Registration of Sterile Compounding Pharmacies With The FDA: When "Voluntary" Becomes Mandatory

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The deadly outbreak of fungal meningitis linked to the New England Compounding Company (NECC) in Massachusetts in 2012 led to new federal legislation in 2013 which clarified and in some instances increased FDA's control of drug compounding. The Drug Quality and Security Act (DQSA)[1], signed by President Obama, on November 27, 2013, was clearly enacted in response to the view that the Food and Drug Administration (FDA) both failed to act soon enough to shut down NECC. The new legislation also was a response to FDA's contention that this failure was largely the result of uncertainty in the law governing drug compounders and FDA's resulting inability to regulate drug compounding aggressively. Indeed, as Congressional scrutiny ramped up over the NECC tragedy, FDA Commissioner Hamburg urged the passage of new federal legislation that would require all compounding pharmacies to register with the FDA, create a uniform standard for compounded product safety, and give FDA inspectional authority and full access to a compounding pharmacy's records. She also requested legislation that would better define the difference between a drug manufacturer and a drug compounder.

The DQSA did remove the unconstitutional advertising and promotion provisions of section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), which addresses drug compounding and, for years, had plagued FDA's effective enforcement of this statutory provision.[2] However, the DQSA stopped short of requiring mandatory registration with FDA for drug compounders. Instead, a new section 503B was added to the FDCA creating a new category of voluntary FDA registrant, called "outsourcing facilities."[3] In return for the voluntary registration, outsourcing facilities are allowed to compound and ship sterile drugs under the supervision of a licensed pharmacists without first obtaining individual patient prescriptions—a requirement that had long been the centerpiece of what FDA viewed as allowable "traditional" compounding. Under the DQSA, outsourcing facilities upon registration with FDA and compliance with requirements such as an annual registration fee, compliance with FDA's current Good Manufacturing Practices (CGMP), consent to FDA inspections, and adverse event reporting, are exempt from the new drug approval and the adequate directions for use requirements of the FDCA.

A number of critical questions remain regarding the implementation of the DQSA, but perhaps the most significant uncertainty was whether FDA would try to "push" sterile compounders into the section 503B outsourcing facility category, and if so, how would FDA accomplish this approach? The answer now seems clear.

FDA, the first week of the new year, posted the names of the drug compounders who have registered to date on its website.[4] Moreover, on January 8, 2014, Commissioner Hamburg sent letters to hospitals and purchasers of compounded drugs encouraging them "to consider requiring compounders from which you purchase compounded sterile drugs to meet the medical needs of patients that cannot be met by FDA-approved products to register" with the agency.[5] This "encouragement" was merely a disguised command.

But how is this possible given the fact the DSQA makes such registration voluntary? Section 705

1 https://www.govtrack.us/congress/bills/113/hr3204/text.
2 21 U.S.C. § 353a.
3 21 U.S.C. § 355b.
4 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm.
5 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm380599.pdf.

of the FDCA affords FDA various publicity options.[6] In particular, FDA can disseminate information regarding drugs in situations involving danger to public health or gross deception to the consumer. FDA has also used widespread publicity to signal new enforcement postures to solicit voluntary industry compliance. It is obvious that Commissioner Hamburg's letter is designed to suggest to hospitals, who are major purchasers of sterile compounded drugs, that failure to buy exclusively from registered outsourcing facilities entails high risk and is not recommended. For example, Commissioner Hamburg makes these, not so subtle, points in her letter:

- In the year since the NECC-caused fungal meningitis outbreak, the FDA conducted more than 70 inspections of compounding pharmacies across the country, both for cause and as a proactive measure to identify pharmacies with deficient sterile compounding practices. During these inspections, "FDA observed serious quality problems, including contaminated products and poor sterile practices that create a risk of contamination. Numerous recalls of sterile products have been conducted, and numerous pharmacies chose to stop sterile compounding after FDA identified [these] problems."
- "When a drug is FDA-approved, patients are assured that FDA has reviewed the safety and efficacv of the drug and the adequacy of the manufacturing process." But "because they do not go through the drug approval process, compounded drugs do not provide such assurance."
- If compounders register with FDA as outsourcing facilities, hospitals and other health care providers that purchase compounded drugs necessary to meet the medical needs of their patients "can provide patients with drugs that were compounded in outsourcing facilities, which are subject to CGMP requirements and increased federal oversight."

She concluded her letter by emphasizing that *"[a]s a purchaser of compounded drugs, you can play an important role in improving the quality of compounded drugs by requiring compounding pharmacies that supply drugs to your facility to register as outsourcing facilities. Once they register, you and the patients you serve can be assured that FDA will inspect these facilities on a risk-based schedule, hold them to CGMP requirements, monitor the adverse event reports they are required to submit to the agency, and require appropriate labeling."* In short, the message is if you elect to buy from unregistered drug compounders you do so at your peril and that of your patients. In today's risk management environment at hospitals, can the inferred message be more cogent?

Those of us who have followed drug compounding developments over the last 18 months are not surprised. FDA wanted mandatory registration of all compounders and when it failed to achieve that objective the agency quickly elected to use the power of publicity to suggest that non-registered compounding pharmacies were "second class" facilities that pose a danger to public health. Although, based on recent experience, it is difficult to argue against the potential for risk with any sterile drug that is not subject to compliance with CGMP requirements, it is striking that FDA's advocacy occurred notwithstanding that, as Dr. Hamburg acknowledges in her letter to hospitals, "[r]egistration as an outsourcing facility is voluntary," and the DQSA clearly permits compounders of sterile drugs to operate solely within the parameters of section 503A of the FDCA and be regulated primarily by state boards of pharmacy.[7]

When does "voluntary" mean "must"? As a practical matter, it appears when FDA deems it so.

6 21 U.C.C. § 375.

7 Compounding pharmacies that do not register with FDA are allowed under section 503A of the FDCA to compound a certain amount of product in advance of receiving a prescription, but unlike registrants under section 503B they are not allowed to distribute without a prescription. FDA can inspect those facilities in response to a complaint, but would need a court order to access records.

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