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email alert

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Confused About Compounding Regulations?
A Brief Primer on FDA Compounding Oversight and Inspection Trends, in Two Charts

By Nathan Brown, Christin Carey, and Eli Tomar*

On November 27, 2013, Congress passed the Drug Quality and Security Act (DQSA). The DQSA clarified the U.S. Food and Drug Administration's (FDA's) oversight of "traditional" pharmacy compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), and created a pathway for "outsourcing facilities" to engage in larger-scale compounding of certain sterile drugs for use in hospital and provider settings. Under this new program, outsourcing facilities that register with FDA under the new Section 503B to the FDCA may compound without receiving individual patient prescriptions, must meet higher quality standards than traditional pharmacies, must register with the FDA, and are subject to FDA inspections.[1]

There have been many questions about the regulation of pharmacy compounding in the wake of the DQSA, which is still being implemented by FDA. For hospitals, providers, and others who rely on outsourced drugs, the FDA's recent oversight practices have led to uncertainty about the regulatory status of compounding entities and the safety of their products. The charts found at the links below explain some of the key terminology related to FDA oversight and enforcement, and the implications of specified FDA actions. The FDA's recent inspection activity is also analyzed, relating to traditional 503A compounding and new 503B outsourcing facility compounding.

Please see Key Concepts Regarding FDA Oversight of Compounding Activities and Recent FDA Oversight of Compounding Operations for more detailed information.

We would like to thank Nathan A. Brown, Christin H. Carey, and Eli Z. Tomar (Akin Gump Strauss Hauer & Feld LLP, Washington, DC) for providing this email alert.

[1] See here for a helpful infographic comparing compounding quality standards for outsourcing facilities under 503B and traditional pharmacies under 503A.

Member benefit educational opportunity:
Participate in the webinar--Academic Medical Centers under the Spotlight: New Sunshine Act Questions for Teaching, Research, and Patient Care (January 8).

Key Concepts Regarding FDA Oversight of Compounding Activities

Many hospitals, pharmacies, and new compounding outsourcing facilities have only limited familiarity with FDA oversight and enforcement practices. The FDA's regulatory terminology, and the implications of agency actions, can be difficult to decipher. This chart provides a primer on key concepts and terminology applicable to oversight of compounding activities.

Concept	Description
503A Traditional Compounding Pharmacies (503As)	Section 503A of the FDCA provides exemptions from certain federal drug requirements for "traditional" pharmacy compounding. If pharmacy compounding falls within the statutory safe harbor, it is exempt from certain federal standards that otherwise apply to drugs, such as the need for premarket approval and the need to follow "good manufacturing practices." Pharmacies exempt under 503A may compound drugs for individual patients, generally based on a prescription, and subject to certain restrictions.
503B Outsourcing Facilities (503Bs)	Section 503B of the FDCA, added in 2013 as part of the DQSA, provides exemptions from certain federal drug requirements for "outsourcing." Like 503A, if outsourcing falls within this statutory safe harbor, it is exempt from certain federal standards that otherwise apply to drugs, such as the need for premarket approval. But 503B outsourcing must follow "good manufacturing practices," unlike traditional pharmacy compounding. Outsourcing facilities under 503B are not limited to compounding a drug for an individual patient and are not required to receive prescriptions, but they must meet other regulatory requirements, including registering with FDA and listing their products, reporting adverse events, and following specified labeling standards.
Sterile-to-Sterile Compounding	Compounding sterile preparations from FDA-approved finished sterile drug products and sterile components. Facilities were considered to be engaged in sterile-to-sterile compounding if, at the time of registration, they indicated that they do not compound sterile drugs from bulk drug substances.
Non-Sterile-to-Sterile Compounding	Compounding sterile preparations from non-sterile bulk substances (active pharmaceutical ingredients). Facilities were considered to be engaged in non-sterile-to-sterile compounding if, at the time of registration, they indicated that they compound sterile drugs from bulk drug substances.

Form 483	Issued by FDA inspectors at the conclusion of an inspection when an investigator has observed any conditions that the investigator believes may constitute violations of the FDCA. Typically, the conditions or practices observed would indicate that the product has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated.
Warning Letter	Generally issued after a Form 483, for potential violations that are more significant or when corrective actions or proposed corrective actions are deemed insufficient. Warning letters are advisory in nature, and are issued for violations that may lead to enforcement action if not promptly and adequately corrected, and are FDA's principal means of achieving prompt voluntary compliance with the FDCA.
Product Recall	An action that removes a product from the market. Recalls may be initiated by FDA request, by FDA order, or by the product manufacturer. Most product recalls are initiated by the manufacturer voluntarily or at FDA's request, rather than by FDA order.
Letter to State Board	The FDA may issue a letter to a State Board of Pharmacy (State Board) relaying FDA's concerns observed during a compounding facility inspection, typically of a facility that is a state-licensed pharmacy. Such letters provide that FDA will not take further action, and refer the matter to the State Board to ensure appropriate corrective action is taken.

Recent FDA Oversight of Compounding Operations

The following charts analyze recent FDA inspection and enforcement relating to concerning facilities, as of **December 29, 2014**.[1]

Registered with FDA		
	503A	**503B**
Sterile-to-Sterile	**n/a**	**17**
Nonsterile-to-Sterile	**n/a**	**40**
Total	**n/a**	**57**
FDA Inspections of 503B Outsourcing Facilities		
	Number Inspected	**Percentage**
Registered Prior to 2014	**13/13**[2]	**100 %**
Registered 2014 Q1	**18/22**	**82 %**
Registered 2014 Q2	**10/12**	**83%**
Registered 2014 Q3	**1/9**	**11 %**
Registered 2014 Q4	**1/1**	**100 %**
Total	**43/57**	**75%**

	503A		**503B**	
Inspection Occurring:	**Pre-DQSA** (Feb. 1, 2013-Nov. 26, 2013)	**Post-DQSA** (since Nov. 27, 2013)	**Pre-DQSA** (Feb. 1, 2013-Nov. 26, 2013)	**Post-DQSA** (since Nov. 27, 2013)
FDA Inspections of Compounding Facilities				
Total	**Unknown**		**13**	**30**
FDA Issuance of Form 483				
None Issued	**Unknown**		**0**	**3**
Issued	**42**	**26**	**13**	**27**
Investigation Remains Open	**Unknown**		**2**	**26**
FDA Issuance of Warning Letter				
None Issued	**21**	**22**	**2**	**29**
Warning Letter Issued Pre-DQSA	**3**	**n/a**	**1**	**n/a**
Warning Letter Issued Post-DQSA	**18**	**4**	**11**	**0**
Total Issued	**21**	**4**	**12**	**0**
Product Recall Issued				
Voluntary/ Requested	**15**	**6**	**3**	**1**
Total	**21**		**4**	
FDA Referral to State				
Letters to State Board	**6**	**0**	**0**	**1**

Observations

- Registration Data: Under the DQSA, 503B outsourcing facilities are required to register with FDA and identify their products. The FDA is placing this registration data on its website. As a result, stakeholders can identify which entities have registered as outsourcing facilities and have some sense of their practice. Similar data is not available for 503A compounders. After an initial flurry of 503B registration activity, new registrations have tailed off. Over the summer, FDA issued draft guidance proposing Good Manufacturing Practices (GMPs) for 503B entities. It may be that other entities considering 503B registration will wait until FDA finalizes the GMP standards before deciding whether to participate.

- Inspections of Outsourcing Facilities: Stakeholders have questioned whether FDA is equipped to exercise sufficient oversight of outsourcing facilities, and some states have sought to impose separate restrictions on 503B entities. Inspection data suggests FDA has generally been proceeding chronologically in inspecting new outsourcing facilities as they register.

- Findings of Deficiencies in 503A Compounding: As noted, 503A entities do not register with FDA and are not subject to routine inspections; rather, they are inspected "for cause" in response to a complaint or safety concern. Recent data suggests that FDA continues to find deficiencies in traditional compounding operations. In particular, there continue to be a fair number of warning letters and, more significantly, product recalls—which are indicative of more-serious safety concerns.
  - Common observed deficiencies include: Lack of monitoring of environmental conditions for aseptic processing areas; inappropriate clothing of personnel; lack of proper procedures for preventing microbiological contamination; lack of batch testing; and insufficient testing programs for stability characteristics.

- Findings of Deficiencies in 503B Compounding: Most 503B entities have received a Form 483 after their inspection, and some have received warning letters. It must be emphasized that the applicable GMP quality standards applicable to outsourcing facilities have not been finalized by FDA, so the precise standards to which FDA is inspecting are somewhat ambiguous. It will likely take time for some of these facilities to transition from the traditional pharmacy quality standards to the higher, GMP-level quality standards. It is also noticeable that FDA has issued a number of warning letters since passage of the DQSA based on inspections that occurred prior to passage of the new law—in some cases after more than a year had passed. Although there is often a lag between the agency's inspection and issuance of a warning letter, it is somewhat surprising that FDA issued these warning letters without a re-inspection, given the intervening passage of the DQSA and FDA's issuance of draft GMP guidance.
  - Common observed deficiencies include: Lack of monitoring of environmental conditions for aseptic processing areas; inappropriate clothing of personnel; and lack of proper procedures for preventing microbiological contamination.

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[1] Numbers reflect most-recent available information as of December 29, 2014, based on FDA Inspections, Recalls, and other Actions, *available at*: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm

(last updated Oct. 10, 2014) and FDA Registered Outsourcing Facilities, *available at*: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm (last updated Dec. 19, 2014). Only the pharmacy's or facility's most-recent inspection is counted.

[2] One inspection remains open.