Drug Quality Security Act Conference
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FDA and Inspections: What to Consider When FDA Visits Your Facility

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Almost Five Years Have Passed Since NECC...
Where are we going?

- Verdict in criminal trial of co-owner and head pharmacist of New England Compounding Center, Barry Cadden
  - Cleared of second degree murder
  - Convicted of racketeering
  - Convicted of multiple counts of mail fraud
  - Sentenced to 9 years in prison
- Verdict in criminal trial of Glenn Chin, Supervisory Pharmacist
  - Convicted of Mail Fraud
  - Convicted of racketeering
  - Acquitted of second degree murder
  - Sentencing is pending
- The NECC matter was impetus for unprecedented changes in the regulatory and legal landscape for compounded human drug medications.
  - Congress revitalized Section 503A, removing unconstitutional provisions
  - Congress created Section 503B Outsourcing Facilities

FDA Inspection Reminders

- The FDA investigator asks the questions; but feel free to ask clarifying questions or ask why FDA is engaging in a certain activity or process
- Always answer questions truthfully
- Do not speculate or guess; if you don't know the answer then tell FDA you will get back to them.
- FDA does not expect you to know every answer
- Refrain from volunteering any information beyond the scope of the question asked
- Answers should be based on SOP requirements, Section 503A requirements, USP or state law
- Some answers will come from different personnel; direct questions to appropriate individuals
- Have a scribe taking notes on everything, and make notations or copies of all documents FDA reviews, or takes with them
- Escort the investigators to a designated room where the inspection data review will be conducted. This room should be secure and free from routine traffic of operations.
- Ask the investigator not to leave the area without escort. Identify the escort and the individual who will be the prime contact during the inspection if, for some reason, it is a different person.
- Do not leave the investigators alone anywhere in your facility, or give them unfettered access to it.

FDA Inspections

System Based Approach (6 Systems)

- Quality
- Facilities and equipment
- Materials
- Preparation (production)
- Packaging and labeling
- Laboratory

The "New" Regulatory Framework for Pharmacy Compounding

- A Quick Refresher: What is the Drug Quality and Security Act (DQSA) of 2013?
  - Title I: The Compounding Quality Act
    - Added new § 503B: Established a pathway to legally compound drugs for "office use" (i.e., nonprescription-based compounding)
    - Reenacted § 503A: Struck unconstitutional provisions to reaffirm prior legal framework for traditional pharmacy compounding
  - Title II: The Drug Supply Chain Security Act
    - Established a national "track & trace" program

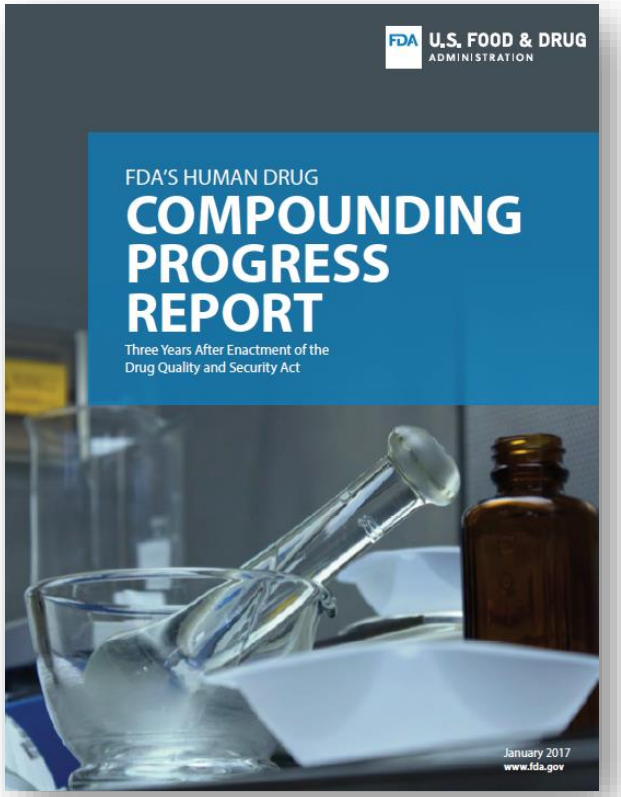
What is Section 503A?

- § 503A exempts compounded **drugs** from 3 requirements of the FDCA:
  - (1) FDA premarket approval (§ 505);
  - (2) Drug labeling with adequate directions for use (§ 502(f)(1)); and
  - (3) Compliance with CGMPs (§ 501(a)(2)(B))
- …Only if **all** of these conditions are met:
  - The drug is compounded by a licensed pharmacist or physician, only in limited quantities before the receipt of a valid prescription, and is not dispensed before receipt of a valid prescription for an identified individual patient
  - No more than 5 percent of prescriptions are being distributed across state lines unless the state has entered into a Memorandum of Understanding (MOU) with FDA
  - Other restrictions relating to the drug being withdrawn from the market, not demonstrably difficult to compound, and quality of ingredients
- § 503A does **NOT** exempt pharmacies from any other requirements of the FDCA for new drugs, including:
  - Tracking and tracing requirements (§ 582)
    - But DSCSA includes exemptions for dispensing (i.e., pursuant to a prescription)
  - Prohibition on adulterating drugs (§ 501)
  - Prohibition on misbranding drugs (§ 502)

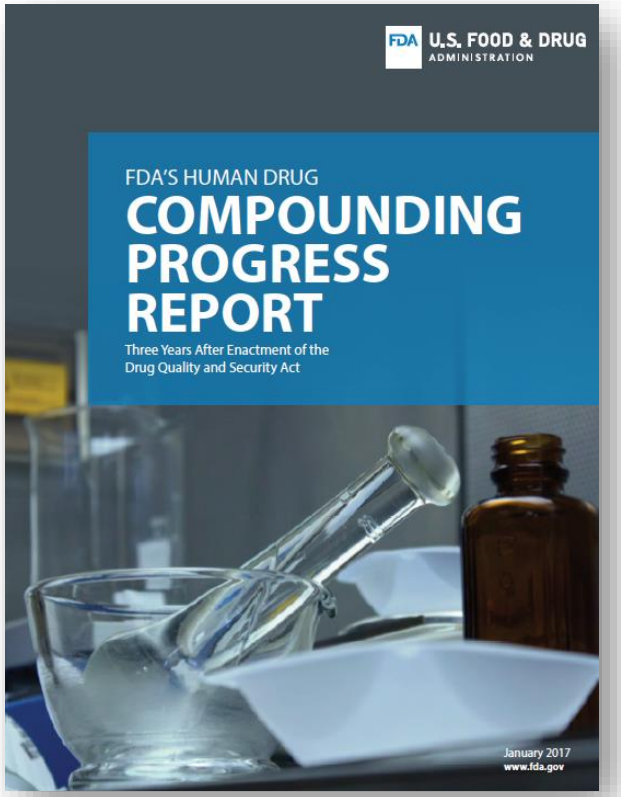
What is Section 503B?

- Premise: All compounded drugs are "*new drugs*" subject to the requirements of the federal Food Drug & Cosmetic Act (FDCA).
- § 503B exempts compounded **drugs** from 3 requirements of the FDCA:
  - (1) FDA premarket approval (§ 505);
  - (2) Drug labeling with adequate directions for use (§ 502(f)(1)); and
  - (3) Tracking and tracing requirements (§ 582)
- …**Only if all** of these conditions are met:
  - The drugs are compounded under a licensed pharmacist's supervision, are labeled as compounded drugs, are not made using bulk substances (except under narrow circumstances such as a drug shortage), and are not "*essentially a copy*" of an approved product, have not been withdrawn from the market, and other restrictions
  - The outsourcing facility registers with FDA annually, submits to risk-based inspections, pays all applicable fees, electronically reports all production to FDA biannually, reports adverse events, and does not engage in wholesaling
- § 503B does **NOT** exempt outsourcing facilities from any other requirements of the FDCA, including:
  - Compliance with current good manufacturing practices (CGMPs) (§ 501(a)(2)(B));
  - Prohibition on adulterating drugs (§ 501)
  - Prohibition on misbranding drugs (§ 502)

Released: January 2017

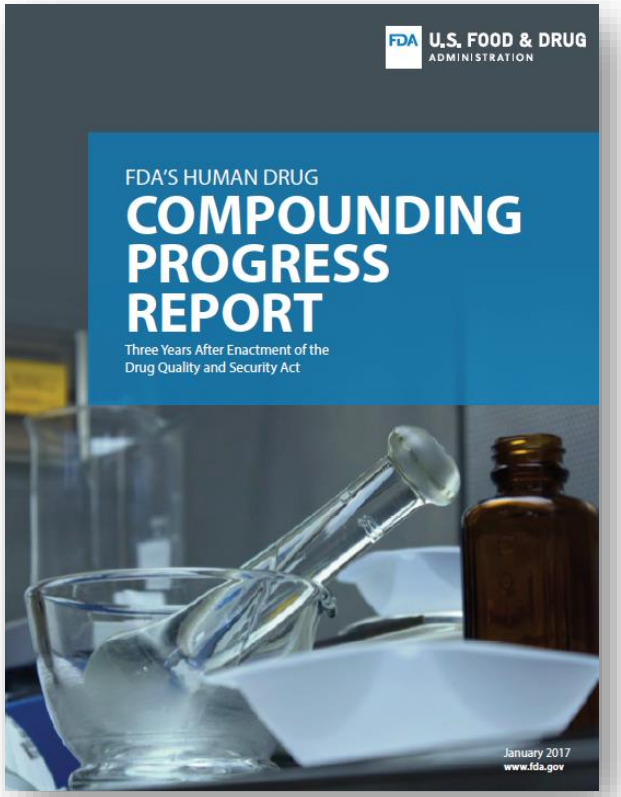


- FDA's Inspection Statistics for Section 503A and 503B Facilities
  - (Added Statistics up to March 1, 2017)
  - 403 Inspections
  - 285 are 503A Pharmacies
  - 114 are 503B Outsourcing Facilities
  - 1 Physician (and a second very recent one)
  - 3 Makers of Allergenic Extracts
  - Count does not include 6 testing laboratories
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM536549.pdf



Of the 400+ inspections

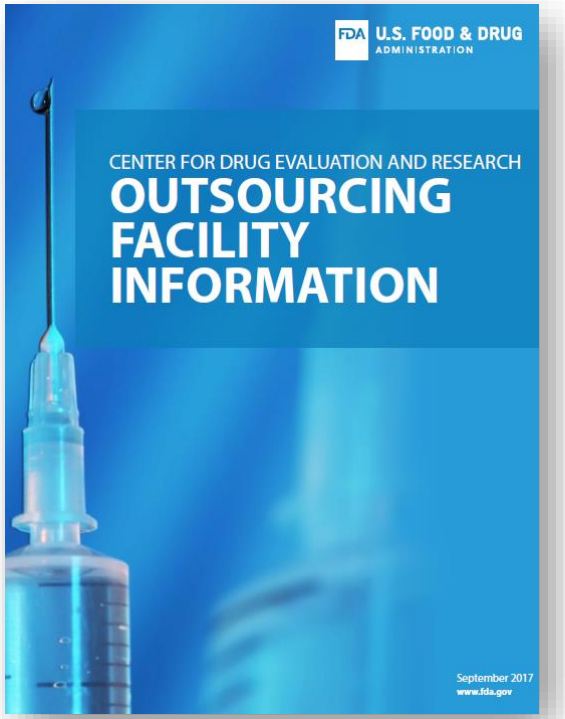
- 346 facilities in total
  - 20 non-sterile facilities
  - 272 Section 503As
  - 70 Section 503Bs
- 331 FDA investigators
  - 19.3 person years on 503A pharmacies
  - 10.4 person years on 503B facilities
- 42 facilities have dropped their 503B registration



Policy Developments

(as of November 27, 2016)

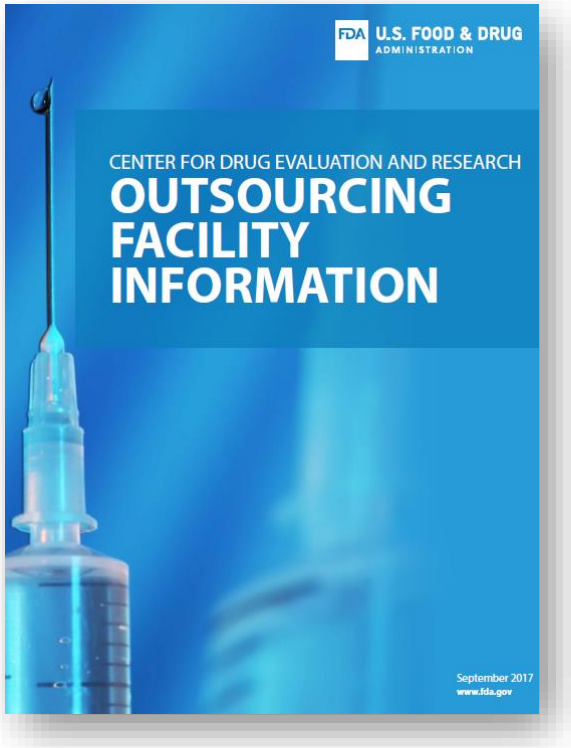
- 20 Draft Guidance
- 7 Final Guidance
- 2 Proposed Rules
- 1 Final Rule
- 1 Draft Memorandum of Understanding
- Re-Established Pharmacy Compounding Advisory Committee (PCAC)
- 4 Intergovernmental Working Meetings
- 4 Listening Sessions (Industry, Hospitals, Pharmacies, Advocates, Insurers…)



Released: September 2017

The following information is intended to assist outsourcing facilities in locating provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA policy and procedures that are relevant to their operations, *and to assist compounders in deciding whether to register with FDA as outsourcing facilities (emphasis added)*.

- 42 facilities have dropped their 503B registration
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM577334.pdf

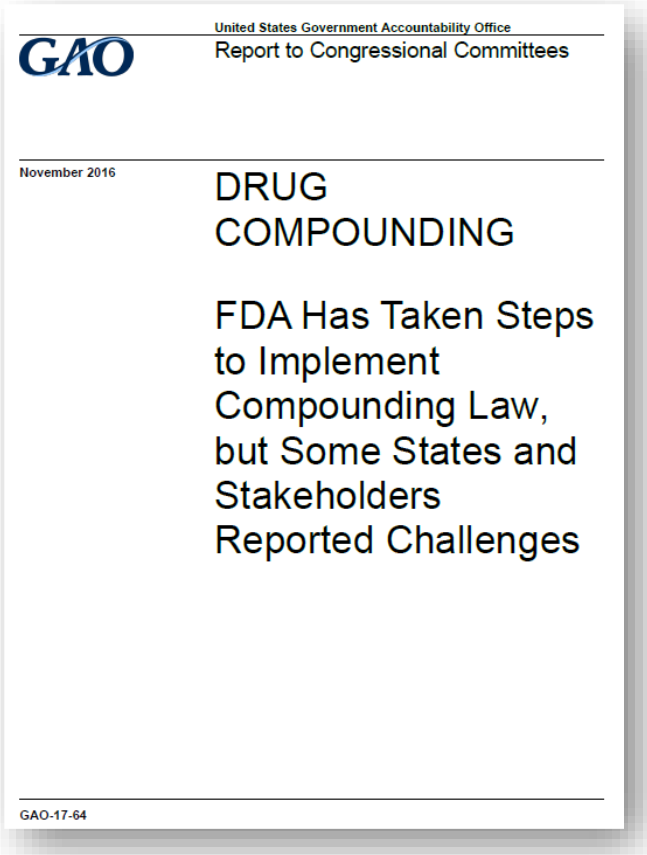


Of the 59 outsourcing facilities that FDA has inspected as of August 2017:

- **25** engage in both sterile and non-sterile compounding
- **24** engage in both patient-specific and non-patient specific compounding
- **22** compound a portion of their drugs in small batches

  (10 units or fewer)
- **45** compound drugs from bulk drug substances
- Outsourcing facilities are located in **25** states
- **51** ship compounded drugs in interstate commerce

- In a six-month period, outsourcing facilities that submitted drug product reports to FDA compounded 12,305,873 units of drugs.


United States Government Accountability Office

GAO

Report to Congressional Committees

November 2016

DRUG COMPOUNDING

FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges

GAO-17-64

- GAO Survey –Released: November 2016
  - Surveyed State Pharmacy Regulatory Bodies
  - Reviewed with FDA and 25 Stakeholder Organizations
  - 60% "Very or somewhat satisfied"
    - Understanding in a Transition Period
    - DQSA "seems" to be improving communication
  - 23% "Very or somewhat dissatisfied"
    - No real partnership between state and FDA
    - Lack of response from FDA (one way communication)
    - Long times for FDA to finalize guidances and regulations
    - Uncertainty regarding "office-use compounding" anticipatory need stocking
      - Guidance states that FDA intends to describe its policies regarding the documentation requirement in a future policy document
  - http://www.gao.gov/assets/690/681096.pdf

Top Observations for 503A Pharmacies

- FDA makes similar observations across pharmacy inspections:
  - Deficiencies in Environmental Monitoring program (59.6% – 170 occurrences)
  - Gowning of personnel engaged in compounding of sterile products inadequate (58.2% – 166 occurrences)
  - Room and Equipment cleaning, sanitization & disinfection deficiencies that frustrate preservation of aseptic conditions (53.3% – 152 occurrences)
  - No written stability program to assess the stability characteristics of drug products (41.1% – 117 occurrences)
  - Procedures designed to prevent microbial contamination of drug products purporting to be sterile are not established written and followed (37.5% – 107 occurrences)

Top Observations for 503B Facilities

- And, FDA makes similar observations across 503B inspections:
  - Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. (72 occurrences – 63.2 %)
  - Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed (66 occurrences– 57.9%)
  - Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions. (65 occurrences – 57%)
  - There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. (62 occurrences – 54.4%)
  - The labels of your outsourcing facility's drug products do not include the information required by section 503B(a)(10)(A)&(B). (62 occurrences – 53.5%)
  - Clothing of personnel engaged in the manufacturing, processing, packing, and holding of drug products is not appropriate for the duties they perform. (53 occurrences, 46.5%)

Subpart C – Buildings and Facilities – "Insanitary Conditions"

- Applies to both 503A and 503B Compounding Facilities
- Insanitary conditions are conditions that could cause a drug to become contaminated with filth or rendered injurious to health; the drug need not be actually contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act
  - Toaster ovens used for sterilization
  - Operators processing sterile drug products with exposed skin
  - Use of soap, tap water, and non-sterile disinfectants to clean and sanitize sterile compounding areas
  - Vermin (e.g., insects, rodents) observed in production areas or areas immediately adjacent to production.
  - Visible microbial contamination (e.g., bacteria, mold) in the production area.
  - Non-microbial contamination in the production area (e.g., rust, glass shavings, hairs).
  - Dog beds and hairs in close proximity to sterile compounding room
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

- Much of FDAs concerns with Compounders reflects historical compliance enforcement with Sterile Drug Manufacturers
- Industry Group Technical Publications
  - International Organization for Standardization (ISO)
    - ISO 14644: Cleanrooms
    - ISO 13408: Aseptic Processing
  - International Society of Pharmaceutical Engineers (ISPE)
    - Baseline Guide #3 “Sterile Product Manufacturing Facilities”
  - International Council for Harmonization (ICH)
    - ICH Q1: Stability
    - ICH Q2: Analytical Validation
    - ICH Q7: Good Manufacturing Practice
    - ICH Q9: Quality Risk Management
    - ICH Q10: Pharmaceutical Quality System

Parenteral Drug Association (PDA) – Technical Reports (TR)

- TR #1 – Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control (2007)
- TR #13 Fundamentals of an Environmental Monitoring Program (2014)
- TR #22 Process Simulation for Aseptically Filled Products (2011)
- TR #26 Sterilizing Filtration of Liquids (2008)
- TR #33 Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods (2013)
- TR #44 Quality Risk Management for Aseptic Processes (2008)
- TR #53 Guidance for Industry: Stability Testing to Support Distribution of New Drug Products (2011)
- TR #62 Recommended Practices for Manual Aseptic Processes (2013)
- TR #70 Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities (2015)
- Points to Consider for Aseptic Process in: Part 1 (2015)
- Points to Consider for Aseptic Process in: Part 2 (2016)

Why?

Commitment to protect Public Health

- A compounded morphine sulfate injectable drug product after laboratory results showed the product was superpotent by 2,460 percent.
- A compounded multivitamin capsules containing high amounts of Vitamin D3 (cholecalciferol), distributed nationwide by a compounder.
- A compounder recalled all purportedly sterile drugs within expiry and ceased sterile operations after 15 patients developed bacterial bloodstream infections, and two patients died, from an infusion of contaminated compounded calcium gluconate.
- 26 patients experienced adverse events, including skin abscesses, after receiving injections of methylprednisolone acetate that a compounder distributed to health care facilities in 17 states.