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The Need for Clarity: Where Should FDA Focus Its Resources When Implementing the Compounding Provisions of the Drug Quality and Security Act?

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The Need for Clarity: Where Should FDA Focus Its Resources When Implementing the Compounding Provisions of the Drug Quality and Security Act?

I. INTRODUCTION

After months of Congressional consideration throughout the year, on November 27, 2013, President Obama signed into law the "Drug Quality and Security Act"[1] ("DQSA"). Title I of the DQSA, titled the "Compounding Quality Act," both removes the unconstitutional advertising and promotion provisions that for years plagued Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA")[2] and attempts to clarify long-standing confusion concerning enforcement of 503A.[3] The law became effective upon enactment, and Section 503A again is enforceable nationwide. As discussed below, the law likely raises significant concerns about oversight and enforcement, and the ability of pharmacies and "outsourcing facilities" — a compounding category created by DQSA — to meet the recognized need for compounded medications.

II. SECTION 503A AND NEW 503B GENERALLY

Pharmacy compounders that continue to fill prescriptions for identified individual patients must comply with the revitalized Section 503A and will "primarily" be regulated by state boards of pharmacy. Among other limitations, they must abide by Section 503A's limitations on compounding and distribution of "inordinate amounts" shipped interstate; which is limited to either five percent of total prescriptions filled at the pharmacy, or, if the state enters into a memorandum of understanding ("MOU") with FDA, subject to the terms of that MOU. FDCA § 503A(b)(3). They also cannot compound "regularly or in inordinate amounts" drugs that are essentially copies of commercially available drug products, subject to limited exceptions. *Id.* § 503A(b)(1)(D). They can only compound in advance of individual prescriptions in limited, defined circumstances. If compounders comply with Section 503A, then they are exempt from FDA's current good manufacturing practice ("cGMP") requirements, adequate directions for use, and new drug approval requirements contained in FDCA Sections 501(a)(2)(B), 502(f)(1), and 505, respectively.

POLICY RECOMMENDATIONS

- FDA and state boards of pharmacy must quickly come to terms on enforcement authority and priorities for Section 503A compounders so that patient access to needed compounded medications remains unthreatened.
- FDA's anticipated enforcement of its prohibition on office use compounding under Section 503A likely will be met with constitutional challenges as well

as patient and physician decrials of unmet patient needs for compounded medications.

- Section 503A's failure to require "traditional compounders" to comply with USP production standards cannot be remedied by draft guidance "requiring" compliance with USP.
- Outsourcing facilities' ability to compound from bulk substances depends on successful articulation of a "clinical need" for such compounded drug products; until FDA's promulgation of a "permissible" list, patients' need for and access to compounded medications, again, likely will be left unmet.
- The twenty or so outsourcing facilities that FDA anticipates will register in the first year after DQSA's enactment will be unable to meet the demand for compounded drugs listed on FDA's shortage website, especially given the thousands of compounding pharmacies that previously ameliorated drug shortages.

The Act's Section 503B creates a new category of voluntary FDA registrant, deemed "outsourcing facilities." Distinguished from Section 503A's pharmacy compounders engaged in compounding for identified patients based on individual prescriptions, outsourcing facilities will be permitted to compound and ship intra- or interstate sterile drugs under the supervision of a licensed pharmacist without first obtaining individual patient prescriptions. These compounded drugs are commonly referred to as "office use" prescriptions or orders. Upon registration with FDA, these outsourcing facilities must pay a yearly registration fee, must comply with FDA's cGMP, and are subject to risk-based FDA inspections. Outsourcing facilities that comply with Section 503B are exempt from FDCA's new drug approval and adequate directions for use requirements. Note that *all* compounders will still be subject to all other applicable provisions of the FDCA; for example, a compounded product cannot be contaminated or compounded in unsanitary conditions.[4] Also, the new law prohibits all compounders from making claims that are false or misleading in any particular. Furthermore, if the compounded drug product fails to qualify for the exemptions under Sections 503A or 503B of the FDCA, then the drug would be subject to all of the requirements of the FDCA that are applicable to drugs made by drug manufacturers, including cGMP, adequate directions for use, and new drug approval requirements at FDCA Sections 501(a)(2)(B), 502(f)(1), and 505, respectively. *Id.*

Before the ink dried on President Obama's signature enacting the new law, FDA issued three draft guidance documents and three requests for nominations as part of the statute's implementation process. The draft guidance documents, which are explicitly not binding on industry, address registration of outsourcing facilities under Section 503B,[5] mechanics of required interim reporting to FDA by outsourcing facilities of products compounded,[6] and pharmacy compounding of products under Section 503A.[7] Written comments on the draft guidance documents may be made at any time, but in order to ensure the Agency considers the comments prior to finalizing guidance documents, comments should be received by February 3, 2014. FDA also published three proposed rules seeking nominations for drugs to be included on the Agency's statutorily required lists of

drugs that are demonstrably difficult to compound,[8] or drugs that may be compounded from bulk substances under Sections 503A[9] and 503B[10]. Nominations for the lists must be received by March 4, 2014.

The hard-fought law's passage leaves in its wake several questions concerning, among other things, oversight and enforcement of its provisions, the scope of permissible compounding under revitalized Section 503A, and whether new Section 503B outsourcing facilities can meet the nation's significant demand for compounded medications to fill the void when manufactured drugs are unavailable.

III. FDA'S GUIDANCE FOR COMPOUNDERS ACTING PURSUANT TO SECTION 503A — SHOULD COMPOUNDERS EXPECT CONTINUED STATE *AND* FEDERAL OVERSIGHT?

While traditional compounding pharmacies were and are familiar with the provisions in Section 503A first passed over 15 years ago,[11] most state-regulated pharmacies were not accustomed to FDA inspections — let alone enforcement actions based on those inspections. As has been well publicized, the catalyst for an unprecedented wave of FDA scrutiny of compounding pharmacies was the New England Compounding Center's ("NECC") widespread distribution of 17,000 vials of allegedly contaminated sterile products to 23 states, which resulted in a fungal meningitis outbreak in October 2012 that reportedly killed more than 50 people and sickened over 700.[12] In the past nine months, FDA has inspected over fifty compounding pharmacies and five contract testing laboratories that test products for those facilities, issued dozens of FDA Form 483 inspection observations, issued several warning letters to pharmacies, and overseen approximately sixteen product recalls.[13] FDA inspected these pharmacies according to then (and still) undefined "federal standards regarding aseptic practices."[14] The compounding industry likely hoped that the new law would shed additional light on the scope of those "federal standards" to which FDA now holds pharmacy compounders accountable, but the subject is not addressed in the legislation.[15]

While the DQSA Title I does provide some clarity, it also continues to leave those pharmacies that compound pursuant to Section 503A in a murky area subject to both state and federal regulatory oversight. For example, DQSA anticipates coordination between state and federal authorities. The new law requires FDA to establish (in consultation with the National Association of Boards of Pharmacy) a mechanism to receive submissions from state boards of pharmacy describing actions taken against compounding pharmacies (e.g., recalls, license suspensions, imposition of sanctions, etc.), or expressing concerns that a compounding pharmacy may be acting contrary to Section 503A.[16] In addition, state boards of pharmacy must be notified when FDA receives certain state submissions *or* makes *its own* determination that a compounding pharmacy is acting contrary to Section 503A.[17]

So, are state pharmacy boards left to regulate traditional pharmacy compounding activities or will FDA continue to be an active enforcer as it has since inception of its April 2013 pharmacy inspection assignment? The Section 503A Draft Guidance states that FDA expects state boards of pharmacy to continue their "oversight and regulation of the practice of pharmacy" including traditional pharmacy compounding. But the Draft Guidance outlines FDA's own enforcement

approach, noting that those pharmacies that do not meet the requirements of Section 503A will be subject to warning letters, seizure, injunctions, and/or criminal prosecution for violations of the FDCA. Section 503A Draft Guidance at 6. While FDA states it will take a risk-based approach to enforcement, it "emphasizes that it need not identify a particular safety problem before pursuing enforcement action." *Id.* at 8.

IV. FDA'S ENFORCEMENT OF THE PROHIBITION ON OFFICE USE COMPOUNDING UNDER SECTION 503A AND THE FIVE PERCENT LIMITATION ON INTERSTATE DISPENSING OR DISTRIBUTION: DO THEY UNNECESSARILY OR UNLAWFULLY RESTRICT THE PRACTICE OF PHARMACY?

Congress's revival of Section 503A will require compounding pharmacies to significantly readjust their business practices with respect to compounding for office use. The federal statute makes clear that, in order to qualify for exemptions from other provisions of the FDCA, the drug must be compounded for an individual patient based on a prescription or a notation that the compounded "product is necessary for the identified patient." FDCA § 503A(a). Notwithstanding the individual prescription requirement, compounders historically have compounded varying quantities of drug products for office use. Some compounders relied on state laws — approximately 42 states permit (or permitted until recently) office use compounding. Other compounders interpreted Section 503A's five percent rule to permit limited office use compounding (i.e., drugs "distributed" but not in "inordinate" amounts). Notwithstanding contrary state pharmacy law provisions, Section 503A Draft Guidance plainly states that compounders will not be permitted to engage in office use compounding under 503A and benefit from the DQSA's exemptions from cGMP, or new drug or adequate directions for use requirements. Office use compounding must be performed pursuant to the new statutory framework in Section 503B.[18]

A related issue involves who is primarily responsible for enforcing the five percent limit on interstate distribution of compounded products, and how that limit will be enforced. FDA has stated that it does not intend to enforce the five percent limit on interstate distribution until "90 days after FDA has finalized an MOU and made it available to the States for their consideration and signature." Section 503A Guidance at 6. Notwithstanding, not only does the five percent rule (or any FDA-crafted MOU) potentially limit or cripple the established compounding practices of many pharmacies, particularly those located anywhere near a state line, but it also leaves one wondering (1) how states or FDA will enforce the rule or the subsequent MOUs FDA intends to enter into with states, (2) whether prescribers and patients that need critical or lifesaving compounded drugs will have limited or no access to them based primarily on the geographic location or their neighborhood pharmacy; (3) what the five percent limit or MOU intends to permit or prevent,[19] and (4) whether any compounder will seek to challenge the limitation based on, for example, its potentially unconstitutional interference with interstate commerce.

V. APPLICABILITY OF USP STERILE PRODUCTION STANDARDS TO COMPOUNDERS UNDER SECTION 503A: FEDERAL STATUTORY SILENCE YET NON-BINDING REGULATORY DRAFT "GUIDANCE"?

As to methods or procedures that compounders must use for compounding sterile products under Section 503A, although many states require compounders to apply production guidelines in United States Pharmacopeia ("USP") <795> (Pharmaceutical Compounding -Non-Sterile Preparations)[20] and USP<797> (Pharmaceutical Compounding — Sterile Preparations)[21], Section 503A remains silent. Section 503A only requires compounders, when compounding from bulk substances, to use *ingredients* that comply with USP or National Formulary ("NF") guidelines. Section 503A(b)(1)(A). FDA's non-binding Section 503A Draft Guidance nevertheless asserts that the products must also be "*compounded in compliance with*" the USP chapters on pharmacy compounding," including USP <795> (Non-Sterile Preparations) and <797> (Sterile Preparations).[22] Thus FDA is not relying on any statute (new or not new), or a regulation promulgated by notice and comment rulemaking, but instead on a statement in a non-binding draft guidance document to inform Section 503A compounders that products compounded from bulk substances should comply with compounding standards set forth in USP <795> and USP <797>.

The DQSA's failure to mandate — or otherwise reference — USP's non-sterile or sterile production standards, is surprising. After all, Congress enacted DQSA because of an outpouring of concern with sterility and safety of compounded products — whether those products are compounded for individual identified patients or for office use. Given the continued lack of clear federal regulatory or statutory authority, whether FDA can hold Section 503A compounders to USP <795> or <797>production standards remains an open question.

VI. COMPOUNDING FROM BULK SUBSTANCES PENDING PUBLICATION OF FDA'S LIST OF PERMISSIBLE SUBSTANCES: WHAT ABOUT PATIENTS' ACCESS TO NEEDED COMPOUNDED MEDICATIONS?

FDA's enforcement of Section 503A's provisions on compounding from bulk substances, as interpreted in FDA's Section 503A and Section 503B's Draft Guidance also raises potentially disconcerting issues. Compounders have been compounding from bulk substances for decades. FDA never finalized a list of permissible bulk substances as required by FDAMA, and in fact withdrew its 1999 proposed rule just last week when it published its guidance documents.[23] In the interim, numerous physicians prescribed drugs that were compounded from bulk drugs not found in FDA approved drugs. Despite patients' and prescribers' reliance on drugs compounded from bulk that are not yet included on a "permissible" list, FDA's Section 503A Draft Guidance warns that, until a permissible bulk drug compounding list is published in the Federal Register, drugs should only be compounded with bulk substances that are components of approved drugs. Section 503A Guidance at 5. The Section 503B Draft Guidance on the issue contains a similar caveat. Section 503B Draft Guidance, at 3. This leaves otherwise compliant Section 503A and Section 503B compounders — as well as physicians and patients — without access needed drug products that have been compounded from bulk substances and are not yet on an FDA "permissible" list and may not be added for a long time.

VII. OUTSOURCING FACILITIES MAY COMPOUND DRUGS IN SHORT SUPPLY — BUT WILL THEY MEET PATIENTS' NEEDS FOR COMPOUNDED MEDICATIONS?

The single biggest change in the DQSA is the creation of a new type of entity: outsourcing facilities. The open question is how much of an impact this will have. Outsourcing facilities'[24] ability to compound from bulk substances is even more restricted than that of traditional compounders under Section 503A. Concerning compounding from bulk substances, outsourcing facilities may compound drugs under two scenarios: (1) the drug must appear on FDA's published drug shortage list, or (2) the drug must appear on a permissive list promulgated by FDA by notice and comment rulemaking. *See* Section 505B(a)(1) and (2).

FDA's draft guidance document for interim reporting by outsourcing facilities (addressing the "estimated reporting burden" on the Agency) reveals that FDA does not anticipate a groundswell of outsourcing facility registration activity. FDA estimates that, through September 30, 2014, approximately fifteen outsourcing facilities will submit registration information to FDA using email, and about five others will register using the "SPL format" specified in the draft guidance. Thus, FDA expects a total of twenty facilities to register in the first year or so.[25]

Juxtaposed against FDA's anticipated twenty outsourcing facilities engaging in office use compounding that may evolve from the thousands of compounding pharmacies across the United States, is the reality that under revitalized Section 503A, "traditional" compounders cannot engage in any office use compounding. A formidable — and troubling — question is whether these twenty or so anticipated outsourcing facility registrants will be able to compound products in sufficient quantities to meet the critical needs of hospitals and patients that regularly rely on drugs that are compounded for office use because of shortage of manufactured drugs.[26] In order to meet patient needs and the demands of an increased market for compounded medications due to, among other reasons, manufacturer shortages, the practice of pharmacy has evolved to the point where pharmacies ship compounded products interstate and compound for office use. Given the DQSA's immediate effectiveness date, and the fact that office use compounding is impermissible unless performed by an outsourcing facility under Section 503B, the DQSA likely will negatively affect availability of those medications in short supply.

The Department of Health and Human Services' Office of Inspector General ("HHS OIG") recently confirmed the medical community's reliance on outsourced medications. In April 2013, it found that a significant number (62%) of acute care hospitals surveyed used compounded sterile preparations purchased from outside sources.[27] The report highlights the important role compounders play providing necessary medications to meet patients' medical needs. HHS OIG also reported that ensuring an adequate supply of compounded sterile products was "very important" to hospitals when determining whether to obtain outsourced sterile compounded products. Outsourcing facilities will be instrumental in filling critical gaps created by the lack of manufactured drugs — but will there be enough outsourcing facilities to fill these gaps?

ENDNOTES

1. Pub. L. No. 113-54 (2013).

2. 21 U.S.C. § 353a.

3. Specifically, after a challenge to the advertising provisions of the Food and Drug Administration Modernization Act of 1997 ("FDAMA") relating to compounded drug products (Section 503A), the United States Court of Appeals for the Ninth Circuit found those provisions unseverable from the statute's other provisions and struck down Section 503A in its entirety. *See W. States Med. Ctr. v. Shalala,* 238 F.3d 1090 (9th Cir. 2001). In 2002, the Supreme Court upheld the Ninth Circuit's finding that Section 503A was an unconstitutional restriction on commercial speech. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002). As a result, FDA stated that "the Court of Appeals declared section 503A *invalid* in its entirety." FDA, Compliance Policy Guide for FDA Staff and Industry, § 460.200 (Pharmacy Compounding) (2002) *(emphasis added).* Subsequently, pharmacies filed another lawsuit in Texas in 2005 challenging FDA's authority to regulate compounded drugs under FDAMA. The United States Court of Appeals for the Fifth Circuit refused to be bound by the Ninth Circuit's decision in *Western States*, and held in 2008 that the commercial speech provisions of 503A, while unconstitutional, were severable from the statute's other provisions, leaving the rest of 503A in effect. *Med. Ctr. Pharmacy v. Mukasey,* 536 F.3d 383 (5th Cir. 2008).

4. FDCA §§ 501(a)(1), (a)(2)(A). *See* FDA, FDA Implementation of the Compounding Quality Act, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm375804.htm.

5. FDA, Draft Guidance, Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 78 Fed. Reg. 72,899 (Dec. 4, 2013) [hereinafter "503B Draft Guidance"].

6. FDA, Draft Guidance, Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act,78 Fed. Reg. 72,897 (Dec. 4. 2013).

7. FDA, Draft Guidance, Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act,78 Fed. Reg. 72,901 (Dec. 4, 2013) [hereinafter "Section 503A Draft Guidance"].

8. Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations, 78 Fed. Reg. 72,840 (Nov. 4, 2013).

9. List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Proposed Rule; Request for Nominations, 78 Fed. Reg. 72,841 (Dec. 4, 2013).

10. Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations, 78 Fed. Reg. 72,838 (Dec. 4, 2013).

11. A recent Congressional investigation into FDA's role in investigating NECC, after receiving complaints for almost a decade, found, "While the agency has pointed to confusion over its authority, the documents obtained by the [Energy and Commerce] Committee reveal that inefficiency, indecisiveness, skewed priorities, and a lack of leadership are what primarily hampered FDA's ability to prevent NECC's products from killing over 50 Americans." *See* U.S. House of Representatives, Committee on Energy and Commerce, Preliminary Majority Staff Report, "FDA's Oversight of NECC and Ameridose: A History of Missed Opportunities," at 4 (Apr. 16, 2013).

12. *See id.*

13. FDA, Compounding: Inspections, Recalls, and other Actions, *available at* http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339771.htm.

14. FDA, Summary: 2013 Pharmacy Inspection Assignment, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm. Many of the Form 483 observations were derived from cGMP. Presumably, under DQSA FDA would not apply cGMP to a pharmacy that meets the elements of Section 503A.

15. See *infra* at 11.

16. DQSA § 105.

17. *Id.* *See* FDA, FDA Implementation of the Compounding Quality Act, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm375804.htm. FDA advises that until additional information regarding how this process will work becomes available, states that wish to provide information to FDA should submit the information by email to the following mailbox: StateCompounding@fda.hhs.gov.

18. At least one recent statement by FDA since passage of the DQSA renders unlikely the continued permissibility of any office use compounding, even in limited amounts, under Section 503A. Compounding Stakeholder Conference Call, December 4, 2013 (statement from Jane Axelrad, FDA) ("Section 503A was not changed by the new law and patient specific prescriptions are required under Section 503A. As you know, as you observe, 503B provides a pathway in which hospitals and health care professionals can purchase compounded drugs without prescriptions.")

19. For example, is the five percent interstate limitation in fact any indication of whether a compounder is engaging in manufacturing when the amount of compounding *intrastate* within the bounds of Section 503A is subject to *no* limitation?

20. This chapter provides guidance on applying good compounding practices in the preparation of non-sterile compounded formulations for dispensing and/or administration. *See* U.S. Pharmacopeial Convention, USP-NF General Chapters on Compounding, *available at* http://www.usp.org/usp-healthcare-professionals/compounding/compounding-general-chapters.

21. This chapter provides procedures and requirements for compounding sterile preparations. It describes "conditions and practices to prevent harm to patients that could result from microbial contamination, excessive bacterial endotoxins, variability in intended strength, unintended chemical and physical contaminants, and ingredients of inappropriate quality in compounded sterile preparations." *See* U.S. Pharmacopeial Convention, *available at* http://www.usp.org/usp-healthcare-professionals/compounding/compounding-general-chapters.

22. Section 503A Guidance at 4 (emphasis added); at 4, n.5.

23. *See* 78 Fed. Reg. at 72,841.

24. Outsourcing facilities will be subject to FDA oversight similar to drug manufacturers, including compliance with cGMP for those products that they compound. In addition to registering with the Agency, and paying the $15,000 annual registration fee, outsourcing facilities must report to FDA every six months products that they compound, and they must report adverse events concerning those products. Section 503B also provides FDA the resources and authority to conduct risk-based inspections. In addition, the Agency must maintain a list of FDA-regulated outsourcing facilities on its website. FDA's guidance document on Section 503B registration also suggests that each separate outsourcing facility location must register separately, but the facilities do not need to be a licensed pharmacy, and it "may or may not obtain prescriptions for individual patients." Section 503B Draft Guidance at 2.

25. *See* 78 Fed. Reg. at 72,900.

26. FDA, Current Drug Shortages Index, *available at* http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm. Exacerbating the problem, FDA's website lists about 130 drug products, including several injectable and critical life saving drugs. FDA's shortage list, however, likely understates America's drug shortages. For example, the American Society of Health-Systems Pharmacists ("ASHP") also maintains a drug shortage list. As of September 2013, ASHP lists over 200 drugs on its current drug shortage list, of which 147 do not appear on FDA's list.

27. HHS OIG, Report to Margaret A. Hamburg, Commissioner, FDA, *High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals That Use Them*, OEI-01-13-00150 (Apr. 10, 2013).

ABOUT THE AUTHORS

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