Compounded Drugs and Lack of Premarket FDA-Approval

Sara Rothman, MPH
Senior Policy Advisor
Office of Unapproved Drugs and Labeling Compliance
FDA/CDER Office of Compliance

Compounding Background

- Compounded drugs can be important for patients whose medical needs cannot be met by an approved drug, such as for patients who:
  - Have an allergy to an ingredient of an approved drug
  - Cannot swallow a tablet or capsule and need a medicine in a liquid dosage form that is not otherwise available
- Compounded drugs are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing.
- Poorly compounded drugs can cause serious injury or death, and FDA has observed concerning conditions at compounding facilities during inspections.

Compounding Provisions of Federal Law

Section 503A Enacted 1997	Section 503B Enacted 2013
Conditions under which drug products compounded by a **licensed pharmacist in a State-licensed pharmacy or Federal facility**, or by a **licensed physician**, can qualify for exemptions from certain requirements of the FD&C Act: (1) New drug approval requirements (section 505), (2) Labeling with adequate directions for use (section 502(f)(1)), and (3) Current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B))	Conditions under which drug products compounded by or under the direct supervision of a licensed pharmacist in an **outsourcing facility** can qualify for exemptions from certain requirements of the FD&C Act: (1) New drug approval requirements (section 505), (2) Labeling with adequate directions for use (section 502(f)(1)), and (3) Drug supply chain security requirements (section 582). **Outsourcing facilities remain subject to CGMP requirements.**

Compounders under Section 503A

- State-licensed pharmacies (e.g., home infusion pharmacies), Federal facilities, physicians
- Number in the many thousands
- Generally do not register with FDA
- Pharmacies primarily overseen by the states
- Frequency and depth of state oversight of pharmacies varies from state to state
- Quality standards vary from state to state
- Compounding by physicians generally is not subject to routine oversight by any regulatory body

Outsourcing Facilities under Section 503B

- 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
- Outsourcing facilities are subject to CGMP requirements.
- Approximately 70 entities registered with FDA as outsourcing facilities

Compounded Drugs are not FDA-Approved

Examples of Requirements for Approved Drugs

- Manufacturers, packers, and distributors register their establishments and list their drug products with FDA
- Undergo premarket review for safety, effectiveness, and quality, including:
  - FDA review of application to ensure that the drug is safe and effective in its proposed use(s).
  - FDA review of labeling to ensure, e.g., appropriate warnings, adequate directions for use
  - Manufactured in a facility that is subject to premarket assessment, including site inspection
  - Quality standards and controls for ingredients and specific processes and facilities used to produce the bulk drug substance are assessed
    - Review of evidence to evaluate the safety of the bulk drug substance and any inactive ingredients used in the product
    - Evaluate proposed specifications for purity, potency, and other attributes of the bulk drug substance to ensure they are appropriate for its use in the drug product
    - Assess whether studies demonstrate the safety of impurities levels and stability of the bulk drug substance through the product's expiration date
- Manufacturers undergo routine post-market inspections on a risk-based schedule
- Specific adverse event reporting and field alert reporting requirements

Compounded Drugs are not FDA-Approved

Compounded Drugs

- No premarket inspection requirement before the compounder can begin producing and distributing drugs
- No premarket review of the quality standards, specifications, and controls for compounding, including for the use of bulk drug substances in compounding
- No premarket site inspection of the manufacturer of the bulk drug substance to verify manufacturing operations are under control
- No post-market inspections of the vast majority of compounders in the U.S., which typically do not register with FDA
  - But specific FDA inspection requirement for outsourcing facilities
- 503A compounders typically do not report adverse events to FDA
  - But specific adverse event reporting requirements for outsourcing facilities

Concerns associated with lack of premarket review

- Unknown safety and efficacy profile of a compounded drug product with attribute(s) that differ from those of an approved drug product.
- Unknown safety profile of inactive ingredients in a particular compounded formulation.
- The quality of the bulk drug substance used in compounding may not be appropriate for the drug product produced.
- The labeling of an unapproved drug product may omit warnings relevant to its use.
- Uncertainty about the characteristics and potential effects of a bulk drug substance that is not a component of an approved drug.

Value of this Research

- Inform FDA's compounding work, including evaluation of which active ingredients may be used in compounding by outsourcing facilities.
- Inform healthcare providers' prescribing decisions and patients' choices about "bioidentical" hormone therapy.
- Inform consumers, professional societies as well as other federal agencies