

Major Changes in Drug Compounding and Drug Distribution Requirements (Part 1 of 2)

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On September 28, 2013, the U.S. House of Representatives passed the Drug Quality and Security Act (H.R. 3204). The bill is compromise legislation crafted by the Senate Health, Education, Labor, and Pension (“HELP”) and House Energy and Commerce Committees, and is expected to pass the Senate soon after it reconvenes on October 28. Once signed into law, H.R. 3204 would fundamentally change the regulation of drug compounding and drug distribution in the United States.

In this first of two Client Alerts, we focus on the bill’s drug compounding provisions, collectively known as the Compounding Quality Act (“CQA”).¹ The immediate consequences of the CQA are to create a new kind of federally authorized compounding entity and to establish two “safe harbors” for drug compounding under the Food, Drug, and Cosmetic Act (“FDCA”):

- **FDCA Section 503A**, which exempts state-licensed pharmacies and federal facilities from FDCA new drug approval, good manufacturing practice (“GMP”), and certain labeling requirements: Section 503A is intended for smaller “traditional” compounding operations, which compound in response to prescriptions (or, in limited quantities in anticipation of prescriptions) and are engaged in minimal out-of-state distribution.
- **FDCA Section 503B**, which exempts sterile drug compounders (called “outsourcing facilities”) from FDCA new drug approval requirements, as well as some labeling and drug distribution requirements: Outsourcing facilities are subject to GMP requirements and can only compound with drug substances that are on a “clinical need” list established by the U.S. Food and Drug Administration (“FDA”). However, outsourcing facilities can distribute out of state without

¹ In the upcoming second Client Alert, we will address new drug distribution requirements that would be added by the Drug Supply Chain Security Act, which was included in H.R. 3204.

limitation and can compound large quantities of products on FDA's drug shortage list without prescription.

Compounders that fail to comply with one of these two safe harbors would potentially be subject FDA enforcement; FDA would presumably argue that the compounder was, in fact, a drug manufacturer that was marketing unapproved new drugs and violating various provisions of the FDCA.

In this Client Alert, we also review the history of drug compounding, the requirements for compounding within the FDCA safe harbors, and the many questions that the CQA leaves unanswered.

The History of Drug Compounding

Drug compounding is a process of combining different ingredients to create customized pharmaceutical products for patients.² The practice predates the rise of mass-produced drugs in the United States, and was essentially unregulated by FDA for 50-plus years after passage of the FDCA.³ In the early 1990s, fearing that some facilities were manufacturing (i.e., mass-producing) drugs under the guise of compounding, FDA made its first foray into compounding regulation by announcing an enforcement policy that tried to draw a line between compounding and FDCA-regulated manufacturing.⁴

In 1997, Congress took steps to bring pharmacy compounding under FDA's authority as part of the Food and Drug Modernization Act. The law created a federal framework for compounding by adding Section 503A to the FDCA,⁵ which included (amongst various provisions) unconstitutional prohibitions on promotion.⁶ These prohibitions led some courts to invalidate some or all parts of 503A,⁷ and resulted in confusion about FDA's authority to regulate compounding pharmacies as drug manufacturers.⁸

Then, in 2012, a major outbreak of fungal meningitis was traced to drugs compounded by New England Compounding Centers. The outbreak included approximately 750 confirmed cases and has resulted in 64 deaths to date.⁹ Tragedies of this scale have often been the impetus for major changes to federal food and drug laws in the past; the FDCA itself was enacted in 1938 in response to a tragedy in which the use of an

² *Western States Med. Ctr. v. Shalala*, 535 U.S. 357 (2002).

³ *Id.*

⁴ See FDA Compliance Policy Guide Sec. 460.200: Pharmacy Compounding, available at <http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074398.htm> (last accessed 9/30/13).

⁵ Pub. Law 105-115, Section 127.

⁶ FDCA Section 503A(c).

⁷ *Western States Med. Ctr. v. Shalala*, 238 F. 3d 1090 (9th Cir. 2001) (invalidating Section 503A), *aff'd in part*, *Western States Med. Ctr. v. Shalala*, 535 U.S. 357 (2002); *Medical Center Pharmacy v. Mukasey*, 536 F. 3d 383, 401 (8th Cir. 2008) (invalidating free speech restrictions, but leaving other provisions of Section 503A intact).

⁸ *E.g.*, *United States v. Franck's Lab, Inc.*, 816 F.Supp.2d 1209 (M.D. Fla. 2011) (limiting FDA regulation of pharmacy compounding).

⁹ <http://www.cdc.gov/hai/outbreaks/meningitis.html> (last accessed 9/30/13).

improperly manufactured drug (elixir sulfanilamide) led to over 100 patient deaths.¹⁰ The CQA follows in this mold.

Compounding Under FDCA Section 503A

The CQA amends FDCA Section 503A by removing unconstitutional prohibitions on promotion and replacing them with a requirement that compounded drugs (like drugs produced by manufacturers) not be promoted in a false or misleading manner.¹¹ Presumably, these changes will cure the constitutionality issues and revive Section 503A, which exempts compounding pharmacies from the FDCA's new drug approval requirements, misbranding provisions related to requirements for adequate directions for use, and GMP requirements.¹²

Key requirements of Section 503A include:¹³

1. Compounding in a state-licensed pharmacy or federal facility;
2. Compounding by a licensed pharmacist or physician:
 - a. In response to a prescription for an individual patient, or
 - b. In limited quantities in anticipation of prescriptions based on prescribing histories;
3. Using drug substances that (a) comply with United States Pharmacopeia ("USP")/National Formulary ("NF") standards or other accepted standards, (b) are manufactured at FDA-registered facilities, (c) and are accompanied by certificates of analysis;
4. Using inactive ingredients that meet USP/NF requirements or other accepted standards;
5. Not compounding drugs that:
 - a. Have been withdrawn for safety or effectiveness reasons, or
 - b. Are "demonstrably difficult" to compound;

¹⁰ C. Ballentine, Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident, *available at* <http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm> (last accessed 9/30/13).

¹¹ H.R. 3204, Section 103, 106.

¹² FDCA 503A(a).

¹³ FDCA Section 503(a)-(b).

6. Compounding drugs that are essentially copies of commercially available drug products either (1) on a regular basis, or (2) in inordinate amounts; and
7. Compounding in a state that:
 - a. Has entered into a memorandum of understanding with FDA addressing, among other things, the interstate distribution of compounded drugs; or
 - b. Has not entered into a memorandum of understanding, in which case, the out-of-state distribution of compounded drugs must not exceed 5 percent of the pharmacy's prescription drug orders.

The CQA also has provisions intended to facilitate communications between state boards of pharmacy and FDA, by tasking FDA with creating a system to receive reports from state boards informing FDA about ongoing compounding activities in a state, including (1) assessments of compliance with FDCA Section 503A, and (2) sanctions that a state has levied against compounders.¹⁴ FDA will also inform states if it believes that FDCA Section 503A has been violated.¹⁵ These provisions will leverage the use of continued state regulation of pharmacy compounding to help ensure compliance with 503A.

Sterile Compounding Under FDCA Section 503B

The CQA also creates an alternative safe harbor for sterile compounders: FDCA Section 503B.¹⁶ Compliance with Section 503B exempts a sterile compounder (called an “outsourcing facility” under this provision) from the FDCA’s new drug approval requirements, misbranding provisions related to requirements for adequate directions for use, and new distribution laws that are included elsewhere in the Drug Quality and Security Act.¹⁷

A sterile compounder that chooses to voluntarily register with FDA as an outsourcing facility and comply with 503B requirements would not be subject to out-of-state distribution restrictions and could compound large quantities of drugs on FDA’s drug shortage list. An outsourcing facility would not, however, be exempt from other FDCA requirements, including the requirement to comply with GMPs.¹⁸ This is an important consideration to any sterile compounder that considers whether to register as an outsourcing facility. Several recent FDA inspections reported gaps between pharmacy

¹⁴ H.R. 3204 Section 105.

¹⁵ *Id.*

¹⁶ H.R. 3204 Section 101(a); FDCA Section 503B(c)(4) (proposed legislation). Hereinafter, all references to “Section 503B” will refer to the proposed legislation unless otherwise stated. The current FDCA Section 503B, which addresses the review of television advertisements will be recodified at FDCA Section 503C.

¹⁷ FDCA Section 503B(a).

¹⁸ Under FDCA Section 502(a)(1), a drug that is manufactured under non-GMP conditions is deemed “adulterated” in violation of the FDCA.

compounding practices and GMP requirements,¹⁹ meaning that the compounders would likely need to invest in developing a GMP-compliant operation.

Section 503B outsourcing facilities must meet following requirements.²⁰

1. *Register and Report.* Outsourcing facilities must register annually with FDA and submit semiannual reports listing the drugs that were compounded during the preceding period.

2. *Use Only FDA-Designated Drug Substances (Active Ingredients).* Facilities may only compound drugs that contain active ingredients designated by FDA for compounding based on “clinical need.” Ingredients are designated by FDA through either:

- a. A notice-and-comment process through which FDA adds the ingredient to the list of drug substances for which there is clinical need, or
- b. Inclusion on the drug shortage list that FDA maintains under FDCA Section 506E.

In addition, all active ingredients must be produced at FDA-registered facilities, meet USP or other accepted FDA standards, and be accompanied by a certificate of analysis.

3. *Use Inactive Ingredients That Meet Recognized Standards.* All ingredients other than active ingredients must comply with USP/NF standards, or other standards recognized by FDA.

4. *Do Not Compound Products Withdrawn for Safety or Effectiveness Reasons.* Products included on the FDA list of drugs that were withdrawn or removed from the market for safety or effectiveness reasons may not be compounded.

5. *Do Not Compound a Drug That Is “Essentially a Copy of a Marketed and Approved Drug.”* A compounder cannot produce a drug that is either:

- a. “Identical or nearly identical to” an FDA-approved new drug or an over-the-counter (“OTC”) drug that can be marketed without approval (e.g., a drug that complies with an OTC monograph) unless it is on the drug shortage list in FDCA Section 506E at the time of “compounding, distribution, and dispensing,” or
- b. Contains a drug substance found in an FDA-approved drug or OTC drug unless it is changed for an “individual patient” based on a prescribers determination that it will provide a clinical difference for the patient.

¹⁹ FDA Actions: Pharmacy Compounding, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm> (last accessed 9/30/13).

²⁰ FDCA Section 503B(a)(1)-(11).

It is unclear whether the “individual patient” referred to in Section 503B would be a single individual patient or a patient who represents the needs of several patients (e.g., patients who are allergic to a preservative found in a manufactured drug). The interpretation of this provision could have a significant impact on the extent to which outsourcing facilities could compound. If FDA takes a restrictive interpretation—that a drug could only be compounded for an individual patient—it could substantially limit the volume of non-shortage sterile drugs compounded under Section 503B.

6. *Do Not Compound Drugs That FDA Explicitly Excludes from Compounding.* FDA will publish a list of drugs for which there are “demonstrable difficulties in compounding that are reasonably likely to lead to adverse events.” Drugs on this list cannot be compounded unless the compounding is done in accordance with FDA-published requirements (when provided) that are intended to reduce the risk of adverse events.

7. *Get Pre-Approval of Elements to Assure Safe Use for REMS-Like Drugs.* Since 2007, FDA has had authority under FDCA Section 505-1 to require that drug manufacturers institute risk evaluation and mitigation strategies (“REMS”) as a condition of drug approval.²¹ REMS can include specialized labeling called “medication guides,” special patient and physician certifications regarding product use, controlled distribution, or other means of reducing risks. Under the CQA, before an outsourcing facility can compound with a drug substance found in a REMS drug, it must demonstrate to FDA that it will use “elements to assure safe use” that provide comparable protection to the REMS.

8. *Do Not Engage in Wholesale Distribution.* With the exception of administering a drug or dispensing a drug pursuant to a valid prescription, a compounded sterile drug may not be transferred or sold by anyone other than the outsourcing facility that compounded the sterile drug.

9. *Pay Your Fees.* The CQA establishes annual registration fees and inspection fees for outsourcing facilities. These fees are subject to various adjustments but will probably start in the neighborhood of \$15,000 for each registration fee and each inspection.

10. *Follow New Labeling Requirements.* The CQA establishes various statements that must be included on labels for compounded products, including a phone number and website for reporting adverse drug events to FDA.

11. *Function Only as an Outsourcing Facility.* To meet the requirements of 503B, a drug must be “compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance” with Section 503B. This suggests that if a facility compounds both sterile and non-sterile drugs, even the non-sterile drugs must comply with all outsourcing facility requirements in order to take advantage of the 503B safe

²¹ A list of drugs with FDA-approved REMS is available at <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm> (last accessed 9/30/13).

harbor. This seems to include GMP requirements and the use of only drug substances on the “clinical need” list.

Outsourcing facilities are also required to report adverse drug events to FDA in accordance with 21 CFR Section 310.305²² and will be subject to GMP requirements of the FDCA. For its part, FDA is required to establish a risk-based inspection system for outsourcing facilities²³ and develop and maintain the various lists of drug substances described above.

Consequences of the CQA

The immediate consequences of the CQA are to create this new kind of federally authorized compounding entity—the outsourcing facility—and to help revive FDCA Section 503A. But the CQA would still leave many uncertainties regarding compounding regulation. For example:

- How will the CQA be phased in? The CQA does not include a phase-in period, so once it is signed into law, it would become effective immediately and, potentially, put compounders in the position of ceasing operations while determining how to come into compliance with laws or risking serious penalties.
- How will compounders and others request additions to the list of compoundable drug substances for which there is a “clinical need”? Will requests be made following an FDA’s citizen petition process, or will the FDA develop another approach?
- Section 503A allows a “limited quantity” of drug to be compounded based on prescribing and compounding “history.” How limited is a “limited quantity,” and how much “history” is needed?
- Will FDA limit the compounding of non-shortage drugs under Section 503B to compounding for a specific individual patient? If FDA takes a more expansive reading, will pharmaceutical manufacturers challenge its interpretation?
- Section 503B defines compounding to include “the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug.” What forms of “otherwise altering” the drug would be included in this definition?

²² FDCA Section 503B(b)(5).

²³ FDCA Section 503B(b)(4)(B).

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- Will FDA attempt to rely on the definition of “compounding” in Section 503B when interpreting Section 503A (which does not contain a clear definition of this key term)?
- Will FDA try to “push” sterile compounders into the 503B outsourcing facility category? To do so, would it use carrots (e.g., expanding the list of drugs for which there is “clinical need”), sticks (e.g., rigorously enforcing out-of-state distribution restrictions and anticipatory compounding limits), or both?
- How will compounding with biologicals be addressed by FDA? Biological products must generally be “licensed” (approved) by FDA under Section 351 of the Public Health Service Act (“PHSA”). The CQA exempts products from new drug approval requirements under FDCA Section 505, but does not explicitly address exemptions from PHSA licensing requirements.
- Will compounders argue that there is still a distinction between drug compounding and drug manufacturing that the FDCA does not reach, even if a compounding pharmacy operates outside of the 503A and 503B safe harbors?

The answers to these and other questions—answers that will come as FDA implements the new law—could have a profound impact on the availability of compounded drugs in the United States.

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*This Client Alert was authored by **James A. Boiani** and **Kim Tyrrell-Knott**. For additional information about the issues discussed in this Client Alert, please contact one of the authors or the Epstein Becker Green attorney who regularly handles your legal matters.*

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