Compounding Regulatory Policy Update

Inter-governmental Working Meeting on Drug Compounding September 20, 2016

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Overview

- Overview of sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Summary of draft and final policy documents issued since our last Intergovernmental Working Meeting in November 2015
- Update on draft policy documents issued before our last meeting

Section 503A

- Describes conditions under which certain compounded human drug products qualify for exemptions from three sections of the FD&C Act 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))
- Although pharmacies whose drugs qualify for the exemptions are primarily regulated by the states, some Federal requirements still apply (e.g., no insanitary conditions)

Compounding Quality Act of the Drug Quality and Security Act

- Removed 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
- Clarified that section 503A is applicable to compounders nationwide
- Added new section 503B: “Outsourcing Facilities”

Section 503B

- Describes conditions under which certain human drug products compounded by or under the direct supervision of a licensed pharmacist at a facility registered as an outsourcing facility qualify for exemptions from certain sections of the FDCA requiring:
  - FDA approval prior to marketing (section 505); and
  - Labeling with adequate directions for use (section 502(f)(1))
  - Compliance with drug supply chain security provisions (section 582)
- Drugs compounded by outsourcing facilities are not exempt from CGMP requirements, and outsourcing facilities are 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

Draft Guidance – Insanitary Conditions

- Issued in August 2016
- Comment period closes October 3, 2016
- Describes examples of conditions that FDA considers to be “insanitary conditions” within the meaning of section 501(a)(2)(A) of the FD&C Act
- To be discussed in further detail during tomorrow’s session on quality standards and insanitary conditions.

Draft Guidance – Prescription Requirement

- Issued in April 2016
- Explains the requirement in section 503A that compounding under this section be based on the receipt of a valid prescription for an identified individual patient.
- Approximately 100 comments submitted
- To be discussed in further detail during this afternoon's session on the prescription requirement

Draft Guidance – Hospital and Health System Compounding

- Issued in April 2016
- Describes how FDA proposes to apply section 503A of the FD&C Act to drugs compounded by licensed pharmacists or physicians in state-licensed hospital or health system pharmacies for use within the hospital or health system.
- 75 comments submitted
  - Concerns that proposed policies would not be flexible enough to accommodate hospital/health system compounding needs
  - Concerns that proposed policies would result in disparate treatment of hospital pharmacies and stand-alone pharmacies
  - Some comments supportive of proposed policies

Draft Guidance – Hospital and Health System Compounding

- All of the conditions of section 503A, including the prescription requirement, apply to drugs compounded by hospital and health system pharmacies (that are not registered as outsourcing facilities).

Draft Guidance – Hospital and Health System Compounding

Draft guidance proposes the following policy:

> FDA does not intend to take action if a hospital pharmacy distributes compounded drug products without first receiving a patient-specific prescription or order provided that:
>
> - (1) The drug products are distributed only to healthcare facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located within a 1 mile radius of the compounding pharmacy;
> - (2) The drug products are only administered within the healthcare facilities to patients within the healthcare facilities, pursuant to a patient-specific prescription or order; and
> - (3) The drug products are compounded in accordance with all other provisions of section 503A, and any other applicable requirements of the FD&C Act and FDA regulations (e.g., drugs are not under insanitary conditions (section 501(a)(2)(A)) or misbranded (e.g., section 502(g))

Draft Guidance – Hospital and Health System Compounding

- Certain characteristics differentiate them from stand-alone pharmacies and from conventional manufacturers
  - Proposed policy would apply to drugs distributed only to hospitals or healthcare facilities under common ownership and control and located within close proximity
  - Administered only to patients within the healthcare facility
  - Health care facility responsible for both compounding and treatment
  - Cause of compounding-related adverse events more readily identified
- However, a health system pharmacy that compounds drugs without patient-specific prescriptions and distributes them over a broader geographic area could function like a conventional manufacturer, but without the necessary conditions to ensure drug quality.
- Health system pharmacy could elect to register as an outsourcing facility.

Draft Guidance – Facility Definition Under Section 503B

- Issued in April 2016
- "Section 503B defines an outsourcing facility, in part, as 'a facility at one geographic location or address.' FDA has received questions from outsourcing facilities and other stakeholders about the meaning of this term, such as whether multiple suites used for compounding human drugs at a single street address constitute one or multiple facilities, or whether a single location where human drugs are compounded can be subdivided into separate operations compounding under different standards. FDA is issuing this guidance to answer these questions."
- 25 comments submitted
  - Concerns that proposed policy could discourage outsourcing facility registration
  - Questions about "close proximity"
  - Support for proposed policies

Draft Guidance – Facility Definition Under Section 503B

- Draft guidance states:
  - "A facility at one geographic location or address" means a business or other entity under one management, direct or indirect, engaged in human drug compounding at a geographic location or street address.
  - The agency considers all activities, equipment, appurtenances, and materials part of such a facility if they are related to human drug compounding under the supervision of the facility's management at the same street address, or in the same building, or in buildings in close proximity to each other.

Draft Guidance – Facility Definition Under Section 503B

As background, FDA's final guidance for entities considering whether to register as outsourcing facilities explains that:

- If you register a facility as an outsourcing facility, you are indicating your intent for the facility's compounded drugs to be regulated under section 503B of the FD&C Act. Under section 503B(a)(11), a compounded drug can only qualify for the exemptions from sections 502(f)(1), 505, and 582 of the FD&C Act if ***all*** of the facility's compounded drugs are compounded in accordance with section 503B.

- By registering as an outsourcing facility, an entity is electing to have its compounded drugs regulated under section 503B of the FD&C Act, not section 503A. Drugs compounded in an outsourcing facility are not eligible for the exemptions provided in section 503A, even if the conditions in that section are met with respect to a particular drug.

Draft Guidance – Facility Definition Under Section 503B

Proposed policies intended to address:

- Commingling of drugs compounded under sections 503A and 503B
  - CGMP requirements for drugs compounded under section 503B
  - Prescription requirement for drugs compounded under section 503A
- Clarity for purchasers of compounded drugs
- Inspections
- Best interest for public health for patient-specific and non-patient specific compounded drugs to be made in accordance with section 503B and CGMP requirements

Draft Guidance – Facility Definition Under Section 503B

- If a conventional manufacturer registers as an outsourcing facility, the compounded drugs must meet the conditions of section 503B
- All drugs must be made in accordance with CGMP requirements
  - Compounded drugs eligible for the policy in interim CGMP guidance
  - Conventionally manufactured drugs are not
  - For CGMP requirements that cannot be applied differently to different types of drugs, the facility must comply with the higher standard (i.e., not the interim guidance)

"Essentially a Copy" Provisions of Sections 503A and 503B

- Sections 503A and 503B of the FD&C Act contain conditions concerning compounding drugs that are "essentially" copies of "commercially available" drug products (section 503A) or "approved" drugs (section 503B).
  - Compounding copies restricted under section 503A
  - Compounding copies prohibited under section 503B

"Essentially a Copy" Provision of Section 503A

- For a drug to be eligible for the exemptions under section 503A, it must be compounded by a licensed pharmacist or licensed physician that "does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product" (section 503A(b)(1)(D)).

- "The term 'essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug" (section 503A(b)(2)).

What does the draft section 503A "essentially a copy" guidance do?

- Explains FDA's proposed policies concerning:
  - "Commercially available"
  - "Essentially a copy of a commercially available drug product"
  - "Significant difference" determination
  - "Regularly or in inordinate amounts"

Proposed Policy - "Commercially Available" under Section 503A

- Includes marketed drug products
- Does not include:
  - Drugs that have been discontinued and are no longer marketed (see "Orange Book" on FDA's website)
  - Drugs on FDA's drug shortage list

Proposed Policy - "Essentially a Copy" under Section 503A

- Characteristics of a drug that is "essentially a copy" of a commercially available drug product:
  - Same active pharmaceutical ingredient(s) (API)
  - API(s) have same, similar, or easily substitutable dosage strength
  - Commercially available drug product can be used by the same route of administration as prescribed for the compounded drug

Proposed Policy - "Significant Difference" under Section 503A

- A compounded drug is not "essentially a copy of a commercially available drug" if a prescriber determines that there is a change, made for an identified individual patient, which produces for that patient a significant difference from the commercially available drug product.
- Examples:
  - "No Dye X, patient allergy" (if the comparable drug contains the dye)
  - "Liquid form, patient can't swallow tablet" (if the comparable drug is a tablet)
  - "6 mg, patient needs higher dose" (if the comparable drug is only available in 5 mg dose)

Proposed policy - “Regularly or in Inordinate Amounts”

- Proposed policy: four or fewer prescriptions for the compounded drug that is essentially a copy of a commercially available drug per calendar month
- Examples of factors to be considered:
  - Compounded drugs that are essentially copies represent more than a small percentage or small number of the prescriptions that the compounder fills
  - Routine substitution of compounded drugs that are essentially copies
  - Pre-printed prescription pads used to write a prescription for a drug that is essentially a copy
  - Compounding copies on a routine or pre-set schedule

"Essentially a Copy" Provision of Section 503B

- Compounded drug must not be "essentially a copy of one or more approved drugs"

- "Essentially a copy of an approved drug" means:
  - "A) a drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under section 506E at the time of compound, distribution, and dispensing; or
  - (B) a drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and is not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug."

Scope of this Provision of Section 503B

- "Copies" provision applies to:
  - "Marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505"
    - Unapproved non-prescription drug products ("covered OTC drug products")
  - Approved prescription and non-prescription drugs

Proposed Policy - "Essentially a Copy of an Approved Drug" Under Section 503B – Subsection (A)

- "Identical or nearly identical" – compounded drug and the approved or covered OTC drug have the same:
  - API(s)
  - Route of administration
  - Dosage form
  - Dosage strength, and
  - Excipients
- Policy for drugs that were in shortage within 60 days of distribution or dispensing

Proposed Policy - "Essentially a Copy of an Approved Drug" under Section 503B – Subsection (B)

- Drug is essentially a copy if
  - A component of the compounded drug is a bulk drug substance that is a component of an approved drug or a covered OTC drug, unless
  - there is a change between the compounded drug and the comparable approved drug that produces a clinical difference, as determined by the prescribing practitioner, for an individual patient.

"Essentially a Copy of an Approved Drug" under Section 503B – Summary of Proposed Policy

- If a compounded drug is identical or nearly identical to an approved drug on FDA's drug shortage list, it is not essentially a copy under section 503B.

- If a compounded drug is identical or nearly identical to an approved drug that is not on FDA's shortage list, or to a covered OTC drug, it is essentially a copy and cannot qualify for the exemptions under section 503B.

- If a compounded drug is not identical or nearly identical to an approved drug or to a covered OTC drug, but a component of the compounded drug is a bulk drug substance that is also a component of an approved or covered OTC drug, it is essentially a copy under section 503B *unless* a prescriber has determined that there is a change between the compounded drug and the comparable approved drug that produces a clinical difference for an individual patient.

Final Guidance – Interim 503B Bulks Policy

Under section 503A, bulk drug substances used in compounding must be:

- Subject of an applicable USP or NF monograph; or if not,
- Components of FDA-approved drugs; or if not,
- **On FDA list of bulk drug substances for use in compounding under section 503A ("503A bulks list").**

FDA's interim policy:

- Until a bulk drug substance has been considered and dealt with in a final rule as being included or not included on the 503A bulks list, FDA does not intend to take action against a compounder that is compounding with a bulk drug substance that is not a component of an FDA-approved drug or the subject of an applicable USP or NF monograph, and that was nominated with sufficient supporting information for FDA to evaluate it, and that has not been identified by FDA as a substance that appears to present significant safety risks, provided that several conditions are met.

Final Guidance – Interim 503B Bulks Policy

Bulk drug substances used in compounding under section 503B must:

- Be used to compound a drug that appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing; or
- **Appear on a list developed by FDA of bulk drug substances for which there is a clinical need ("503B bulks list).**

FDA's interim policy:

- Until the substance has been considered and dealt with in a *Federal Register* notice (after soliciting and evaluating public comments on the substance) as being included or not included on the 503B bulks list, FDA does not intend to take action against an outsourcing facility that is compounding with bulk drug substances nominated with sufficient supporting information for FDA to evaluate them and that have not been identified by FDA as a substance that appears to present significant safety risks, provided that several conditions are met.

Status Update - Regulations

- Final Rule: *Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness*
  - Add substances to the list of drugs that cannot be compounded under sections 503A or 503B because they have been withdrawn or removed from the market for reasons of safety or effectiveness ("withdrawn or removed list")
- Proposed Rule: *Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness*
  - Propose to add additional substances to the withdrawn or removed list
- Proposed Rule: *List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act*
  - Propose to add or not add certain nominated substances to the list of bulk drug substances that can be used in compounding under section 503A

Status Update – Draft Guidances and MOU

- Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert STATE] and the U.S. Food and Drug Administration
- Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug and Cosmetic Act
- Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
- Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application
- Electronic Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Inter-governmental Working Meeting on Pharmacy Compounding

U.S. Food and Drug Administration
Silver Spring, Maryland

September 20-21, 2016