even successfully obtained language in a House Appropriations Committee report directing FDA to rescind the draft guidance and issue alternative guidance permitting the distribution of compounded drugs for "office use" under Section 503A.¹⁰

Undeterred, FDA not only finalized its policy in late 2016, but it took the additional step of directly responding to the Budget Request in 2017.¹¹ When the Trump administration maintained steadfast opposition to pharmacy office stock compounding, advocates shifted course and, instead of seeking to direct FDA to reinterpret the law, sought legislation to write the prescription requirement out of Section 503A.¹² Recognizing that the ability to prepare drugs for office use is the core distinguishing factor to entice entities to register under Section 503B and meet its many requirements, FDA has consistently enforced the prescription requirement on traditional pharmacies and enlisted states to

cease allowing the activity, long permitted under many state pharmacy codes.

The memorandum of understanding (MOU) has had a more checkered history, but FDA has made recent progress. Under Section 503A, pharmacies are limited to distributing no more than 5 percent of their compounded drugs out of state, unless their resident state enters into an MOU with FDA directing the state's board of pharmacy to police compounding activities, and especially, interstate distribution.¹³ The initial draft MOU, issued in 1998, would have restricted interstate distribution to 20 percent of all drugs distributed or dispensed by the pharmacy. The first draft MOU post-CQA, issued in early 2015, would have upped the threshold to 30 percent. In response to FDA's proposal, Rep. Buddy Carter (R-GA) offered an amendment to the fiscal year 2018 FDA appropriations bill that would have prohibited FDA from using its funding to implement the MOU provision required by Section 503A. The amendment was defeated,¹⁴ and, in the ensuing fiscal year, FDA issued a revised draft MOU.

What is ahead?

Despite FDA's strong defense of Section 503A's prescription requirement, the agency has not quite gotten a handle on the access concerns raised by detractors of the prohibition on compounding for office use under Section 503A, including prominent physician associations. It has been difficult to evaluate whether these office stock needs could ultimately be met through outsourcing facilities, particularly if FDA adopts a "503B

¹⁰ H.R. Rep. No. 115-232, at 69 (2017).

¹¹ FDA, Fiscal Year; Justification of Estimates for Appropriates Committees (2017) ("Compounding for office stock by 503A facilities would undermine the incentive for compounders to become outsourcing facilities, a critical measure that Congress put in place in the DQSA...")

¹² Preserving Patient Access to Compounded Medications Act of 2017, H.R.2871, 115th Cong. (2017).

¹³ 21 U.S.C. § 353a(b)(3)(B).

¹⁴ 163 Cong. Rec. H7065 (daily ed. Sept. 6, 2017) (recorded vote on Carter of Georgia Part B Amendment No. 17).

Lite” option. Nevertheless, there may be legitimate concerns about the demand for office stock of compounded drugs—particularly nonsterile drugs—not being met. As noted, in September 2018, FDA issued its third—and possibly final—draft MOU. By increasing the threshold for interstate distribution to 50 percent of all compounded drug products distributed, and by triggering federal oversight (rather than a hard limit), FDA may have assuaged political opposition enough to finally implement the policy. The revised draft also puts forward a new definition of “distribution” that avoids creating a back door for Section 503A office use. Comments on the revised draft MOU are due in December, and, given the anticipated level of interest, the agency is unlikely to finalize the MOU before mid-2019. FDA has proposed giving states 180 days to review the MOU before beginning to enforce Section 503A’s default 5 percent limit on interstate distribution.

KEY CQA IMPLEMENTATION

FDA policymaking:

- final guidance issued: 15
- currently issued draft guidance: 6
- final rules: 2
- proposed rules: 1.

Section 503B registrations:

- 73 registrants
- 68 registrants inspected to date.

3. The Role of Hospitals and Other Providers

What is it?

Hospitals, health systems and other health care providers occupied a central role in

devising the CQA. Foremost, Section 503B affords health care providers a reliable supply of sterile preparations to stock in anticipation of future need, including situations in which the approved, finished version of the drug is not ready to administer. In addition to outsourcing preparation, health care providers themselves engage in compounding drugs for patient use. As a result, providers are beneficiaries of the new regulatory category and may also be regulated under either Section 503A or 503B, or both.

Provider compounding runs the gamut, from a major health system preparing sizable quantities of sterile drugs (e.g., admixed IV bags) in anticipation of need and distributing it to its hospitals, to a physician’s office preparing medication for an individual patient. Any time a drug is compounded, these sections of the FDCA are implicated. How FDA has opted to accommodate providers has been an important part of the implementation story.

What has happened?

During the negotiations over the CQA, Congress considered a broad carveout for compounding occurring within a single health system. Since the final bill ultimately omitted this carveout, FDA has interpreted the law to apply to hospitals the same as any other entity. Shortly after the law’s passage, several hospital systems engaged in “central fill” compounding registered with FDA as outsourcing facilities.

The viability of hospital registration with FDA under Section 503B was called into question by the issuance of a draft guidance that would have precluded traditional pharmacies and outsourcing facilities from co-locating. Under the draft guidance, compounding activities occurring at the same geographic location would have been held to the stricter conditions

of Section 503B, including uniform cGMPs. In 2018, FDA issued final guidance on the “Facility Definition” that made co-location more feasible, and again reopened the door to hospital registration under Section 503B.¹⁵

What is ahead?

There is unlikely to be a substantial increase in hospitals registering as outsourcing facilities, at least until FDA finalizes policies on their treatment under Section 503A. In 2016, FDA issued draft guidance making clear that, unless hospitals register, their in-house pharmacies are bound by the same requirement as other pharmacies and must receive a prescription prior to distributing a compounded drug. However, the guidance proposed to allow hospitals to distribute compounded drugs, on an anticipatory basis, so long as the product did not change ownership and stayed within a one-mile radius of the pharmacy. This proposal proved so unpopular and unworkable that FDA took the unusual step of publicly disavowing it without issuing a revised draft guidance or a final guidance.

At the five-year mark, it remains unclear how FDA plans to deal with hospital-based compounding. The agency may seek to modify its campus-based approach with a little more geographic leniency, or it may pursue a temporal-based approach (e.g., 24 hour beyond use date), as touted by some advocates. The agency is also facing pushback from stakeholders who oppose any erosion of Section 503A’s prescription requirement, as well as those who would use it to argue for more categorical exemptions. At present,

the list of compounding policies features the “Hospital and Health System” draft guidance alongside other draft guidance, such as the cGMPs.¹⁶ How providers ultimately proceed turns not only on this policy, but also on whether FDA adopts a more flexible treatment of different types of compounding operations under a revised cGMP (or 503B Lite) framework. Ultimately, most hospitals likely prefer that the outsourcing facility sector becomes a reliable and competitive source for anticipatory preparation of sterile drugs.

4. Protecting the drug approval system

What is it?

FDA’s premarket review of drugs is the global gold standard for ensuring safety and effectiveness. During the legislative debate, some stakeholders worried that the ability of outsourcing facilities to mass-produce sterile drug products for unidentified patients, with no limitations on the size of batches or the total volume of production for specific formulations, could open a viable workaround to the premarket approval system for new drugs. In 2013, Dr. Scott Gottlieb, then a resident fellow with the American Enterprise Institute, stated, “If FDA doesn’t exercise its authority evenly, which means not allowing firms to compound identical versions of FDA approved products, then FDA will give incentive for drug makers to re-mask themselves as [outsourcing facilities] to skirt the new drug requirements.”¹⁷ Legislators, too, worried that the unfettered ability to produce large quantities of drug products could displace demand for approved drugs.

¹⁵ FDA, Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry (May 2018), <https://www.fda.gov/downloads/Drugs/Guidances/UCM496288.pdf>.

¹⁶ FDA, Regulatory Policy Information (Oct. 1, 2018), <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Pharmacy-Compounding/ucm166743.htm>.

¹⁷ Examining Drug Compounding Before the Subcomm. on Health, H. Comm. On Energy and Commerce, 113th Congr. (2013) (statement of Scott Gottlieb, Resident Fellow, American Enterprise Institute).

What has happened?

To protect the drug approval system, Congress crafted several interrelated provisions to curb opportunities to circumvent new drug applications. First, Section 503B prohibits outsourcing facilities from compounding using bulk drug substances—the raw active ingredients from which FDA-approved drugs are manufactured—unless one of two conditions is met: (1) the drug is in shortage, or (2) FDA has determined that there is a legitimate clinical need for the substance. Separately, the law prohibits outsourcers from copying FDA-approved drugs and broadly defines a copy to include any compounded drug “a component of which is a bulk drug substance that is a component of an approved drug . . . unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner.”¹⁸ The effect of these two provisions is to require outsourcing facilities to compound using FDA-approved drugs, unless there is a valid reason that they cannot. Finally, Section 503B prohibits wholesaling,¹⁹ which limits the scalability of the outsourcing model.

This issue has been more challenging than perhaps any other aspect of CQA implementation to date. While FDA has found success in reducing the threat posed by large-volume traditional compounding, a broader threat to the drug approval system has arisen through outsourcing facilities’ use of bulk drug substances. Almost immediately following enactment, FDA solicited nominations of bulk drug substances for which there is a claimed

clinical need. In response to the incomplete nominations of thousands of substances, FDA established a new docket in 2015 and asked questions that were more likely to elicit the responses necessary to adjudicate the statutory criteria. In 2015, FDA proposed and, in early 2017, finalized, an “Interim Policy” on bulk drug substances, announcing enforcement discretion toward the use of hundreds of substances for which FDA determined that the nomination was sufficient for FDA to review. FDA had not determined that the use of these substances was appropriate in accordance with the statutory standard and process. As Commissioner Gottlieb later explained to Congress, however, “the idea was to freeze the market” while FDA evaluates each nominated substance individually.²⁰

Of the more than 250 substances that were granted extrastatutory enforcement discretion, the vast majority are available as components of FDA-approved drugs. In principle, the prohibition on compounding what is essentially a copy of an approved drug serves as a check on the enforcement discretion toward bulk-compounding approved drugs. However, FDA’s guidance on what is “Essentially a Copy” incorrectly interprets the definition of copy (e.g., “a drug, a component of which is a bulk drug substance that is a component of an approved drug . . .”) to apply the same to **all** compounded drugs, whether they are prepared from bulk drug substances or are finished pharmaceuticals.²¹ As a result, FDA established what seems to be a low bar for documenting clinical difference (e.g.,

¹⁸ 21 U.S.C. § 353b(d)(2)(B).

¹⁹ *Id.* § 353b(a)(8).

²⁰ *Examining Implementation of the Compounding Quality Act Before the Subcomm. on Health, H. Comm. On Energy and Commerce, 115th Congr. (2018)* (statement of Scott Gottlieb, Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services).

²¹ FDA, *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry* (Jan. 2018), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf>.

“diluted for infusion”), reducing the potency of this provision as a check on the legitimacy of compounding from bulk ingredients.

FDA’s prolonged development of policy, combined with ambiguous statements and sparse enforcement, has led to an environment in which large quantities of compounded drugs are prepared from bulk ingredients without meeting the statutory bases for doing so. This circumstance prompted several pharmaceutical companies to take matters into their own hands, filing lawsuits against compounders, and the FDA itself, beginning in 2017.²²

What is ahead?

More recently, FDA adopted a different approach toward bulk-compounding. In January 2018, FDA issued a Compounding Policy Priorities Plan stating its plans to “ensure that outsourcing facilities do not compound using a bulk drug substance when an FDA-approved drug can be used to meet patient medical needs.”²³ In March, the agency followed up with a draft guidance establishing a robust framework for evaluating the clinical need of each substance that had been nominated for the Section 503B bulks list,²⁴ and, in August, it issued a notice in the Federal Register to determine the fate of three substances: bumetanide, nicardipine hydrochloride and vasopressin.²⁵ With a comment period that closed in October, FDA is poised to make its first formal decision

regarding the clinical need for compounding (a little more than five years following the law’s passage).

If FDA proceeds to remove the bases to compound these three bulk drug substances—or litigants persuade a court to enjoin the practice—FDA is likely to accelerate its review of nominated substances. Commissioner Gottlieb has cautioned that reviewing all nominated substances could take some time,²⁶ however, so it remains to be seen how quickly FDA can apply the statutory review process to all of the substances that are currently subject to enforcement discretion.

5. Protecting the public from dangerous compounded medications

What is it?

For FDA and Congress, the utmost priority for the CQA is protecting the public health, and specifically preventing another mass tragedy from contaminated medications. It is therefore no surprise that the agency’s initial implementation has prioritized inspections, enforcement and other oversight. At the same time, FDA has attempted to clarify the applicable responsibilities of the federal government and state governments. Congressional leaders identified as a key component of the tragic meningitis outbreak the lack of clearly defined oversight responsibilities between FDA and state boards of pharmacy; as a result, they made

²² See, e.g., *Par Sterile Products, LLC v. Hargan*, No. 1:17-cv-02221 (D.D.C. filed Oct. 26, 2017); *Allergan USA, Inc. v. Imprimis Pharmaceuticals, Inc.*, No. 8:17-cv-01551 (C.D. Cal. filed Sept. 7, 2017).

²³ Scott Gottlieb, 2018 Compounding Policy Priorities Plan, FDA (Jan. 2018), <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm592795.htm>.

²⁴ FDA, Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry; Draft Guidance (Mar. 2018), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM602276.pdf>.

²⁵ List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 83 Fed. Reg. 43,877 (Aug. 28, 2018).

²⁶ *Examining Implementation of the Compounding Quality Act Before the Subcomm. on Health, H. Comm. On Energy and Commerce*, 115th Congr. (2018) (statement of Scott Gottlieb, Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services).

clear that FDA would be “on the flagpole” for outsourcing facilities. Although traditional pharmacy compounding would primarily be overseen by state pharmacy boards, FDA would inevitably play a critical role in enforcing the limitations on Section 503A.

What has happened?

Although FDA has been slow to establish manufacturing standards tailored to outsourcing facilities, the agency has been active in overseeing facilities’ operations. Relying on the underlying regulatory standards applicable to drug manufacturing, with modest accommodations, FDA investigators conducted frequent inspections, noting deficiencies and seeking corrective actions to enhance environmental controls and product testing. The agency has followed up with untitled letters, warning letters and occasional enforcement actions.

FDA has taken the unusual step of publishing its inspectional findings on a webpage, posting all Form-483s, untitled letters and warning letters to its online list of registered outsourcing facilities. It has also issued risk alerts following voluntary recalls of compounded drugs.

In addition, FDA has emphatically communicated that traditional pharmacy compounding must be prescription-based to qualify for the exemptions in Section 503A. Anecdotally, the combined efforts of FDA and state boards have seemingly reduced the types of large-scale compounding that led to the widespread meningitis outbreak.

FDA REGULATORY ACTIONS EXPLAINED

- **Inspections:** FDA investigators verify on site that products are produced in compliance with relevant regulations and applicable standards.
- **Form 483s:** These forms are issued by FDA investigators at the conclusion of an inspection and identify potential FDCA violations:
 - This does not constitute a final agency determination of whether any condition violates the FDCA.
- **Warning Letters:** These letters are generally issued after a Form 483 for potentially significant violations or when corrective actions or proposed corrective actions are insufficient:
 - These are advisory in nature and are issued for violations that may lead to enforcement action if they are not promptly and adequately corrected.
- **Untitled Letters:** These letters can be issued after a Form 483 for violations that may not meet the threshold of regulatory significance for a warning letter:
 - These are advisory in nature and may be followed by a warning letter or enforcement action if the violations are not promptly and adequately corrected.
- **Voluntary Recalls:** A recall is made by manufacturers to remove or correct products that are in violation of laws and regulations that are administered by FDA.

What is ahead?

FDA's oversight of compounders has not been entirely without setbacks. Several compounders have refused to comply with FDA's requests, especially pharmacies operating under Section 503A. The agency has sometimes been slow to inspect new registrants, and it has apparently not yet inspected five out of 73 registered outsourcing facilities.²⁷ FDA's prioritization of sterility assurance seems to have resulted in the agency taking fewer actions to rectify other FDCA violations by compounders. FDA has done little to prevent outsourcers from misusing bulk ingredients, distributing copies of approved drugs, failing to issue biannual drug production reports or making unsubstantiated promotional claims. Looking ahead, the agency will need to be prepared to address proactively new potential risks to public health relating to drug compounding. Stakeholders have raised concerns about physician office compounding, for example. More broadly, the widespread use of bulk drug substances, if not checked, may disincentivize the continued production of certain approved drugs and, as FDA has cautioned, may disincentivize drug sponsors from seeking premarket approval for new formulations.

²⁷ FDA, Registered Outsourcing Facilities (Nov. 2, 2018), <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>.

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