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The Compounding Quality Act

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The regulatory landscape for pharmacy compounders is rapidly changing. In October 2012, a compounded drug caused a fungal meningitis outbreak, claiming 64 lives and sickening nearly 700 others across 20 states.[1] Both the Food and Drug Administration and Congress responded to this tragedy.

In just over a year, FDA inspected scores of sterile compounding pharmacies, and found what they believed to be objectionable conditions at over 60 facilities. This resulted in warning letters and more than 20 compounders voluntarily recalling compounded drugs. Congress then passed the Compounding Quality Act (CQA) as part of the Drug Quality and Security Act (DQSA). FDA immediately began to implement the CQA, and FDA officials, including Commissioner Margaret Hamburg, have made it clear that FDA will strictly enforce CQA requirements.

[1] http://www.cdc.gov/hai/outbreaks/meningitis.html.

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What does this mean for Compound Pharmacies?

To avoid FDA enforcement, compounders have two choices: operate a small-scale ''traditional'' compounders, and register with the FDA as an ''outsourcing facility.''

Traditional Compounders — Section 503A

Federal Food, Drug, and Cosmetic Act (FDCA) Section 503A exempts state-licensed pharmacies and federal facilities from FDCA new drug approval, good manufacturing practice (GMP), certain labeling and DQSA distribution requirements. Basically, the law applies to ''traditional'' compounding operations, which compound in response to prescriptions (or in limited quantities in anticipation of prescriptions based on prescribing histories) and are engaged in minimal out-of-state distribution.

To meet the requirements of Section 503A:[2]

1. 'Compounding must be done by a licensed pharmacist or physician.

2. Compounding with drug substances and inactive ingredient must only use:

   a. Drug substances that comply with United States Pharmacopeia (USP)/National Formulary (NF) standards or other accepted standards, are manu-

[2] FDCA Section 503A.

factured at FDA-registered facilities, and are accompanied by certificates of analysis; and

b. Inactive ingredients that meet USP/NF requirements or other accepted standards.

3. Facilities must not compound drugs that:

a. Have been withdrawn for safety or effectiveness reasons (listed at 21 CFR 216.24);

b. Are ''demonstrably difficult'' to compound (which will be included in an FDA ''do not compound'' list); or

c. Are essentially copies of commercially available drug products either on a regular basis, or in inordinate amounts.

4. Pharmacies must either compound in a state that has entered into a memorandum of understanding with FDA addressing, among other things, the interstate distribution of compounded drugs, or not distribute more than 5 percent of the pharmacy's prescription drug orders out of state.

Outsourcing Facilities — Section 503B

FDCA Section 503B exempts a new category of sterile compounder called ''outsourcing facilities'' from FDCA new drug approval requirements, as well as certain labeling and DQSA distribution requirements. Unlike 503A pharmacies, outsourcing facilities are subject to GMP requirements and can only compound with drug substances that are on a ''clinical need'' list established by FDA.

However, outsourcing facilities can distribute out of state without limitation and can compound large quantities of products on FDA's drug shortage list, and potentially other drugs, without prescription.

To compound under 503B, the following requirements must be met:[3]

1. Compounding must be done under supervision of a licensed pharmacist or physician;

2. If compounding using a drug substance, the substance must be produced at FDA-registered facilities, meet USP or other accepted FDA standards, be accompanied by a certificate of analysis and be on the ''clinical need'' list, as designated by FDA.

3. Use inactive ingredients that meet USP/NF standards, or other standards recognized by FDA.

4. Do not compound drugs that:

a. Have been withdrawn for safety or effectiveness reasons;

b. Are ''demonstrably difficult'' to compound; or

c. Are drugs that are essentially copies of marketed and approved drugs, including drugs that are either: ''identical or nearly identical to'' an FDA-approved new drug or an over-the-counter (''OTC'') drug unless it is on FDA's drug shortage list, or contain a drug substance found in an FDA-approved drug or OTC drug unless it is changed for an ''individual patient'' based on a prescriber's determination it will provide a clinical difference for the patient.

It is unclear whether ''individual patient'' means 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. If FDA interprets narrowly by finding 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.

5. If compounding with a drug substance found in a drug subject to a risk evaluation and mitigation strategy (REMS), get FDA approval for a risk mitigation plan comparable to the REMS.

6. Do not engage in wholesale distribution.

7. Function only as an outsourcing facility, which seems to prohibit hybrid outsourcing facility and traditional compounding operations.

8. Register annually with FDA, and submit semiannual reports listing the drugs that were compounded during the preceding period.

9. Pay annual registration fees and inspection fees, which are likely to start in the neighborhood of $15,000.

Outsourcing facilities are also required to follow new labeling requirements, and report adverse drug events. For its part, FDA is required to establish a risk-based inspection system for outsourcing facilities[4] and develop and maintain the various lists of drug substances described above.

First Steps at Implementation

FDA issued three draft guidance for public comment on FDCA Section 503A,[5] outsourcing facility registration,[6] and interim product reporting.[7] Of note –

- The draft guidance on interim reporting suggests FDA will not immediately enforce product reporting requirements upon initial registration for all facilities that register before June 2, 2014, as long as the facility submits its report within two months after its initial registration.
- The draft guidance on outsourcing facility registration states that the registration fees will not be assessed or owed until after Oct. 1, 2014.

FDA has also issued three Federal Register notices requesting nominations for (1) all drug substances that may be compounded by outsourcing facilities (if it's not on the list, it can't be compounded),[8] (2) unapproved and non-USP/NF monographed drug substances that may be used by 503A compounders,[9] and (3) drugs that should be added to a ''do not compound'' list because they are demonstrably difficult to compound. [10]

[3] FDCA Section 503B(a)(1)-(11).

[4] FDCA Section 503B(b)(4)(B).

[5] Draft Guidance for Industry: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act (December 2013) (11 PLIR 1437, 12/6/13).

[6] Draft Guidance for Industry on Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (December 2013).

[7] Draft Guidance for Industry on Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (December 2013).

[8] 78 Fed. Reg. 72838 (Dec. 4, 2013).

[9] 78 Fed. Reg. 72841 (Dec. 4, 2013).

[10] 78 Fed. Reg. 72840 (Dec. 4, 2013).

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We encourage you to read these documents, and go to www.regulations.gov to submit comments to FDA. Comments on the draft guidance are due to FDA by Feb. 3, and comments on the notices by March 4.

Future Steps in CQA Implementation

Despite the overwhelming support of the act, senators emphasized the need to ensure patients and doctors had continued access to compounded drugs that meet a critical public health need and that FDA not overstep the authority granted under CQA. Senators Tom Coburn (R-OK), a physician, and Lamar Alexander (R-TN), ranking member of the Senate HELP committee, said there was no intent to interfere with accessing safe, high-quality compounded drugs that patients need, or with the practice of medicine.

Others cautioned FDA not to infringe upon states' rights in regulating certain pharmacy practices, the practice of medicine or other areas not covered by the act. Sen. John Boozman (R-AR) warned the FDA during Senate floor statements that he would be monitoring their activities to ensure they do not ''encroach upon state authority to regulate office use,'' a kind of anticipatory compounding that gives doctors and patients ready-access to compounding drugs. Sen. Tom Harkin (D-IA), chairman of the Senate Health, Education, Labor and Pensions Committee and an architect of the CQA, stated that the law was not intended to address repackaging or biologics.

Their statements also reflect the uncertainty about what will happen next, and many questions that remain to be answered. Here are just a few of the more important questions:

- 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?
- In Section 503B, compounding means ''combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug *or* bulk drug substance to create a drug.'' Although use of bulk drug substances will be limited to a list designated by FDA, will it be permissible to compound with approved drug *products* that contain unlisted substances?
- Will FDA limit the compounding of non-shortage drugs under Section 503B to compounding for a specific individual patient?
- Will FDA try to push sterile compounders into the outsourcing facility category by expanding the list of drugs for which there is clinical need, rigorously enforcing out-of-state distribution restrictions and anticipatory compounding limits or both?
- How will compounding with biologicals be addressed by FDA? FDA has recognized this as an open question.
- What will FDA do about animal drug compounding, an issue that was not addressed by the CQA but has been the subject of FDA enforcement action and litigation in recent years?

Answers to these questions will likely emerge as FDA begins to implement CQA. Compounders should actively monitor FDA's compounding web page[11] for additional guidance documents and the Federal Register for notices regarding the implementation of CQA.

[11] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.