Health Law Daily Wrap Up, STRATEGIC PERSPECTIVES: Traps in the Compounding Quality Act—Don't get caught!, (Jul. 24, 2014)

Click to open document in a browser

By Kathryn S. Beard, JD

Introduction. In 2012, the American public became aware of a serious gap in the FDA's authority to ensure the safety of drugs in interstate commerce when a multistate fungal meningitis outbreak was traced to a drug compounding facility. Drug compounding, the process by which a pharmacist combines, mixes, or alters ingredients to create a tailor-made drug to address the medical needs of an individual patient, is a traditional component of pharmaceutical practice. The drug compounding industry has shifted from compounding one prescription treatment for one patient to compounding large quantities in anticipation of future prescriptions for multiple patients. The vast majority of hospitals in the United States purchase compounded drugs from at least one outside pharmacy, including those located in other states. Prior to the fungal meningitis outbreak, three court decisions resulted in a lack of consensus on whether large-scale drug compounding without individual prescriptions being sold across state lines remains part of the practice of pharmacy, and thus subject to state oversight, or has become part of the drug manufacturing industry, giving the FDA authority to regulate these entities.

To clarify the FDA's authority, Congress enacted the Compounding Quality Act (CQA) as Title I of the Drug Quality and Security Act (DQSA) (P.L. 113-54). One week after President Barack Obama signed the DQSA into law, the FDA began implementing the law by releasing three draft guidances regarding the agency's enforcement policies under the CQA. Seven months later, the FDA released additional regulatory and guidance documents to further implement the DQSA, but portions of the law remain ambiguous in the absence of applicable regulations. This Strategic Perspective looks at the CQA and the documents the FDA promulgated in support of it, considers the steps the FDA has yet to take in implementing the CQA, and discusses risks that health care providers and drug compounders may face as these regulations become effective.

Compound drugs. Drugcompounding is "preparing a medication that is not commercially available in the strength, concentration, or form needed for a specific patient pursuant to a prescription," according to Michael D. Tucker, an associate at Baker, Donelson, Bearman, Caldwell, & Berkowitz, P.C. There are two types of compounding: traditional and non-traditional. Tucker explains, "Traditional, non-sterile, drug compounding includes medication patients drink, swallow, insert, or apply to skin. In contrast, non-traditional, sterile, drug compounding includes medication intended for injection, infusion, or application to the eyes." In anticipation of future prescriptions, some pharmacies compound large quantities of drugs; thecompoundingindustry makes up 1-3 percent of the prescription drug market in the United States, though the exact number of pharmacies creating compound drugs is unknown. In the last decade, providers have increasingly outsourced compound drug manufacturing—according to the Government Accountability Office (GAO), most hospitals purchase compounded drugs from at least one outside pharmacy. Daniel A. Kracov, a partner at Arnold & Porter LLP, explains that "drug compounding has long been part of the practice of pharmacy in the United States, and primary regulation of compounding has historically been within the purview of the states;" however, the fungal meningitis outbreak "ignited concerns surrounding compounding pharmacies that produce drugs—particularly injectable products—on a larger scale (in advance of a prescription for a specific patient)." State pharmacy regulatory bodies are responsible for overseeing pharmaceutical practice. Drugcompoundingis described in laws and regulations for all 50 states, but specifics vary, as do resources to provide the necessary oversight.

FDA authority prior to CQA. Under the Food, Drug, and Cosmetic Act (FDC Act), compounded drugs are considered "new drugs" subject to FDA oversight.Section 503A of the FDC Act was added to address compound drugs—it is not practicable for pharmacies to obtain approval for each compounded drug prepared for individual patients—including when compounded products could be exempted from certain FDC Act requirements. In 2002, theU.S. Supreme Court created legal ambiguities, says Kracov, when it "invalidated a provision in the Food and Drug Administration Modernization Act of 1997 restricting compounders from advertising or promoting

compounded drug products." Following the Court's ruling, a circuit split arose regarding the validity of the remainder of the compounding provisions of the FDAMA, which Kracov states, "hampered FDA's ability to take effective action against violative compounding operations." In 2013 GAO Report, the GAO recommended that Congress clarify the FDA's authority to regulate drug compounding entities, particularly with regard to the circuit split.

CQA. Congress responded by passing the CQA "to clarify FDA's authority over compounds for human use," according to Rachael G. Pontikes, a partner at Duane Morris LLP. The CQA, Tucker says, contains "two prominent sections, 503A and 503B. Sec. 503A governs traditional compounding, while 503B allows non-traditional or traditional compounders to be classified as outsourcing facilities. Together, they provide two separate exemptions to certain requirements of the FDC Act applicable to compounded drugs." One distinction Pontikes notes is that traditional compounders "are mainly regulated by the state boards of pharmacy," while outsourcing facilities "are regulated by and required to register with FDA." She continues, "Any facility that is compounding drugs for human use (a hospital, pharmacy, or drug compounding facility) is now subject to certain federal requirements governing either traditional pharmacy compounding or facilities compounding as outsourcing facilities." Tucker cautions, however, "the tension between state boards of pharmacy and the FDA remains, *i.e.*, state boards generally believe that the FDA does not have the authority to regulate traditional pharmacy compounding."

503A facilities. The CQA amends sec. 503A to remove the provisions the Supreme Court found unconstitutional, and also adds a severability clause to end the circuit split. Furthermore, section 503A no longer governs all compounding facilities—Kracov states that, in providing different provisions for traditional compounding facilities and large-scale sterile compounding facilities, "Congress hoped to avoid future health crises by ensuring that facilities engaged in large-scale sterile compounding were subject to inspection, current Good Manufacturing Practices (GMPs), adverse event reporting, and other requirements that will ensure the safety and effectiveness of compounded products." 503A remains applicable for drug products compounded for an identified individual patient based on the receipt of a valid prescription order or a notation; that is, the traditional way compounding has been practiced by pharmacists. Other facilities are now governed by 503B as outsourcing facilities.

503B outsourcing facilities. Pontikes explains that sec. 503B "creates an entirely new regulated entity (the outsourcing facility)." The CQA amends the FDC Act to establish an annual registration for outsourcing facilities, which Kracov describes as "a hybrid between traditional compounding pharmacies and drug manufacturers." "An outsourcing facility under sec. 503B," says Kracov, "is not required to be a licensed pharmacy, and may or may not obtain prescriptions for identified individual patients. Such entities can voluntarily register with FDA as an outsourcing facility and, if compliant with listed criteria, are exempt from certain requirements to which typical drug manufacturers are subject."

Regulatory actions. Following enactment of the CQA, the FDA began implementing the law through regulatory actions. Kracov states that the FDA has "issued several guidance documents addressing registration, product listing and user fees for outsourcing facilities," in addition to finalizing its "guidance on its oversight of traditional compounders under 503A, which is useful." Despite the number of regulatory actions taken by the FDA, many key provisions of the CQA have not yet been fully explained and implemented.

Gaps in section 503A. Tucker believes that the final guidance for sec. 503A has some gaps that will lead to confusion. By way of example, he says "a pharmacist may compound a drug in 'limited quantities' before the receipt of a prescription. How does a pharmacy determine what is and is not a 'limited quantity'?" Similarly, "pharmacies may not compound drugs in 'inordinate amounts' if they are essentially copies of commercially available drugs.Once again, what is an 'inordinate amount' and how are pharmacies supposed to modify their operational protocols to comply with this requirement?"

Lack of Memorandum of Understanding (MOU). More questions are raised regarding the statutorily-required MOU for compounding pharmacies under sec. 503A. Kracov explains "Sec. 503A provides that traditional compounders may only compound in a state that has entered into an MOU with FDA that addresses the

distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State.If a State does not enter into an MOU, the pharmacist or entity cannot distribute or cause to be distributed, compounded drug products out of the State in which they are compounded—more than 5 percent of their total prescription compounding orders." Pontikes says that the FDA, "in consultation with National Association of Boards of Pharmacy, still has to issue its draft Memorandum of Understanding."Regarding the lack of clarity arising from the lack of an MOU, Tucker asks, "For example, will there will be a maximum limit on the total prescription orders dispensed or distributed out-of-state?"

Non-binding provisions and holes in 503B. According to Kracov, "a number of regulations have not been finalized or proposed, and additional guidance and clarity is needed around several terms and issues" regarding registration for outsourcing facilities. As an example, he states that "while FDA has issued draft interim guidance on cGMP requirements for outsourcing facilities under sec. 503B, such guidance is non-binding and the CQA requires FDA to promulgate specific cGMP regulations which may differ from FDA's draft interim guidance." Kracov also states that the CQA's prohibition from compounding products that are "essentially a copy" of one or more approved drugs lacks clarity: "While Congress defined in the CQA what 'essentially a copy' as a 'drug that is identical or nearly identical to an approved drug,' it did not define what 'nearly identical' means and FDA has yet to issue guidance interpreting this issue." Kracov suggests that the voluntary nature of registration as outsourcing facilities is also problematic—"FDA estimates that there are approximately 700 to 1,000 compounders it could oversee, and only about 50 entities have voluntarily registered as outsourcing facilities."

Other unfinished business. In addition to the above, Kracov mentions that the CQA prohibits secs. 503A and 503B compounding facilities from "compounding a drug that is on FDA's list of drugs that present 'demonstrable difficulties' for compounding," or drugs "that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, unless it has been compounded in accordance with all applicable conditions identified by the [HHS] Secretary as conditions that are necessary to prevent the drug from presenting such demonstrable difficulties." He states that the FDA "intends to create and publish a 'single list of drug products and categories of drug products that cannot be compounded and still qualify for any of the exemptions' in secs. 503A and 503B," but has not done so yet. Kracov adds, "The agency must also finalize its proposal to add additional products to its list of drugs that have been withdrawn, as well as a list of bulk substances that can be used in compounding."

Risks for health care facilities. Kracov discussed a number of ways that the CQA's regulations and guidances affect health care facilities. To the extent that hospitals, pharmacies, or other health care facilities engage in compounding, "they will need to ensure compliance with traditional compounding requirements as framed under the CQA and evolving state laws, or shift to sourcing products from outsourcing facilities." Kracov notes, "Compliance with the CQA may be a particular challenge for certain physician practices engaging in in-office compounding." Additionally, he states that health care entities "should anticipate changes in the availability of certain products," explaining that some "products that have been available from compounding pharmacies will now longer be available from those sources. Conversely, some products may be more readily available due to the new category of manufacturing in outsourcing facilities."

Similarly, Kracov cautions: "Entities engaged in compounding in certain states may also face increasing difficulty operating without registering as outsourcing facilities. For example, states may enact legislation prohibiting out-of-state pharmacies from shipping compounded sterile products or any compounded products without first registering with FDA as an outsourcing facility. Alternatively, State Boards of Pharmacy may require out-of-state pharmacies engaged in sterile compounding to undergo inspection by that state's board, FDA, or another qualified entity prior to shipping sterile products into the state, which some states already require. Additionally, hospitals and payors that begin to refuse purchasing sterile products from out-of-state compounders or non-registered facilities may force compounders to register with FDA or otherwise face significant financial difficulties."

Conclusion. As the FDA continues implementing the CQA, health care providers and drug compounding facilities must closely follow new developments to ensure compliance. Tucker says that the CQA "has the

greatest impact on drug compounding facilities (*i.e.*, pharmacies) that ship across state lines." This impact could include "significantly increased regulatory burden and scrutiny, which will lead to greater costs in the long run," according to Tucker. Similarly, Kracov warns that "Hospitals, physicians' offices and other providers will need to re-evaluate their policies for purchasing and accepting compounded products," because the FDA is moving toward requiring "payors to only purchase sterile drugs from registered outsourcing facilities." He says "it will be incumbent upon providers to ensure they verify where compounded products are being purchased from and whether the compounder has any outstanding safety or quality issues."Lastly, Kracov states that there is a possibility of "issues regarding the reimbursement of compounded drugs." He notes, "Since the CQA's passage, FDA Commissioner Hamburg has engaged stakeholders in the healthcare system about the new compounding regulatory framework, including state boards of pharmacy, payors, hospitals, and insurers.On January 8, 2014, Commissioner Hamburg sent letters to hospitals and 'purchasers,' asking them to consider purchasing sterile drugs only from entities registered as outsourcing facilities or to 'requir[e]' compounding pharmacies that supply drugs to their facility to register. The FDA Commissioner's letter emphasized that hospitals and purchasers should purchase compounded drugs from outsourcing facilities because they will be subject to cGMP requirements and 'increased federal oversight,' including risk-based inspection, adverse event reporting, and appropriate labeling."

Attorneys: Michael D. Tucker (Baker, Donelson, Bearman, Caldwell, & Berkowitz, P.C.); Rachael G. Pontikes (Duane Morris LLP); Daniel A. Kracov (Arnold & Porter LLP)

MainStory: StrategicPerspectives DrugNews DrugBiologicalNews GMPNews FDCActNews LaboratoryNews PrescriptionDrugNews SafetyNews