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Pharmacy Compounding Update: Regulators Search for the Right Formula

By Michelle Gabriel McGovern

Last November, the Compounding Quality Act (''Act'') became law after a yearlong national debate about whether—and how—to regulate compounding pharmacies after a tainted injectable prepared at a Massachusetts compounding facility sparked a public health crisis that impacted more than 750 individuals in 20 states, and caused 64 deaths in the fall of 2012.

In the months since the Act's passage, the U.S. Food and Drug Administration (''FDA'') has issued guidance on the law, ranging from proposed current good manufacturing practices to requests for nominations of drug substances that may be used at compounding facilities to technical guidance on registering as an outsourcing pharmacy. This article will discuss the history of compounding leading up to the Act's passage, recap key provisions of the Act, and will discuss the steps that have been taken to date to interpret the new law.

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History of Compounding

Before discussing the guidance that has been issued on compounding since the Act's passage, it is important to understand the history of compounding regulation, as such history provides critical insight into the areas that require regulatory oversight by the FDA.

Under the traditional definition of compounding, compounders prepare customized drugs for patients who are unable to take a product in its commercially available, FDA-approved form. These prescriptions are prepared on a patient-specific basis, and they are commonly used for elderly or infant patients (for instance, where a patient has trouble swallowing a pill), or for patients who may be allergic to commonly used inactive ingredients.[1]

Although compounding involves the preparation of drug products that would otherwise require FDA approval, because each preparation is patient-specific, compounders have generally been exempt from federal regulation as manufacturers, as it would be impracticable (and nearly impossible) to require a new drug application (''NDA'') for each drug prepared for a specific patient. Traditionally, compounding pharmacies are regulated at the state level, where they are subject to, among other things, state-specific licensing, registration, sterility, professional practice and quality assurance requirements.

Until the passage of the Act, compounding pharmacies generally operated without regulation by the FDA. In 1997, the FDA Modernization Act (''FDAMA''),

[1] *See Thompson v. Western States Medical Center et al.*, 535 U.S. 357, 360-61 (2002).

which modified certain provisions of the Federal Food, Drug, and Cosmetic Act (''FDCA''), became law. The FDAMA added Section 503A of the FDCA, which excepted compounded drugs from various ''new drug'' requirements, so long as they complied with certain restrictions. Among other things, the FDAMA prohibited compounders from behaving as manufacturers and making copies of FDA-approved products.[2] The law was challenged in court for restricting free speech, as one provision prohibited compounders from soliciting prescriptions and advertising compounded products. The case was eventually sent to the Supreme Court, which in 2002 held that the speech-related restrictions were unconstitutional.[3]

The Supreme Court did not decide on whether the non-speech related provisions of Section 503A could stand, however. Therefore, the underlying case, which struck down the remaining regulations on compounding, became the national standard. In 2008, the Fifth Circuit came to a different conclusion, and held that the remaining provisions of the law were enforceable.[4] However, the decision applied only to the states in the Fifth Circuit—Texas, Louisiana, and Mississippi—thus creating a patchwork of enforcement standards across the United States.

In the rest of the country, the FDA's authority to regulate compounders came from a compliance guide issued by the agency after the 2002 Supreme Court decision. As this guide did not carry the force of law, it provided the FDA uncertain authority over compounders, and created an environment whereby some ''bad actor'' compounders were functioning as unregulated manufacturers not subject to federal authority. Certain of these so-called ''bad actors'' functioned for years as unregulated pharmaceutical manufacturers, in some cases copying FDA-approved drugs in large quantities and selling them for far less than their FDA-approved counterparts.

While providers use compounded products for a variety of reasons, the appeal of compounded products is strengthened by ever-tightening hospital budgets, as payors shift to capitated models and hospital purchasers look to cut back on costs. In addition, when group purchasing organizations make purchasing decisions without appropriate provider education and buy-in, hospitals can be stocked with compounded products without necessarily knowing the origins of—or understating the risk associated with—the products they are using.

Before the passage of the Act, because the FDA had no enforcement jurisdiction over compounders, federal regulators were unable to ensure that they were adhering to appropriate quality and safety measures.

In the fall of 2012, a tainted injectable prepared by the New England Compounding Center, a Massachusetts compounding pharmacy, sickened 751 individuals nationwide; 64 individuals died. This incident shined the national spotlight on pharmacy compounding, and set off a year of debate about whether—and how—compounding pharmacies should be regulated.

Compounding Quality Act

After much debate on both the national stage and on Capitol Hill, on November 27, 2013, the Act was signed into law, and gave the FDA clear enforcement jurisdiction over registered compounding pharmacies.[5] The Act represented a compromise between legislators, regulators and industry stakeholders, many of whom disagreed on the role the FDA should play in the regulation of compounding facilities, and whether clear federal regulatory authority over compounders was necessary at all.

Among other things, the Act standardized the patchwork of compounding regulation by requiring all compounders to adhere to quality and sterility standards. In addition, the Act created a mechanism for the voluntary registration of ''outsourcing facilities,'' which are subject to a specific regulatory scheme providing for quality and sterility standards, FDA inspection, and enforcement action.

Compounders who choose to register as outsourcing facilities are subject to, among other things, restrictions relating to the quality of the products they prepare, and also on engaging in behaviors more traditionally associated with manufacturers. For example, registered facilities are not permitted to compound certain drugs and drug products (such as drugs withdrawn or removed from the market for being unsafe or ineffective), preparing as compounds drugs that are essentially copies of FDA-approved products, and acting as wholesalers of compounded products. Outsourcing facilities will also have to comply with heightened reporting requirements (e.g., adverse event reporting, and reporting of products prepared at the facility), which will facilitate federal oversight and help prevent public health crises at their sources. In addition, the Act requires labels on compounded products to alert providers and patients about the nature of drugs that are being prescribed and administered.

Registered facilities will be required to pay an annual fee that will start at $15,000 in fiscal year 2015, adjusted for inflation. Facilities that require reinspection by the FDA in any fiscal year will have to pay a reinspection fee of $15,000 in that fiscal year. These inspection and reinspection fees will help fund enforcement actions; however, appropriations will likely also be necessary to supplement such payments. The FDA released its rates for fiscal year 2015 in August 2014, which total $16,442 (note that this does not include an adjustment offered to small businesses).[6] Small business will be asked to pay $5,103 in fiscal year 2015, and facilities that require reinspection will have to pay a fee of $15,308.[7]

The Act also struck the speech-related provisions of Section 503A of the FDCA, resolving the constitutional question of whether it applies to compounders (except for those exempt by nature of their registration under Section 503B).

In addition, the Act provides that the FDA will receive submissions from states with concerns about compounding pharmacies that may be violating the requirements set forth in Section 503A of the FDCA, and de-

[2] *See* 21 U.S.C. § 353a.

[3] *Western States Medical Center*, 535 U.S. at 357.

[4] *Medical Center Pharmacy, et al., v. Mukasey*, 536 F.3d 383 (2008).

[5] Pub. L. No. 113-54; 127 Stat. 587. The Compounding Quality Act is part of the new Drug Quality and Security Act, which also includes supply chain provisions that are not discussed in this article.

[6] 79 Fed. Reg. 44806 (August 1, 2014).

[7] 79 Fed. Reg. 44805-6 (August 1, 2014).

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scriptions of actions taken against compounding pharmacies. Increased collaboration between the federal and state governments could help isolate ''bad actors'' in the industry, and aims to prevent public health crises like the spinal meningitis outbreak of 2012 from occurring.

The Act leaves regulation of traditional compounders who prepare products based on individualized, patient-specific prescriptions to the states.

FDA Guidance on Pharmacy Compounding

To date, the FDA has released a number of guidance documents in light of the Act's passage, including (but not limited to) guidance on registering as an outsourcing facility, and interim guidance describing the FDA's expectations regarding compliance with current good manufacturing practice (''CGMP'') requirements for registered outsourcing facilities. Key guidance documents are discussed in detail below.

Guidance on Compounding Products Under Section 503A

With respect to Section 503A, a final FDA guidance for industry—which does not establish legally enforceable responsibilities, but which does describe the FDA's thinking on a topic—provides that, for compounders that are not registered as outsourcing facilities, to be exempt from certain regulations that apply to drug manufacturers, compounded products must:

- Be prepared for individual patients based on the receipt of a valid prescription order;
- Be prepared by a licensed pharmacist either upon receipt of an individual prescription or in limited advance quantities based on the pharmacist's history and under orders generated by a physician with whom the pharmacist has an established relationship;
- Be compounded in compliance with United States Pharmacopeia (''USP'') standards on pharmacy compounding using bulk drug substances;
- Be prepared using bulk substances manufactured by establishments registered under the FDCA;
- Be prepared using bulk substances accompanied by valid certificates of analysis for each product;
- Be prepared using ingredients other than bulk substances that comply with USP or National Formulary (''NF'') standards, if one exists, and comply with the USP chapters on pharmacy compounding;
- Not be prepared with products that appear on the list of drug products withdrawn or removed from the market for being unsafe or not effective;
- Not be prepared by a licensed pharmacist or physician who compounds regularly in inordinate amounts drug products that are essentially copies of commercially available drug products;
- Not be a product identified by the FDA by regulation as a product that presents demonstrable difficulties for compounding and that reasonably demonstrates an adverse effect on the safety or effectiveness of the product; and
- Be prepared in a state that has entered into a Memorandum of Understanding (''MOU'') with the FDA addressing the distribution of inordinate amounts of compounded products interstate and providing for appropriate investigations by a state agency of complaints relating to compounded drug products distributed outside such state; or, in states that have not entered into such an MOU with the FDA, the compounder cannot distribute out of the state in which they were prepared more than 5 percent of the total prescription orders dispensed or distributed by such compounder.[8]

In addition, the FDA stated that it intends to periodically update the list of drug products that cannot be compounded because they have been withdrawn or removed from the market for being unsafe or ineffective. The FDA also stated that it is in the process of publishing a list of bulk substances that are safe for compounding, even if such substances do not have an applicable USP or NF monograph, or if they are not components of FDA-approved drugs. Until this list is finalized, human drug products should be compounded only using bulk substances that are components of drugs approved under the FDCA, or if they are the subject of USP or NF monographs.[9]

The FDA has also requested information about compounded drug products that present demonstrable difficulties in compounding; drugs published in the resulting list would not otherwise be eligible for exemption from certain FDCA requirements under Section 503A. As this list has not been published at this time, the FDA draft guidance provides that the statute setting forth this requirement is not currently enforceable.

The FDA also announced that it will be developing an MOU for use between states and the FDA to address the distribution of compounded products interstate. Once this MOU is finalized (and after an appropriate time period to permit states to sign this MOU), the FDA will begin to enforce the requirement that compounders located in a state that has *not* entered into an MOU with the FDA cannot distribute compounded products in amounts greater than 5 percent of the total prescription orders dispensed or distributed by such entity out of state.[10]

The draft guidance described certain sterility and quality requirements for drug products compounded under Section 503A, and also noted that the product labeling, advertising and promotion must not be false or misleading.[11] The draft guidance described enforcement action for compounders whose products do not meet the conditions of Section 503A, including the issuance of a warning letter, product seizure, injunction, criminal prosecution, application of CGMP requirements (for producing adulterated compounded products), required adherence to the NDA requirements (for producing unapproved new drugs), and required inclusion of adequate directions for use (for misbranded drugs).[12]

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[8] *See* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf.

[9] *Id.*

[10] *Id.*

[11] *Id.*

[12] *Id.*

Finally, the FDA discussed its enforcement approach with respect to compounded products, indicating that the highest enforcement priority included regulations posing the greatest public health risks. However, as the FDA's compliance guidance is simply an indication of the organization's thinking with respect to enforcement, the requirements set forth in the guidance do not, at this time, carry the force of law.

CGMP for Outsourcing Facilities

Registered outsourcing facilities are required to conform to CGMP under the Act. Currently, CGMP for drug products are found in federal regulations; however, those regulations are not necessarily generally applicable to compounding facilities, which have different considerations and operational procedures than manufacturers.

As the FDA is working to develop specific CGMP regulations for outsourcing facilities, interim guidance was released to describe the FDA's current thinking on best practices for outsourcing facilities. In the guidance document, the FDA provided that it understands that there are differences between outsourcing facilities and conventional drug manufacturers, and that CGMP requirements must be tailored to the business of compounding.[13]

The technical, detailed outsourcing facility CGMP standards cover areas such as facility design; control system implementation; environmental and personnel monitoring; equipment, containers and closures; product component source and quality; production and process controls; testing of drugs before they are released for distribution; laboratory controls; the establishment of a stability program; expiration dating; and product packing and labeling.

In general, the topic areas covered by the outsourcing facility CGMP guidance track the CGMP for manufactured products, but take into account the particularities of compounding that would make strict adherence to requirements for manufacturers difficult—if not impossible.

List of Registered Compounders

As of September 5, 2014, 55 compounders have elected to register as outsourcing facilities with the FDA, triggering an FDA inspection of each facility (16 facilities have yet to be inspected, however).[14] As of that date, 12 of the 55 registered facilities had been issued an FDA warning letter as a result of an inspection, and one facility received a recall letter.

On its website, the FDA cautions that drugs made by compounders, including those made at compounding outsourcing facilities, are not FDA-approved, and that they have not undergone the same NDA process as approved drugs.[15] The website also states that, although the drugs are not FDA-approved, ''purchasers of drugs compounded at a registered outsourcing facility that has had a recent satisfactory FDA inspection will have some assurance that the conditions at that facility met applicable current good manufacturing practice standards at the time of the inspection, and the compounded drugs are labeled with the required information.''[16]

In other words, although passing an FDA inspection captures a ''snapshot in time,'' providers who purchase compounded products from registered outsourcing facilities have—at least in part—the comfort that the registered facility is held to FDA-mandated standards of quality and sterility.

Guidance on Bulk Substances to Be Used in Compounded Products

In addition to the guidance documents discussed above, the FDA has requested input from industry stakeholders on the types of bulk substances that can—and cannot—be used safely in compounds prepared by both registered outsourcing facilities and compounders subject to Section 503A of the FDCA. In general, these requests replaced outdated proposed rules on similar topics, and will account for new developments in drug production since the proposed rules were released.

The FDA is also requesting nominations for drug products that present demonstrable difficulties for compounding under Sections 503A and 503B of the FDCA, and for additions and modifications to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness. The stakeholder nominations, and subsequent FDA rulemaking, will help ensure quality and safety of products prepared by compounders nationwide.

What's Next

While the FDA has released draft guidance on the new regulatory regime for compounding pharmacies, the true test of industry change is yet to come. As draft and final regulations are released, compounders and outsourcing facilities alike will begin to understand the technical requirements with which they must comply in order to avoid enforcement action. To that end, the FDA will also need to ensure that it has the resources to enforce the regulations that are implemented—both with respect to registered outsourcing facilities and compounders who have opted out of registration. And until then, stakeholders of all types await further—and final—guidance on how to prepare compounded products in the wake of the Act.

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[13] *See* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf.

[14] *See* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm.

[15] *See* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm389118.htm.

[16] *Id.*

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