Update on Recent FDA Actions and Guidance Documents

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

Policy Documents

- Revised Draft FDA-State Memorandum of Understanding
- Compounded drugs that are essentially copies of:
  - Commercially available drugs (section 503A)
  - Approved drugs (section 503B)
- Adverse event reporting by outsourcing facilities
- Compounded drug product labeling

Revised Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Drugs Under Section 503A

Statutory Framework

Under section 503A(b)(3)(B), a compounded drug may be eligible for the exemptions only if it is compounded in a State—

- (i) that has entered into an MOU with FDA which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or
- (ii) that has not entered into the MOU and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5% of the total prescription orders dispensed or distributed by such pharmacy or physician.

Provisions of Revised Draft MOU: Complaints

- With regard to complaints associated with drugs compounded by a pharmacist that are found to be valid, states would agree to:
  - investigate complaints about compounded drugs made in the state and distributed out of state
    - Complaints to be investigated include adverse drug experiences and product quality issues
    - Investigations include taking steps to assess whether there is a public health risk and whether that risk has been adequately contained

Provisions of Revised Draft MOU: Complaints (cont'd)

- With regard to complaints associated with drugs compounded by a pharmacist, states would agree to:
  - Take action in accordance with state law that the state considers to be appropriate and warranted to ensure that the compounding pharmacy investigates root cause and undertakes sufficient corrective action
  - Notify FDA within 3 business days of complaint if involves serious adverse drug experience or serious product quality issue
  - After notification, share with FDA the results of investigation conducted
  - Maintain records

Provisions of Revised Draft MOU: Complaints (cont'd)

- With regard to complaints associated with drugs compounded by a physician, states would agree to:
  - Notify appropriate regulator of physician compounding in the state
  - If complaint involves serious adverse drug experience or serious product quality issue, notify FDA within 3 business days
  - Maintain records

Provisions of Revised Draft MOU: Inordinate Amounts

- Inordinate amount: If number of prescription orders for compounded drug products distributed interstate by a compounder during any calendar month is **> 50%** of the number of prescription orders for compounded drug products distributed or dispensed both intrastate and interstate by the compounder during that month.

Provisions of Revised Draft MOU: Inordinate Amounts (cont'd)

- States that sign the MOU would agree to:
  - With respect to pharmacies, on annual basis: identify (using surveys, reviews of records during inspections, or other available mechanisms) pharmacies that distribute inordinate amounts
  - With respect to physicians: if the state becomes aware of physician distribution of compounded drugs interstate, coordinate with state regulator of physician compounding to determine whether inordinate amounts distributed interstate

Provisions of Revised Draft MOU: Inordinate Amounts (cont'd)

- States that sign the MOU would agree to:
  - If pharmacy or physician identified as distributing inordinate amounts, State will collect information regarding:
    - Total number of prescriptions for sterile compounded drugs distributed out of state
    - Total number of states in which the compounder is licensed or into which it distributes compounded drugs
    - Whether the state inspected for and found during most recent inspection that the compounder distributed without patient-specific prescriptions
  - Notify FDA within 30 days of this information

Revised Draft MOU: “Distribution”

- *“Distribution* means that a compounder has sent a drug product out of the facility in which the drug was compounded. Such distribution may include, but is not limited to, delivery or shipment to a physician’s office, hospital, or other health care setting for administration, and dispensing the drug product by sending it to a patient for the patient’s own use.”

- “Note: To qualify for the exemptions under section 503A, a compounder must obtain a prescription for an individually identified patient (section 503A(a) of the FD&C Act). This MOU will not alter this condition.”

Revised Draft MOU: “Distribution”

- NOA accompanying the revised draft MOU explains:
  - “[W]e have proposed to revise the definition of distribution to exclude dispensing that occurs at the facility in which the drug was compounded. We intend to consider that when a drug is picked up in this way, dispensing, but not distribution, occurs for purposes of calculating “inordinate amounts” under the MOU or applying the 5 percent limit in section 503A(b)(3)(B)(ii).”

Compounded Drugs that Are Essentially Copies of a Commercially Available Drug Product under Section 503A

Essentially a Copy under Section 503A

- To qualify for the exemptions under section 503A, a drug product must be compounded by a compounder 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.”
- A compounded drug product is not essentially a copy of a commercially available drug product if “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 product.”

“Commercially available” and “Essentially a copy”

- For purposes of FDA’s final guidance, a drug is “**commercially available**” if it is a marketed drug product. A drug is not commercially available if it has been discontinued or if it is on FDA’s drug shortage list.
- FDA generally intends to consider a compounded drug to be “**essentially a copy**” of a commercially available drug product if:
  - It has the same active pharmaceutical ingredient(s) (API) as a commercially available drug product;
  - the API(s) have the same, similar (within 10%), or an easily substitutable dosage strength; and
  - the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug.
- *Unless* 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.

Documentation of a prescriber's determination of significant difference

- If a compounder intends to rely on a prescriber's determination of significant difference (as described in the previous slide) to establish that a compounded drug is not essentially a copy of a commercially available drug product, the compounder should ensure that the determination is documented on the prescription.
- There is no particular format needed for this documentation, provided it makes clear that the prescriber identified the change and significant difference for the patient. For example:
  - "No Dye X, patient allergy"
  - "Liquid form, patient can't swallow tablet"
  - "6 mg, patient needs higher dose"
- However, if a prescription identifies only a patient name and drug product formulation, this would not be sufficient to establish that the prescriber made a determination 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.

Documentation of a prescriber's determination of significant difference

- The guidance also provides that the significant benefit that the prescriber identifies must be produced by the change the compounder will make to a commercially available drug product (i.e., a change in drug product formulation).
  - Other factors, such as a lower price, are not sufficient to establish that the compounded drug product is not essentially a copy of the commercially available drug product.
- If a prescription does not make clear that the prescriber made the determination, a compounder can call the prescriber to confirm that such a determination has been made, and make a note of this on the prescription.

“Regularly or in inordinate amounts”

- A drug product is not eligible for the exemptions in section 503A if it is prepared by a pharmacist or physician who compounds “**regularly or in inordinate amounts**” any drug products that are essentially copies of a commercially available drug product.
- FDA’s guidance describes examples of factors that may indicate that a compounded drug that is essentially a copy has been compounded regularly or in inordinate amounts.
- To focus enforcement on the most significant cases, FDA does not intend to take action if the compounder fills **four or fewer prescriptions per month** of the relevant compounded drug product in a calendar month.
- Note that if the prescriber has determined that there is a change between the compounded drug and the commercially available drug that produces a significant difference for an identified individual patient, the compounded drug is not essentially a copy, and the “regularly or in inordinate amounts” provision does not apply.

Compounded Drugs that Are Essentially Copies of Approved Drug Products under Section 503B

Essentially a Copy under Section 503B

- To qualify for the exemptions under section 503B, the drug must not be essentially a copy of one or more approved drugs.
- A compounded drug is essentially a copy if:
  - It is **identical or nearly identical** to a marketed unapproved OTC drug or an approved drug that is not on FDA's drug shortage list at the time of compounding, distribution, and dispensing; or
  - It is not identical or nearly identical, but it **contains a bulk drug substance that is a component of an approved drug** or a marketed unapproved OTC drug, unless—
    - a prescriber determines that there is a change between the compounded drug and the comparable approved drug that produces a clinical difference for an individual patient.

“Identical or nearly identical”

- FDA generally intends to consider a compounded drug to be “**identical or nearly identical**” to an approved drug or marketed unapproved OTC drug if the compounded drug and the approved drug have the same active ingredient(s), route of administration, dosage form, dosage strength, and excipients.
- However if a compounded drug is identical or nearly identical to an approved drug, and the approved drug is on FDA’s drug shortage list at the time of compounding, distribution, and dispensing, the compounded drug is *not* essentially a copy and can be compounded if all of the other conditions of section 503B are met.

Contains a bulk drug substance that is a component of an approved drug

- If a compounded drug is **not identical or nearly identical** to an approved drug or to a marketed unapproved OTC drug, **but it contains the same bulk drug substance** as an approved drug or marketed unapproved OTC drug, the drug can only be compounded under section 503B if 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 (and all other conditions of section 503B are met).

Documentation of a prescriber's determination of clinical difference

- If an outsourcing facility intends to rely on a prescriber's determination of clinical difference (as described in the previous slide) to establish that a compounded drug is not essentially a copy of an approved drug, the compounder should ensure that the determination is documented on the prescription or order.
- Guidance describes policies concerning the content and format of the documentation of the prescriber's determination of clinical difference.
- Policy recognizes that outsourcing facilities may receive orders for drugs to be maintained in healthcare facilities for office stock, before knowing the identity of the patients who will receive the drugs, and not patient-specific prescriptions.
- In such cases, the outsourcing facility should obtain a statement from the practitioner that specifies the change between the compounded drug and the comparable approved drug and indicates that the compounded drug will be administered or dispensed only to a patient for whom the change produces a clinical difference, as determined by the prescribing practitioner for that patient. Such assurances should be provided by the health care practitioner or a person able to make the representation for the health care practitioner.

Adverse Event Reporting for Outsourcing Facilities under Section 503B

Statutory Framework

Section 503B(b)(5): “Outsourcing facilities shall submit adverse event reports to the Secretary in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations).”

Adverse Event Reporting by Outsourcing Facilities

- Final guidance: Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Oct. 2015)

- Compliance with 21 C.F.R. 310.305

Adverse Event Reporting by Outsourcing Facilities

Regulations at 21 CFR 310.305 require reporting of serious and unexpected adverse events

- Serious
  - Death
  - Life-threatening adverse drug experience
  - Inpatient hospitalization or prolongation of existing hospitalization
  - Persistent or significant disability/incapacity, or
  - Congenital anomaly/birth defect
- Unexpected
  - Any adverse drug experience that is not listed in the current labeling for the drug product

Adverse Event Reporting by Outsourcing Facilities

Regulations at 21 CFR 310.305 require:

- Reporting within 15 calendar days including copy of current labeling
- Follow-up reporting within 15 calendar days of receipt of new information or as requested by FDA

Adverse Event Reporting by Outsourcing Facilities

- Threshold for reporting:
  - When the outsourcing facility has information on at least the suspect drug and the adverse event.
- How to report:
  - Safety Reporting Portal, or
  - Electronic Submissions Gateway

Labeling

- Outsourcing facility labeling for drug to qualify for 503B exemptions: section 503B(a)(10), such as--
  - Statement “This is a compounded drug”
  - Statement “Not for resale”
  - Expiration date
  - Dosage form and strength

- Strength conventions described in USP <7>; see also April 2013 draft guidance titled “Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Labeling

FDA Compounding Risk Alert: FDA investigates two serious adverse events associated with ImprimisRx's compounded curcumin emulsion product for injection

"[B]oth patients reportedly had a history of allergies, reacted adversely within minutes of receiving infusions of curcumin [containing polyethylene glycol-40 (PEG-40) castor oil], and manifested signs and symptoms of hypersensitivity reactions. This suggests that both patients suffered from severe, and for one patient fatal, immediate hypersensitivity reactions upon receiving the infusion of curcumin. Drug products, including FDA-approved products, containing polyethylene glycol castor oil have been associated with severe and sometimes fatal hypersensitivity reactions and include warnings about these reactions in their labels. . . . The risks illustrated in this case include: the absence of a label warning about hypersensitivity reactions associated with the PEG 40 castor oil. . . ."