

## Food and Drug Law Alert

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### **Drug Compounding: Manufacturing Standards Announced for Outsourcing Facilities**

In late 2013, Congress passed the Drug Quality and Security Act (DQSA) in response to a deadly fungal meningitis outbreak linked to a sterile compounded injectable drug shipped across the country and responsible for more than 750 confirmed infections and 60 deaths. A key component of the DQSA is the recognition of a new type of drug compounding entity—outsourcing facilities—that can provide a source of high-quality compounded drugs for hospitals and providers. Unlike traditional state-regulated compounding pharmacies, outsourcing facilities are regulated by the U.S. Food and Drug Administration (FDA) and subject to manufacturing standards for the production of sterile compounds. This week, FDA released draft guidance explaining how the agency intends to apply current Good Manufacturing Practices (cGMPs) to these outsourcing facilities.

This guidance is important to outsourcing facilities (sometimes referred to as “503B” entities, based on the section of the Food, Drug, and Cosmetic Act under which they are regulated) and other entities considering establishing an outsourcing facility; hospitals and other providers relying on outsourcing facilities for their compounding needs; payors considering reimbursement and coverage policies concerning compounded drugs; and other participants in the pharmaceutical industry. The agency is developing proposed rulemaking on this topic, and comments should be submitted by interested parties as soon as possible.

#### **cGMPs for Outsourcing Facilities**

Although the DQSA itself does not provide that outsourcing facility cGMPs will deviate from the regulatory cGMPs for drug manufacturers, congressional negotiators, FDA and many stakeholders recognized that some variations would be needed. The interim guidance is designed to reflect the differences between outsourcing facilities, which produce smaller batches of customized compounds, often from finished sterile drugs, and conventional pharmaceutical manufacturers, which produce larger lots of standardized drug products that have been evaluated by FDA for safety and efficacy. The draft guidance also accounts for the differences among outsourcing facilities and provides for the tailoring of cGMPs to the nature of the facilities’ specific compounding operations. Ultimately, the cGMPs are designed to set minimum standards for outsourcing facilities, with a primary focus on ensuring sterility, strength and accurate labeling.

The interim guidance identifies the relevant sections of the regulations that apply to pharmaceutical manufacturers (21 C.F.R. parts 210 and 211) and explains how the agency will apply these rules to outsourcing facilities. These sections outline the expectations for outsourcing facilities and describe any variation from the rules as they apply to drugmakers. Specifically, these standards relate to:

- **Facility Design:** laying out standards for processing and controlled areas, high-efficiency particulate air filters, and cascading air quality and pressurization for critical areas (set at ISO-5 classification in cleanrooms and ISO-7 in immediately adjacent areas)
- **Control Systems and Procedures:** identifying the protocol and documentation requirements for sanitation schedules and methods, humidity and temperature controls, and air flow and pressure monitoring, as well as built-in alarms to detect deviations and response plans
- **Environmental and Personnel Monitoring:** requiring well-defined systems for monitoring environmental conditions (i.e., air, surfaces, process, operation and personnel practices) in aseptic processing areas with alert limits and response plans, as well as scheduling and monitoring programs for personnel gowning and garbing
- **Equipment, Containers and Closures:** requiring equipment, containers and closures to be tested to ensure adequacy for their intended use, including items that must be sterilized and depyrogenated before use
- **Components:** setting controls over the source and quality of components, including the establishment of specifications (e.g., identity, strength, purity, particle size, sterility, bacterial endotoxin level) for components, with an emphasis on identity testing for nonsterile starting materials
- **Production and Process Controls:** requiring written procedures for general production processes, batch records, hold times and in-process controls relating to sterile filtration and aseptic processes, as well as requirements to investigate any deviation from the procedures; process controls also include criteria for introductory training, mastery of department-specific techniques (e.g., simulating media fills), certification of mastery and recertification
- **Release Testing:** mandating testing for each drug product for identity and strength, visible particles and sterility, as well as authorization from a designated quality control individual prior to release, subject to certain exceptions
- **Laboratory Controls:** specifying analytical methods and equipment necessary for in-house or external laboratory determinations, including the maintenance of complete records of all tests
- **Expiration Dating:** establishing specific and conditional expiration date criteria supported by reliable and specific stability-indicating test methods, as well as the substitution of beyond use dating as appropriate
- **Packaging and Labels:** requiring packaging systems capable of ensuring the integrity of the product against foreseeable external factors until administration with adequate controls for issuing, examining and reconciling labels to prevent mix-ups

- **Quality Assurance Activities:** mandating an independent quality control unit with individuals designated to handle failure investigations, written and oral complaints concerning the drug product quality, and possible adverse reactions.

In many instances, FDA indicates that it does not intend to take enforcement action against an outsourcing facility regarding a particular cGMP requirement if the facility relies on the assurances of certain third parties and fulfills additional obligations. For example, the requirements for testing starting components are moderated for components such as FDA-approved finished human drug products and ready-to-use, sterile single-use items. Similarly, FDA relaxes the cGMP requirements for release testing of very small batches, as well as compounded products composed solely of one or more FDA-approved drugs whose labeling specifies how to assign an “in-use time.”

With regard to testing starting components and laboratory testing prior to release, FDA has requested public comments on alternative approaches that would reduce the need for duplicative testing by multiple outsourcing facilities by instead relying on a drug master file containing specific information reviewed by FDA.

### **Next Steps in Compounding Implementation**

The agency plans to promulgate specific cGMP regulations applicable to outsourcing facilities, but will use these draft guidelines for inspection and enforcement purposes in the interim. The draft guidance on cGMPs joins several other draft guidance documents that describe outsourcing facilities’ obligations regarding registration, product reporting and payment of fees. This cGMP guidance, however, was perhaps the most highly anticipated; many observers have suggested that potential registrants have been waiting to see the standards before registering with FDA.

As of June 27, 2014, 48 outsourcing facilities are registered. The DQSA directs FDA to inspect these facilities according to a risk-based inspection schedule. Since enactment, the agency has begun inspecting new registrants that do not have a prior inspection on record and has issued a Form-483 for observed cGMP violations for all but one of the 17 inspections it has conducted. FDA has asserted in press statements that these interim standards, combined with other recently announced rules, give the agency broad latitude to employ a risk-based enforcement scheme and to act swiftly if it identifies concerns about compounded drugs.

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