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SBIA CHRONICLES

APRIL 20TH, 2017

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Upcoming Events:

1. FDA Small Business Regulatory Education for Industry (REdI): Spring Conference May 9-10 - Attend online or in-person in Atlanta GA
2. FY 2017 Generic Drug Research Public Workshop - May 3rd at FDA White Oak Campus, Silver Spring, MD
3. Public workshop: Roadmap for Engaging with FDA's Center for Drug Evaluation and Research, May 12th at FDA's White Oak campus, Silver Spring, MD

Resources:

1. FDA's Human Drug Compounding Progress Report – January 2017
2. FDA's Human Drug Compounding Webpage
3. Compounding Regulatory Policy Information
4. Compounding and the FDA: Questions and Answers

The Complexities of Compounding

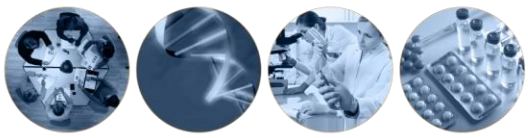
Just over three years ago, Congress amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) by enacting the Drug Quality and Security Act (DQSA). The first title of the DQSA, known as the Compounding Quality Act, was passed in response to numerous serious adverse events, including deaths, linked to poor quality compounded drugs. Since enactment of the DQSA, FDA has worked diligently to mitigate the public health risks associated with compounded drugs by conducting inspections and taking appropriate regulatory and enforcement actions, developing policies, convening advisory committee meetings, collaborating and coordinating with the states, and conducting stakeholder outreach. These efforts are detailed in FDA's Human Drug Compounding Progress Report, released in January 2017.

Compounding is often regarded as the process of combining, mixing, or altering ingredients to create a sterile or non-sterile medication customized to suit the needs of a patient. Compounded drugs can serve an important role when an FDA-approved drug is not medically appropriate to treat a patient, such as when a patient needs a medication to be made without a certain dye because of an allergy. However, compounded drugs are not FDA-approved, which means they have not been reviewed by FDA before they are marketed for safety, effectiveness, or quality. If a compounded drug does not meet appropriate quality standards (e.g., if an injectable drug is contaminated, or if a tablet contains too much active ingredient), it can cause serious injury or death.

FDA has investigated numerous serious adverse event reports associated with contaminated, super-potent, mislabeled, or otherwise poor quality compounded drugs. A fungal meningitis outbreak in 2012 was linked to contaminated compounded drugs that a pharmacy shipped to patients and healthcare providers in 20 states. More than 750 people were seriously harmed and more than 60 people died. Two provisions of the FD&C Act that address human drug compounding are discussed below:

Section 503A of the FD&C Act: Section 503A (signed into law November 21, 1997) describes the conditions that must be met for human drug products compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician, to qualify for exemptions from three sections of the FD&C Act:

- *Section 505 – concerning FDA approval prior to marketing,*
- *Section 501(a)(2)(B) – concerning current good manufacturing practice (CGMP) requirements, and*
- *Section 502(f)(1) – concerning labeling with adequate directions for use.*



CDER Small Business and Industry Assistance (SBIA)
Division of Drug Information | Office of Communications
10001 New Hampshire Avenue | Hillandale Bldg, 4th Floor | Silver Spring, MD 20993
(866) 405-5367 or (301) 796-6707
CDERSBIA@fda.hhs.gov
www.fda.gov/cdersbia

Pharmacies whose drugs qualify for the exemptions are primarily overseen by the states, although certain federal requirements apply to them. For example, the drugs remain subject to the federal prohibition on preparing, packing, or holding drugs under insanitary conditions whereby they may become contaminated with filth or rendered injurious to health (section 501(a)(2)(A) of the FD&C Act).

Section 503B of the FD&C Act: Under section 503B, a compounder can elect to register with FDA as an "outsourcing facility." Outsourcing facilities can compound drugs either pursuant to a patient-specific prescription or in response to an order from a health care provider, such as a hospital, without first obtaining patient-specific prescriptions. Drugs compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility that meet the conditions in section 503B are exempt from three requirements of the FD&C Act:

- *Section 505 – concerning FDA approval prior to marketing,*
- *Section 502(f)(1) – concerning labeling with adequate directions for use, and*
- *Section 582 – concerning drug supply chain security requirements*

If a compounder elects to register with FDA as an outsourcing facility, it is subject to CGMP requirements, inspection by FDA according to a risk-based schedule, and adverse event reporting requirements. Drug products compounded in an outsourcing facility must meet certain conditions in section 503B to qualify for the exemptions listed above. Drug products compounded by outsourcing facilities provide greater quality assurance than drugs compounded by entities that are not required to comply with CGMP requirements and are not routinely overseen by FDA. For this reason, FDA encourages entities and individuals to obtain compounded drugs from outsourcing facilities.

What FDA Has Been Doing: Between 2013 and 2016, FDA has significantly increased its regulatory oversight of compounders by:

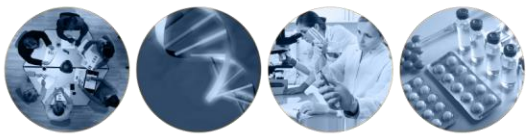
- Conducting more than 350 inspections,
- Issuing more than 130 warning letters advising compounders of significant violations of federal law,
- Issuing more than 30 letters referring inspectional findings to state regulatory agencies,
- Overseeing about 100 recalls involving compounded drugs, and
- Working with the Department of Justice on a number of civil and criminal enforcement actions.

Also between 2013 and 2016, FDA developed numerous policies, convened multiple advisory committee meetings, collaborated and coordinated with state regulators, and conducted stakeholder outreach by:

- Issuing 18 draft guidances, 7 final guidances, 2 proposed rules, a final rule, and a draft memorandum of understanding;
- Convening 6 advisory committee meetings to obtain advice on scientific, technical, and medical issues concerning drug compounding;
- Holding 4 intergovernmental working meetings with state regulators, inviting states to accompany FDA investigators on inspections, and having numerous 1:1 interactions;
- Holding 4 sets of listening sessions with more than 75 stakeholders including pharmacy, hospital, long-term care, and other medical organizations; and
- Obtaining input from stakeholders through a variety of different mechanisms.

Examples of recent policy documents include:

- *Final Guidance: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities* - Describes the conditions under which FDA does not intend to take action for certain violations when a state-licensed pharmacy, federal facility, or outsourcing facility repackages certain drug products.



- *Revised Draft Guidance: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* - Proposes policy regarding the conditions under which FDA does not intend to take action for certain violations when certain biological products are mixed, diluted, or repackaged in a manner not described in their approved labeling.

- *Final Guidance: Prescription Requirement Under Section 503A of the FD&C Act* - Addresses the prescription requirement in section 503A, including FDA's policies regarding compounding after the receipt of a prescription for an identified individual patient, compounding before the receipt of such a prescription, and compounding for office use.

- *Draft Guidance: Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities* - Proposes the policy regarding the conditions under which FDA does not intend to take action for violations of the FD&C Act related to new drug approval requirements, labeling with adequate directions for use, and compliance with CGMP requirements when a state-licensed nuclear pharmacy or federal facility that is not an outsourcing facility compounds or repackages radiopharmaceuticals for human use.

- *Draft Guidance: Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities* - Proposes how FDA would apply the conditions of section 503B to radiopharmaceuticals compounded by outsourcing facilities, and proposes FDA policy regarding the conditions under which the agency does not intend to take action for violations of the FD&C Act regarding new drug approval requirements and labeling with adequate directions for use when an outsourcing facility repackages radiopharmaceuticals.

- *Proposed Rule, List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the FD&C Act* - Addresses six bulk drug substances that FDA has considered and is proposing for inclusion on a list of bulk drug substances that can be used in compounding under section 503A of the FDCA, and proposes that four other bulk drug substances that the agency considered not be included on this list.

What's Next? FDA's efforts have significantly impacted public health, as evidenced by corrective actions implemented by compounders and voluntary recalls of potentially contaminated or poor quality drugs. Policy documents and outreach have helped FDA clarify applicable regulatory requirements. Though progress is being made, there is still a lot of work to be done. Serious adverse events and product quality defects associated with compounded drugs continue to be reported. Follow-up inspections still show that many compounders are failing to comply with applicable requirements of the law.

FDA will continue to oversee drug compounders and will take regulatory action when appropriate to continue to protect public health. The agency is committed to building on its progress to protect patients and will continue to inspect and enforce the law against compounders, develop policy, hold advisory committee meetings, collaborate and coordinate with states, and communicate with stakeholders.

Cheers,
Renu Lal, Pharm.D.
CDER Small Business and Industry Assistance

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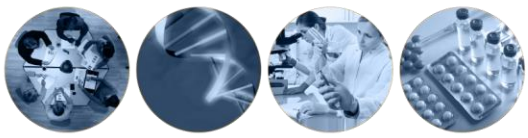

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