



Title I Implementation - Pharmacy Compounding in 2016

FDLI Presentation

Jane A. Axelrad

Associate Director for Policy, CDER
and Agency Lead on Compounding

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Overview

- Statutory framework
- Surveillance and enforcement
- Policy development
- Working with the states

Section 503A

- Describes conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring:
 - FDA approval prior to marketing (section 505)
 - Compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B)); and
 - Labeling with adequate directions for use (section 502(f)(1))
- Pharmacies that qualify for the exemptions are primarily regulated by the states, although some Federal requirements still apply (e.g., no insanitary conditions)

Compounding Quality Act of the Drug Quality and Security Act

- Removes certain provisions from section 503A related to solicitation of prescriptions and advertising and promotion that were found to be unconstitutional by the U.S. Supreme Court in 2002
- Clarifies that section 503A is applicable to compounders nationwide
- Adds new section 503B: “Outsourcing Facilities”

Section 503B

- Describes conditions under which certain human drug products compounded at a facility registered as an outsourcing facility are entitled to exemptions from certain sections of the FDCA, including those requiring:
 - FDA approval prior to marketing (section 505); and
 - Labeling with adequate directions for use (section 502(f)(1))
- Outsourcing facilities are not exempt from Current Good Manufacturing Practice (CGMP) requirements and will be inspected by FDA according to a risk-based schedule

Outsourcing Facilities

- Section 503B defines “outsourcing facility” as a facility that:
 - Is engaged in the compounding of STERILE drugs
 - Has elected to register as an outsourcing facility
 - Complies with all of the requirements in section 503B
- In addition, an outsourcing facility:
 - Is NOT required to be a licensed pharmacy, but compounding must be by or under the direct supervision of a licensed pharmacist
 - May or may not obtain prescriptions for identified individual patients

Inspections

- Since enactment of the DQSA, FDA has:
 - Conducted over 230 inspections of compounders including approximately 60 inspections of compounders registered as outsourcing facilities
 - Approximately 80 of these inspections have been for-cause, generally based on reports of serious adverse events or product quality issues such as drug contamination

Observations

- Dog beds, dog feces, and dog hairs in a compounding facility in close proximity to the compounding room
- Dead insects in ceilings
- Compounding of sterile drugs by personnel with exposed skin, which sheds particles and bacteria
- Coffee filters used to filter particulates
- Toaster ovens used for sterilization
- Kitchen dishwasher and detergent used to clean sterile compounding equipment and utensils
- Renovations conducted next to sterile compounding operations without taking precautions to prevent contamination of the sterile products.

Inspections and Resulting Actions

Since enactment of the DQSA, FDA has:

- Overseen over 85 recalls by compounders, and requested numerous compounders to cease operations
- Issued over 75 warning letters; one addressed violations identified at four facilities
- Issued 20 letters referring findings from inspections of pharmacies that compounded their drugs in accordance with the conditions of section 503A to the state

Enforcement Actions

- Obtained three civil consent decrees of permanent injunction:
 - Main Street Family Pharmacy, Newbern TN
 - Specialty Compounding LLC, Cedar Park TX
 - Downing Labs (formerly NuVision), Dallas TX

Enforcement Actions (cont'd)

- Several criminal prosecutions:
 - **Main Street Family Pharmacy LLC** (Newbern TN) and the company's co-owner pleaded guilty to a misdemeanor criminal violation of the FD&C Act (December, 2014)
 - In a 131-count criminal indictment the owner and head pharmacist of **NECC** (Framingham MA) and its supervisory pharmacist were charged with 25 acts of second-degree murder, among other criminal acts, and 12 others were charged with additional crimes, including FDCA violations. Trial set for April 2016
 - In a 37-count indictment **MedPrep Consulting** (Tinton NJ), its president and owner and its pharmacist-in-charge were charged with wire fraud and violations of the FDCA for introducing adulterated and misbranded drugs into interstate commerce with the intent to defraud and mislead the FDA and Med Prep's customers (February, 2015)
 - Former pharmacist and president and the former pharmacist in charge of **Meds IV** (Bessemer AL) pleaded guilty to two misdemeanor violations of the FD&C Act (January, 2016)

Guidances Issued Since DQSA

- Final Guidances:
 - Compounding under section 503A
 - Outsourcing facility fees
 - Registration of outsourcing facilities
 - Guidance for entities considering whether to register as outsourcing facilities
 - Adverse event reporting for outsourcing facilities
- Draft Guidances:
 - Interim CGMPs for outsourcing facilities
 - Draft and revised draft product reporting guidance for outsourcing facilities
 - Repackaging non-biologics
 - Mixing, diluting, and repackaging biologics
 - Interim policies on compounding using bulk drug substances under sections 503A and 503B (two separate draft guidances)
 - Animal drug compounding from bulk drug substances

Guidance for Entities Considering Whether to Register as Outsourcing Facilities

- If you register as an outsourcing facility, you are indicating your intent for ALL drugs compounded at the facility to be regulated under section 503B and not section 503A
- ALL drugs compounded at the facility must be compounded under CGMP requirements
- Must be engaged in compounding of some sterile drugs; cannot do ONLY non-sterile; compounded non-sterile drugs will qualify for the exemptions if compounded in an outsourcing facility in accordance with the provisions of section 503B

Draft Repackaging Guidance

- Repackaging not specifically addressed in 503A or 503B
- Guidance describes conditions under which FDA does not intend to take action for violations of sections 505 (approval), 502(f)(1) (labeling with adequate directions for use) and if not an outsourcing facility, 501(a)(2)(B) (CGMP) for repackaging that meets the conditions of the guidance
- Over 650 comments submitted on the draft, most concerned about implications for long-term care facilities
- Held a listening session in August with representatives of long-term care community and CMS, and working through all the comments

Mixing, Diluting, or Repackaging Biologics Draft Guidance

- Biologics not addressed in 503A or 503B
- Guidance describes conditions under which FDA does not intend to take action for violations of section 351 of the Public Health Service Act (premarket approval) and FD&C Act sections 502(f)(1) (labeling with adequate directions for use) and if not an outsourcing facility, 501(a)(2)(B) (CGMP) for mixing, diluting, and repackaging biologics that meets the conditions of the guidance
- Over 350 comments submitted, most concerning the short BUDs for repackaging biologics
- Working through all the comments

Other Work

- Issued draft standard Memorandum of Understanding (MOU) under 503A
- Issued proposed rule describing additions and modifications to the withdrawn or removed list (503A and 503B)
- Evaluating nominations for 503A and 503B bulks lists and for drugs that are difficult to compound under sections 503A and 503B
- Held three meetings of the Pharmacy Compounding Advisory Committee covering drugs proposed for the withdrawn or removed list, nominations for the 503A bulks list, and criteria for the difficult to compound list; another meeting is scheduled for March 8-9
- Conducted stakeholder listening sessions with numerous groups

Statutory Basis for MOU

- Section 503A: Unless the drug product is compounded in a state that has entered into an MOU with FDA, a pharmacist, pharmacy, or physician cannot distribute or cause to be distributed compounded drug products outside of the state in which they are compounded in quantities that exceed 5% of the total prescription orders dispensed or distributed by that pharmacy or physician

Statutory Basis for MOU (cont'd)

- The MOU must: address “the distribution of inordinate amounts of compounded drug products interstate” and provide “for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State”
- FDA directed to develop standard MOU in consultation with NABP
- Interstate distribution conditions do not apply to 503B outsourcing facilities

MOU History

- 1999 - FDA published a draft standard MOU for comment
- FDA received over 6,000 comments on the draft
- Because of the Supreme Court decision in 2002, MOU was never finalized
- When DQSA enacted, FDA began again to implement this condition of 503A

Why is interstate distribution a concern?

- State-licensed pharmacies primarily overseen by states
- Congress did not intend for compounders operating under the exemptions in section 503A to grow into conventional manufacturing operations making unapproved drugs and operating a substantial portion of their business interstate
- If a substantial proportion of a compounder's drugs are distributed outside of a State's borders, adequate regulation of those drugs can pose logistical, regulatory, and financial challenges to State regulators; can be difficult to investigate and address multi-state outbreaks
- If a poor performing pharmacy locates in a state with inadequate controls, patients in other states are at risk

How does the draft MOU address concerns?

- Draft MOU addresses how states will handle complaints about drugs compounded by pharmacies within their borders
- Law creates a baseline 5% limit on interstate distribution under 503A
- FDA has proposed a 30% upper limit (“inordinate amounts”) for pharmacies operating under 503A and located in a state that signs the MOU
- Outsourcing facilities operating under section 503B are not subject to volume restrictions on interstate distribution; this could mitigate access concerns associated with the 30% limit

MOU - Next Steps

- Comment period closed June 19, 2015; over 3,000 comments submitted
- We are evaluating all comments received and will prepare final standard MOU in consultation with NABP
- When we publish final standard MOU, we will provide a period of time for states to sign before we begin enforcing the 5% limit

Some Other Policy Issues Under Consideration

- Anticipatory compounding and compounding without a prescription for office use
- Compounding radiopharmaceuticals
- Definition of “facility” under section 503B
- Description of “under the direct supervision of a licensed pharmacist” under section 503B
- Prohibition on resale under section 503B

Office Use and the Section 503A Prescription Requirement

- Section 503A states that certain provisions of the FD&C Act “shall not apply to a drug product if the drug product is compounded for an identified individual patient **based on the receipt of a valid prescription order or a notation** (emphasis added), approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the patient” (section 503A(a))

Anticipatory Compounding

- Under section 503A, a drug product may be compounded “in limited quantities **before** (emphasis added) the receipt of a valid prescription order for such individual patient,” if the compounding is based on a history of the licensed pharmacist or physician receiving valid prescription orders for the compounding of the drug product, among other conditions (section 503A(a)(2)(A)).

503B Outsourcing Facilities

- Under section 503B, an outsourcing facility may, but is not required to, obtain prescriptions for identified individual patients for its compounded drug products.
- Outsourcing facilities are subject to CGMP requirements, FDA inspections according to a risk-based schedule, and other requirements that help to assure the quality of the drug products that they compound.

Why is the Rx Requirement Important?

- The prescription requirement is important:
 - to ensure that compounding by state-licensed pharmacies and physicians under section 503A is based on individual patient need, and to differentiate such compounding from conventional manufacturing; and
 - to differentiate compounding by pharmacists and physicians who are primarily subject to state regulation from compounding by outsourcing facilities, which are primarily subject to FDA regulation.

State Interactions

- Three intergovernmental meetings with representatives of the states since DQSA
- Summaries of the meetings and action items posted on the Web
- Robust communications with the states on specific cases
- Close coordination with NABP