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Food, Drug & Device/FDA ADVISORY ■

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cGMP Requirements for Outsourcing Facilities…For Now

Earlier this month, the U.S. Food and Drug Administration (FDA) issued an Interim Draft Guidance, "Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act" (July 2014) (the "Interim Draft Guidance"). The Interim Draft Guidance delineates the agency's current expectations regarding outsourcing facility compliance with current good manufacturing practice (cGMP) requirements in 21 CFR Parts 210 and 211. Outsourcing facilities, as defined in the 2013 Drug Quality and Security Act, are facilities engaged in the compounding of sterile drugs that have elected to register with the FDA. The Interim Draft Guidance will be in effect for these facilities until more specific cGMP final regulations are promulgated.

In the Interim Draft Guidance, FDA differentiates outsourcing facilities from conventional drug manufacturers by tailoring "cGMP requirements to the nature of the specific compounding operations conducted by the outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products." Interim Draft Guidance at 2. The Interim Draft Guidance focuses primarily on those operations that pose the highest risk to patient safety, including those aspects of 21 CFR Part 211 relating to sterility assurance and safety of compounded drugs, with respect to strength, and labeling or drug product mix-ups. FDA's inspectional and enforcement efforts will focus on these areas.

A. cGMPs Applicable to Outsourcers

The Interim Draft Guidance outlines the agency's thinking regarding outsourcing facility obligations related to facility design, control systems and procedures for maintaining suitable facilities, environmental and personnel monitoring, equipment, containers and closures, components, production and process controls, release testing, laboratory controls, stability/expiration dating, packaging and labels, and quality assurance activities/complaint handling. FDA has requested public comments on alternative approaches that would reduce the need for laboratory testing of incoming components and the need for facilities to have an in-house laboratory.

The Interim Draft Guidance identifies specific cGMP requirements under 21 CFR Part 211 that are critical to ensuring the quality of compounded sterile drug products. It appears that these requirements are more extensive than compounders had anticipated, especially with respect to release and stability testing, and to the responsibilities of the quality control unit.

In certain instances, FDA intends to use its enforcement discretion if an outsourcing facility complies with criteria set forth in the Interim Draft Guidance. Some highlights include:

- **Incoming Inspection:** Outsourcing facilities are required to comply with requirements in 21 CFR §§ 211.84(d) and 211.67(b) to examine each lot of equipment, containers and closures prior to use to verify identity and test to ensure that the equipment, container or closure meets specifications.
  - Components generally must be re-tested or re-examined after lengthy storage or exposure to conditions that might adversely affect the component, but not if the component is stored under the supplier's labeled storage conditions.
  - FDA will exercise enforcement discretion regarding incoming inspection if the component is a finished drug product, purchased directly from the manufacturer, has had its label examined to verify that the component meets required specifications and the package integrity has been verified. Any components not meeting acceptance criteria must be rejected.
  - Outsourcing facilities are also required to test bulk APIs and excipients to verify identity and evaluate for conformity to specifications. Lot testing can be skipped if a Certificate of Analysis (COA) accompanies the lot and meets the requirements in the Interim Draft Guidance.
  - FDA will exercise its enforcement discretion regarding testing of certain non-sterile components (e.g., water) purchased and certified as sterile and non-pyrogenic, and accompanied by a COA.
    - FDA requested comments on alternative approaches that might reduce the need for duplicative testing by multiple outsourcing facilities, while still giving them confidence in the quality of incoming components.
- **Production and Process Controls:**
  - Outsourcing facilities must document that key process parameters are controlled and deviations justified.
    - Batch records must describe batch yield (actual v. calculated).
    - Outsourcing facilities must investigate any failure to meet acceptance criterion before approving lot release and a failure may result in rejection of the lot.
  - Hold time assessments must be conducted as part of the process for validating sterility assurance.
    - For example, sterile drug products that are terminally sterilized should achieve a 10^{-6} sterility assurance level for proper validation of the sterilization process.
- **Release Testing:**
  - The quality control unit must ensure that testing is conducted and test results demonstrate that the finished drug product meets specifications before batch release.

- FDA will exercise enforcement discretion for sterility testing if the batch consists of fewer than 10 dosage units compounded pursuant to a prescription for a single patient, so long as the unit is labeled with a beyond use date (BUD) that provides reasonable assurance of chemical and physical stability. Note that this is more restrictive than the standard established by the United States Pharmacopeia (USP) and adopted by many pharmacy compounders. For high-risk compounded sterile preparations, USP ⟨797⟩ requires release testing on batches of more than 25 dose units, multi-dose vials intended for multiple patients, or for preparations exceeding stated storage temperature conditions. USP ⟨797⟩ at 39–40.
- FDA also plans to exercise enforcement discretion for other testing for batches of less than 10 units (e.g., identity, strength and particulate) if testing is conducted on every other batch or once for every 10 units.

- **Stability Testing:**
  - Outsourcing facilities must establish stability programs to determine appropriate storage conditions and expiration dates, in accordance with 21 CFR § 211.166. In addition, outsourcing facilities must conduct stability testing to ensure that compounded products remain stable and sterile through the expiry period. FDA will exercise enforcement discretion regarding stability studies if the outsourcing facility establishes a BUD (1) in accordance with the Interim Draft Guidance, (2) literature or other scientific information support the chemical and physical stability of the BUD and (3) the BUD is the expiration date.

- **Packaging and Labeling:** Labeling operations must have controls in place to prevent mix-ups and SOPs must be in place to ensure that the requirements of 21 CFR §§ 211.122, 211.125, 211.130, and 211.134 are met.

- **Quality Assurance and Complaint Handling:**
  - The Interim Draft Guidance describes the roles and responsibilities of a quality control unit, which include:
    - Discrepancy and failure investigations [note: the Interim Draft Guidance does not specifically require outsourcing facilities to retain samples, but it is not clear how an outsourcing facility would meet the requirement to conduct a thorough investigation without retaining samples].
    - Sampling and testing to ensure finished drug products meet release criteria.
    - Review of records to evaluate quality standards for each drug product.
    - Adverse event reporting.

The Interim Draft Guidance identifies a substantial portion of the cGMP regulations as "critical." Certain cGMPs are not specifically mentioned; however, their applicability is implied. For example, there is no citation to the cGMP requirement for adequate ventilation and air filtration under 21 CFR 211.46, but air quality and cleanliness are discussed at length in the Interim Draft Guidance. Interim Draft Guidance at 3-4. Similarly, there is no reference to yield calculation under 21 CFR § 211.103, yet the Interim Draft Guidance states a requirement to compare the "actual batch output (yield) . . . to the projected (calculated) output for each

drug product." Interim Draft Guidance at 11. Also, personnel training requirements are detailed under recommendations for aseptic drug processing. Interim Draft Guidance at 12.

B. Other cGMP Requirements Unclear

The Interim Draft Guidance appears to address every general cGMP category, except for Holding and Distribution (21 CFR §§ 211.142, 211.150) and Returned and Salvaged Drug Products (21 CFR §§ 211.204, 211.208).

The following is a list of other cGMPs not mentioned in the Interim Draft Guidance. While FDA never states that these cGMP regulations do not apply to outsourcing facilities, lack of reference to these regulations may be because they describe lower-risk activities, e.g., "use of approved components, drug product containers, and closures" – 21 CFR § 211.86 (mandates that oldest approved stock should be used first).

- **Organization and Personnel**
  - Consultants (21 CFR § 211.34)
- **Buildings and Facilities**
  - Lighting (21 CFR § 211.44)
  - Plumbing (21 CFR § 211.48)
  - Sewage and refuse (21 CFR § 211.50)
  - Washing and toilet facilities (21 CFR § 211.52)
  - Maintenance (21 CFR § 211.58)
- **Equipment**
  - Filters (21 CFR § 211.72)
- **Control of Components and Drug Product Containers and Closures**
  - Use of approved components, drug product containers and closures (21 CFR § 211.86)
  - Rejected components, drug product containers and closures (21 CFR § 211.89)
- **Production and Process Controls**
  - Charge-in of components (21 CFR § 211.101)
  - Reprocessing (21 CFR § 211.115)
- **Packaging and Labeling Control**
  - Tamper-evident packaging requirements for over-the-counter (OTC) human drug products (21 CFR § 211.132)

- **Laboratory Controls**
  - Reserve samples (21 CFR § 211.170)
  - Laboratory animals (21 CFR § 211.173)
  - Penicillin contamination (21 CFR § 211.176) [although there is mention of maintaining separate facilities under 21 CFR § 211.42(d)]
- **Records and Reports**
  - Equipment cleaning and use log (21 CFR § 211.182)
  - Master production and control records (21 CFR § 211.186)
  - Distribution records (21 CFR § 211.196)

C. Subcontracting for Laboratory Control Testing

The Interim Draft Guidance also describes how an outsourcing facility may contract out required laboratory control testing. Under such an arrangement, the outsourcing facility retains regulatory responsibility for the contracted operations. Interim Draft Guidance at 11, n.15. Moreover, failure to exercise appropriate oversight and control of the outside laboratory could result in adulteration of compounded products. *See* The Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 711.[1]

The Interim Draft Guidance references a draft guidance document titled "Contract Manufacturing Arrangements for Drugs: Quality Agreements," which contains explicit recommendations regarding quality agreements, defining a quality agreement as "a comprehensive written agreement that defines and establishes the obligations and responsibilities of the Quality Units of each of the parties involved in the contract manufacturing of drugs subject to CGMP." Quality Agreement Draft Guidance at 4–5. It also makes it clear that parties cannot, by agreement, shift responsibilities that are established by regulation. This point is reemphasized in the Interim Draft Guidance, "[w]hen an outsourcing facility seeks the services of a contract facility to perform all or part of the testing of a drug, the outsourcing facility's quality control unit is responsible for approving and rejecting drugs tested by the contractor." Interim Draft Guidance at 11, n.15.

The Interim Draft Guidance also references guidance on "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" (the "OOS Guidance"). The OOS Guidance establishes a framework for investigating OOS test results, including the responsibilities of the analyst and laboratory supervisor, requirements for the laboratory phase of the investigation, requirements for the formal investigation extending beyond the laboratory, and the evaluation of test results. Outsourcing facilities that are unfamiliar with the OOS Guidance should be aware that they will be held to this standard when conducting OOS investigations and during cGMP inspections.

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[1] Section 711 of FDASIA amended section 501 of the Federal Food, Drug, and Cosmetic Act (FDCA) by adding the following language:

> For purposes of paragraph [501](a)(2)(B), the term "current good manufacturing practice" includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

21 U.S.C. § 351.

D. Additional Guidance

FDA has also recently released other documents related to compounded drug products for human use in order to provide the compounding industry with appropriate tools to comply with the law as FDA continues efforts to implement the compounding provisions of the Drug Quality and Security Act. The other four documents released earlier this month include:

- Proposed Rule, "Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Safety of Effectiveness," 79 Fed. Reg. 37,687 (July 2, 2014);
- Final Guidance, "Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act" (July 2014);
- Federal Register Notice, "Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations" (July 2, 2014); and
- Federal Register Notice, "Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations" (July 2, 2014).

The Interim Draft Guidance and proposed rule are available for public comment for 60 days, due on August 31, 2014, and the dockets are open for the public to nominate bulk drug substances for compounding under Section 503A or 503B for 90 days, due on September 30, 2014.

Alston & Bird can assist pharmacy compounding entities in better understanding these cGMP requirements and how to implement processes and procedures that address these areas. Please contact **Cathy Burgess** at cathy.burgess@alston.com with any questions you may have.

***This advisory was written by* Cathy Burgess, Brendan Carroll *and* Guillermo Cuevas.**

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