Compounding Policy Updates

Compounding Quality Center of Excellence
Virtual Conference: Culture of Quality

September 14, 2021

Tracy Rupp, PharmD, BCPS, MPH, RD
CDER OC Office of Compounding Quality and Compliance
Overview

• Final Standard Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the [insert STATE BOARD OF PHARMACY or OTHER APPROPRIATE STATE AGENCY] and the U.S. Food and Drug Administration (October 2020)

• Insanitary Conditions at Compounding Facilities, Guidance for Industry (November 2020)

• List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act (March 2021)
Final Standard Memorandum of Understanding (MOU)
Final Standard MOU: Current Status

- Notice announcing availability of the final standard MOU for States to consider and sign published in the Federal Register on 10/27/20
- FDA posted MOU information and Q&A webpages
- 2 State agencies have signed the MOU
- FDA providing a two-year period before it intends to enforce the 5% statutory limit on distribution of compounded drugs out of state for compounders located in States that have not signed the MOU, which will end on October 27, 2022
MOU: Statutory Framework

- Section 503A of the Federal Food, Drug, and Cosmetic Act establishes conditions for drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility or a licensed physician to qualify for exemptions from three provisions of the FD&C Act:
  - New drug approval requirements (section 505)
  - Labeling with adequate directions for use (section 502(f)(1))
  - Current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B))

- One such condition is that a compounding must obtain a prescription for an individually identified patient (section 503A(a) of the FD&C Act).
  - The MOU does not alter this or other conditions.
Under section 503A(b)(3)(B), a compounded drug product may be eligible for the exemptions only if it is compounded in a State:

1. 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

2. That has not entered into an 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.

Section 503A directs FDA to develop, in consultation with the National Association of Boards of Pharmacy (NABP), a standard MOU for use by the States in complying with section 503A(b)(3)(B)(i).
Why is the MOU Important?

• Compounders operating under section 503A are mainly overseen by their home State regulator

• Congress did not intend for compounders operating under section 503A to grow into conventional manufacturing operations conducting a substantial portion of their business interstate without adequate oversight

• 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; it can be difficult to investigate and address multi-state outbreaks
Key MOU Provisions

Interstate distribution of compounded drugs

• State signatories agree to:
  • Identify and report to FDA, pharmacy distribution of inordinate amounts (greater than 50%) of compounded drugs interstate.
  • Report to FDA and the appropriate regulator of physicians within the State, any physician distribution of compounded drugs interstate, if state entity becomes aware.

Complaints regarding adverse events or product quality issues related to drugs compounded within the state and distributed outside the state

• State signatories agree to:
  • Investigate complaints when drug is compounded by a pharmacy, and report to FDA when serious. Provides flexibility in how States investigate.
  • Report to FDA, and the appropriate regulator of physicians within the State, such complaints received about drugs compounded by a physician.
Inordinate Amounts Calculation

<table>
<thead>
<tr>
<th>Inordinate Amount: 50% Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{A}{B} = X$</td>
</tr>
</tbody>
</table>

- $A =$ Number of prescription orders for compounded human drug products that the pharmacy distributed interstate during any calendar year.
- $B =$ The sum of the number of prescription orders for compounded human drug products (i) that the pharmacy sent out of (or caused to be sent out of) the facility in which the drug products were compounded during that same calendar year; plus (ii) the number of prescription orders for compounded human drug products that were dispensed (e.g., picked up by a patient) at the facility in which they were compounded during that same calendar year.

If $X$ is greater than 0.5, it is an inordinate amount and is a threshold for certain information identification and reporting under the MOU.
Final Standard MOU: Useful Links

- Final Standard “Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the [insert STATE BOARD OF PHARMACY or OTHER APPROPRIATE STATE AGENCY] and the U.S. Food and Drug Administration”:
  https://www.fda.gov/media/143283/download

- MOU Information: https://www.fda.gov/drugs/human-drug-compounding/memorandum-understanding-addressing-certain-distributions-compounded-drugs


- Compounding MOUs: https://www.fda.gov/about-fda/fda-memoranda-understanding/compounding-mous
Insanitary Conditions at Compounding Facilities
Insanitary Conditions: Statutory Framework

• Section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that a drug is deemed to be adulterated if:
  • It has been prepared, packed, or held under insanitary conditions whereby it may become contaminated with filth or rendered injurious to health
  • The drug itself need not actually be contaminated
  • Note: Sections 503A and 503B do NOT provide an exemption from the insanitary conditions provision in section 501(a)(2)(A)
Insanitary Conditions: Why Is This Important?

- FDA has investigated numerous outbreaks of infections and deaths linked to drugs produced under insanitary conditions
  - 2012 fungal meningitis outbreak resulted in more than 750 illnesses and 60 deaths
- Since the outbreak, FDA has overseen more than 200 recalls conducted by compounders, most following FDA observations of lack of sterility assurance during inspections
  - In many cases, compounders temporarily or permanently ceased sterile operations
Insanitary Conditions at Compounding Facilities: Guidance for Industry (Final)

- Addresses drugs (including biological products) produced by pharmacies, federal facilities, and outsourcing facilities that compound or repackage drugs, or that mix, dilute, or repackage biological products

Policy divided into 3 main sections

- Section III.A Examples of insanitary conditions
- Section III.B Recommended preventive and corrective actions
- Section III.C Regulatory actions that may be taken by FDA

FDA’s Insanitary Conditions at Compounding Facilities, Guidance for Industry is not an exhaustive list of insanitary conditions. This list represents common insanitary conditions FDA has found at compounding facilities but is not all-encompassing.
Insanitary Conditions at Compounding Facilities: Overview of Revisions

Revisions in the final guidance as compared to the 2018 revised draft guidance include clarifications to the following policies:

- Processing of beta-lactams
- Radiopharmaceuticals
- Physician compounding and repackaging
Insanitary Conditions: Examples Applicable to Sterile and Nonsterile Drugs

- Vermin or other animals
- Visible microbial contamination
- Production during construction without adequate controls
- Standing water or evidence of water leakage
Insanitary Conditions: Examples Applicable to Sterile Drugs

- Non sterile critical gown components
- Performing aseptic operations with exposed skin or hair
- Aseptic manipulations outside the ISO 5
- Blocking or disrupting first air in the ISO 5
- Failure to use sterile containers and closures
- Difficult to clean equipment or surfaces in production areas
- Inadequate routine environmental monitoring
- Presence of unnecessary equipment in the ISO 5 area
- Inadequate personnel sampling
- Using a particle shedding filter
- No, improper, or infrequent use of a sporicidal agent
- Using disinfectants in an insufficient manner
Insanitary Conditions at Compounding Facilities: Corrective Actions

- Conduct assessment of insanitary conditions
- Consider if Recall and Cessation of Operations are appropriate
- Conduct a Comprehensive Evaluation of Operations
Insanitary Conditions at Compounding Facilities: Regulatory Actions

• If a compounding facility produces drugs under insanitary conditions, the facility and responsible individuals may be subject to several regulatory actions, including, but not limited to:
  • Warning letter
  • Seizure of product
  • Injunction

• FDA may also recommend that the facility initiate a recall of some or all of its drugs and cease operations until the insanitary conditions have been adequately addressed

• The applicable state regulatory agency may also pursue regulatory action against the facility under applicable state authorities
List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the FD&C Act
• Section 503B condition: the drug is compounded in an outsourcing facility that does not compound using bulk drug substances unless --
  • the bulk drug substance appears on a list established by the Secretary **identifying bulk drug substances for which there is a clinical need**, or
  • the drug compounded from such bulk drug substance appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing
• To establish a list of bulk drug substances for which there is a clinical need, FDA must:
  • publish a notice in the Federal Register proposing bulk drug substances to be included on the list, including the rationale for such proposal;
  • provide a period of not less than 60 calendar days for comment on the notice; and
  • publish a notice in the Federal Register designating bulk drug substances for inclusion on the list
Identifying Bulk Drug Substances for Which There is a Clinical Need

• Final guidance published March 2019: *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B*

• Guidance provides that the 503B Bulks List may include a bulk drug substance if:
  • There is a clinical need for an outsourcing facility to compound the drug product, and
  • The drug product must be compounded using the bulk drug substance
• FDA’s most recent proposed Federal Register Notice (FRN) posted on March 24, 2021. The comment period closed on May 24, 2021 (60 Days).
  • Proposed to include on the 503B Bulks List:
    • Quinacrine HCl
  • Proposed **not** to include on the 503B Bulks List:
    • Bromfenac sodium
    • Mitomycin – C
    • Nepafenac
    • Hydroxychloroquine sulfate

• Depending on its review of the docket comments and other relevant information before the Agency, FDA may finalize its proposed determination without change, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need.
  • FDA will then publish in the Federal Register a final determination for each substance
## 503B Bulk Drug Substance Evaluations (2018-2021)

<table>
<thead>
<tr>
<th>Include</th>
<th>Not to Include</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diphenylcyclopropenone (P)</td>
<td>• Hydralazine HCl (P)</td>
</tr>
<tr>
<td>• Glycolic acid (P)</td>
<td>• Hydroxychloroquine sulfate (P)</td>
</tr>
<tr>
<td>• Squaric acid dibutyl ester (P)</td>
<td>• Hydroxyzine HCl (P)</td>
</tr>
<tr>
<td>• Trichloroacetic acid (P)</td>
<td>• Ketorolac tromethamine (P)</td>
</tr>
<tr>
<td>• Quinacrine HCl (FDA nominated) (P)</td>
<td>• Labetalol HCl (P)</td>
</tr>
<tr>
<td>• Nicardipine hydrochloride (F)</td>
<td>• Mannitol (P)</td>
</tr>
<tr>
<td>• Vasopressin (F)</td>
<td>• Methacholine chloride (P)</td>
</tr>
<tr>
<td>• Bromfenac sodium (P)</td>
<td>• Metoclopramide HCl (P)</td>
</tr>
<tr>
<td>• Bumetanide (P)</td>
<td>• Mitomycin – C (P)</td>
</tr>
<tr>
<td>• Diazepam (P)</td>
<td>• Moxifloxacin HCl (P)</td>
</tr>
<tr>
<td>• Dipyridamole (P)</td>
<td>• Nalbuphine HCl (P)</td>
</tr>
<tr>
<td>• Dobutamine HCl (P)</td>
<td>• Nepafenac (P)</td>
</tr>
<tr>
<td>• Dopamine HCl (P)</td>
<td>• Polidocanol (P)</td>
</tr>
<tr>
<td>• Edetate calcium disodium (P)</td>
<td>• Potassium acetate (P)</td>
</tr>
<tr>
<td>• Ephedrine sulfate (P)</td>
<td>• Procainamide HCl (P)</td>
</tr>
<tr>
<td>• Famotidine (P)</td>
<td>• Sodium bicarbonate (P)</td>
</tr>
<tr>
<td>• Folic acid (P)</td>
<td>• Sodium nitroprusside (P)</td>
</tr>
<tr>
<td>• Glycopyrrolate (P)</td>
<td>• Sodium tetradeyl sulfate (P)</td>
</tr>
<tr>
<td>• Hydroxychloroquine sulfate (P)</td>
<td>• Sodium thiosulfate (P)</td>
</tr>
<tr>
<td>• Hydroxyzine HCl (P)</td>
<td>• Trypan blue (P)</td>
</tr>
<tr>
<td>• Ketorolac tromethamine (P)</td>
<td>• Vecuronium bromide (P)</td>
</tr>
<tr>
<td>• Labetalol HCl (P)</td>
<td>• Verapamil HCl (P)</td>
</tr>
</tbody>
</table>

P: Proposed; F: Final
Questions