Responding to an FDA 483

Jim Melancon
VP, Associate General Counsel - BioScrip, Inc.
Marc Stranz, PharmD
Healthcare Consultant

Disclosure

The speakers declare no conflicts of interest or financial interest in any service or product mentioned in this program.

Clinical trials and off-label/investigational uses will not be discussed during this presentation.

503A vs 503B “lite”

- Under 503A, a compounded drug product qualifies for exemption from sections 501(a)(2)(B), 502(f)(1), and 505 of the Food, Drug and Cosmetic Act (“FD&C”) if drugs are compounded:
  - for an identified individual patient based on a valid prescription or a notation that a compounded product is necessary
  - by a licensed pharmacist in a licensed pharmacy pursuant to a valid prescription or based on a history of the pharmacist receiving prescription orders for the drug product
  - in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding and using bulk FDA-approved drug substances that comply with the USP or NF monograph
503A vs 503B “lite” (cont.)

- using bulk drug substances that are manufactured by an FDA registered establishment
- using bulk drug substances that are accompanied by valid certificates of analysis
- using ingredients other than bulk drug substances that comply with USP/NF monographs and the USP chapters on pharmacy compounding
- not using drugs that appear on the list of drugs withdrawn or removed from the market for being unsafe or not effective
- that are not drugs identified by FDA as a drug product that presents demonstrable difficulties for compounding

503A vs 503B “lite” (cont.)

- in a state that has entered into a memorandum of understanding (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
  - In states with no MOU with FDA, the pharmacy does not distribute out of state compounded drug products in excess of 5% of the total prescription orders dispensed
  - The pharmacist does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drugs

503A vs 503B “lite” (cont.)

- 503A pharmacies are subject to state regulation as long as they dispense in response to traditional individualized prescriptions
- 503B pharmacies are subject to FDA regulation
  - When compliant, 503B pharmacies manufacture and ship interstate large quantities of compounded drugs without individualized prescriptions (Current Good Manufacturing Practice - Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act)
503A vs 503B (light version)

- The FDA is inspecting compounding pharmacies to determine whether they comply with 503A (Inspections of Sterile Drug Compounding Facilities, Ellen Morrison)
  - If not compliant with 503A requirements, the pharmacy is not exempt from:
    - Compliance with current good manufacturing practices (cGMP) (section 501(a)(2)(B));
    - Labeling with adequate directions for use (section 502(f)(1)); and
    - FDA approval prior to marketing (section 505)

The FDA Inspection

- Purpose is
  - Compliance with GMP
  - Quality, stability, and reliability of manufacturing processes
- Based on the manufacturer’s requirement to
  - Implement quality systems
  - Verify GMP compliance
  - Implement remedial/corrective action where noncompliance is found

The FDA Inspection

- Inspection is based on the Compliance Program Guidance Manuals @ http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm
  - 7356.002 Drug Manufacturing Inspections
  - 7356.002A Sterile Drug Process Inspections
- GMP requirements are based on
  - 21 CFR Part 211 Current Good Manufacturing Practices for Finished Pharmaceuticals
The FDA Inspection

• Inspection process
  – FDA inspection protocol exists and manufacturers train for them
  • Alert staff, get credentials, review Form 482, define scope of inspection
  • Have materials and staff ready
  • Inspection will last until investigator(s) satisfied
  • FDA can receive copies of required information
  • Record everything

The FDA Inspection (cont.)

• Inspection process (cont.)
  – Inspection will cover
    • Organizational chart
    • Job descriptions
    • Training records
    • SoPs
    • All records for recent batches of drugs
    • Production and QC/QA - metrics of quality systems looking for areas that need attention

The FDA Inspection (cont.)

• Inspection process (cont.)
  – Inspection will cover (cont.)
    • Production and QC/QA
      – Batch rejection rate
      – Rework/reprocessing rate
      – Number of CAPAs issued (Corrective And Preventive Actions)
      – CAPA completion/closure rate
      – Out-of-specification (OOS) rate
      – Compliant statistics - recalls or product alerts
      – Annual product review completion rate
The FDA Inspection

- Inspection process (cont.)
  - Exit Interview with presentation of Form 483; verbal responses captured
  - Establishment Inspection Report (EIR) with all documents as exhibits
  - Submitted to District/Regional office for review; Final 483 issued

The FDA Inspection

- Inspection process (cont.)
  - Response within 15 business days
    - If citation/observation is inaccurate, provide specific documentation
    - Accept responsibility where appropriate
    - Provide evidence for investigating deficiencies; root cause analysis
    - Propose specific corrective action plans with timeline and proof sources

The FDA Inspection

- Inspection process (cont.)
  - Final letter sent
    - General Letter – NAI. No further action required (NAI = no action indicated)
    - Information Letter – VAI. Minor deviations, response may be required (VAI = voluntary action indicated)
    - Warning Letter – OAI. Major deviations, written response within 15 business days (OAI = official action indicated)
  - Inspection report posted to FDA website
cGMP vs 503A vs 503B

- 21 CFR Part 210
  - Provides definitions for terminology used in Part 211
- 21 CFR Part 211
  - Eleven Subparts: A - K
    • Covers all operational aspects but doesn’t have many details
    • Attempts to tell you what to do, not how to do it

Common 503A pharmacy findings under cGMP
cGMP vs 503A vs 503B

• Subpart C - Buildings & Facilities
  — Space - avoid mix-up; avoid contamination
    • 503A: Beta-lactam antibiotics require separate cleanroom; HVAC systems
  — Aseptic processing – cleanroom, temperature, humidity; filtered air; environmental monitoring; cleaning; disinfecting; monitoring
    • 503A: Manometers alarmed; daily air sampling; smoke testing; surface sampling during and at end of each batch; sample gowns and gloves at least daily

• Subpart C - Buildings & Facilities (cont.)
  — Repair/Sanitation – vermin, trash, chemicals used
    • 503A: Service contracts, chemicals used, sterile disinfectants that are tested/monitored/rotated
  • 503B: may use manufacturer literature initially

• Subpart D - Equipment
  — Compounding devices, filtration, balances
    • 503A: Filter efficacy; prefiltration burden
  — Calibrated, cleaned, maintained, sanitized
    • 503A: Auto-calibration not reliable
  — Computer access; control of templates; data/formula verification; backups

• Subpart E - Components/Containers/Closures
  — Receipt, identification, storage, handling, sampling, testing, approval/rejection of components, containers, closures.
    • 503B: allows precertification of sterile, non-pyrogenic containers, closures
    • 503B: allows drug use without testing from FDA-approved source without repackaging, with CoA, and package integrity
  • 503B: allows component use with CoA from supplier whose reliability is tested annually and one identity test conducted. Nonsterile components require sterility and endotoxin testing.
cGMP vs 503A vs 503B

• Subpart F - Production & Process Controls
  – Production & control procedures: facilities, garb/garbing, compounding (aseptic technique), process simulation, labeling, checking, yields, sampling, timing, equipment use, validation of sterile processes, testing (environment, drug identity, strength, endotoxins, sterility)
  • 503A: testing each batch for strength and sterility

• Subpart G - Packaging & Labeling Control
  – Receipt, testing, storage
  – Labeling is correct, current, and complete. Label is attached to batch record
  – Labeling inspection, expiration dating based on stability data, error control
  • 503A: label attached to batch record; expiration dating by stability testing

• Subpart H - Holding & Distribution
  – Policy & process on distribution, quarantine, stock rotation, recall
  • 503A: quarantine for QC approval
cGMP vs 503A vs 503B

- **Subpart I - Laboratory Controls**
  - Specifications, standards, sampling, testing, for drug identity, strength, particles, endotoxins, sterility; Media validity. Facility, equipment testing also
  - Penicillin contamination testing
    - 503A: Strength, sterility testing, media validity
    - 503B: batch of <10 units can be released under Chapter 797 high risk sterility standards: 24 hrs at RT; 3 days refrigerated

---

Regulatory Standards for Response

- **State regulations.** According to the NABP 2015 Survey of Pharmacy Law (p. 115)
  - "Does Board require compliance with USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations?", the following states answered **NO**:
    - Alaska, Arizona, DC, Idaho, Mississippi, Montana and Nebraska - straight "NO"
    - Hawaii, Illinois, Iowa, Nevada, New York, North Dakota, Ohio, and South Carolina qualified their "NO" with statements about compliance with Chapter <797> being a standard of practice, or that there were similar applicable state rules
    - New York – "NO" but says some current rules apply
    - Pennsylvania – "NO" but now "regulations pending"
Regulatory Standards for Response

- **USP Chapter <797>** is available from the USP in their USP Compounding Compendium along with other Chapters that some state regulations required to be on hand.
  

Regulatory Standards for Response

- **Drug Quality and Security Act of 2013 ("DQSA”): specifically, the Compounding Quality Act**
  - Title I of DQSA, the Compounding Quality Act, Section 503A, describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring:
    - Compliance with current good manufacturing practices (cGMP) (section 501(a)(2)(B));
    - Labeling with adequate directions for use (section 502(f)(1));
    - FDA approval prior to marketing (section 505).
  - [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmaceuticalCompounding/ucm376732.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmaceuticalCompounding/ucm376732.htm)

Regulatory Standards for Response

- **Food, Drug and Cosmetic Act, Compliance Program Guidance Manuals**
  - Guidance for Industry
    - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
    - Questions and Answers on Current Good Manufacturing Practices (cGMP) for Drugs
    - Current Good Manufacturing Practice - Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act
Regulatory Standards for Response

- Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
- Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
- Inspections of Sterile Drug Compounding Facilities. Ellen Morrison. FDA Office of Regulatory Affairs April 2014

Responding to an FDA 483

Questions/Discussion