Compounding Policy Updates

Compounding Quality Center of Excellence
Virtual Conference: Culture of Quality

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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 compounder 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.

MOU: Statutory Framework

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

Collaboration with NABP

· Information Sharing Network (ISN)

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

Inordinate Amount: 50% Threshold	
$\frac{A}{B} = X$	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
- MOU Q&A: https://www.fda.gov/drugs/human-drug-compounding/memorandum-understanding-addressing-certain-distributions-compounded-drugs-questions-and-answers
- Compounding MOUs: https://www.fda.gov/about-fda/fda-memoranda-understanding/compounding-mous

Insanitary Conditions at Compounding Facilities

Insanitary Conditions: Statutory Framework

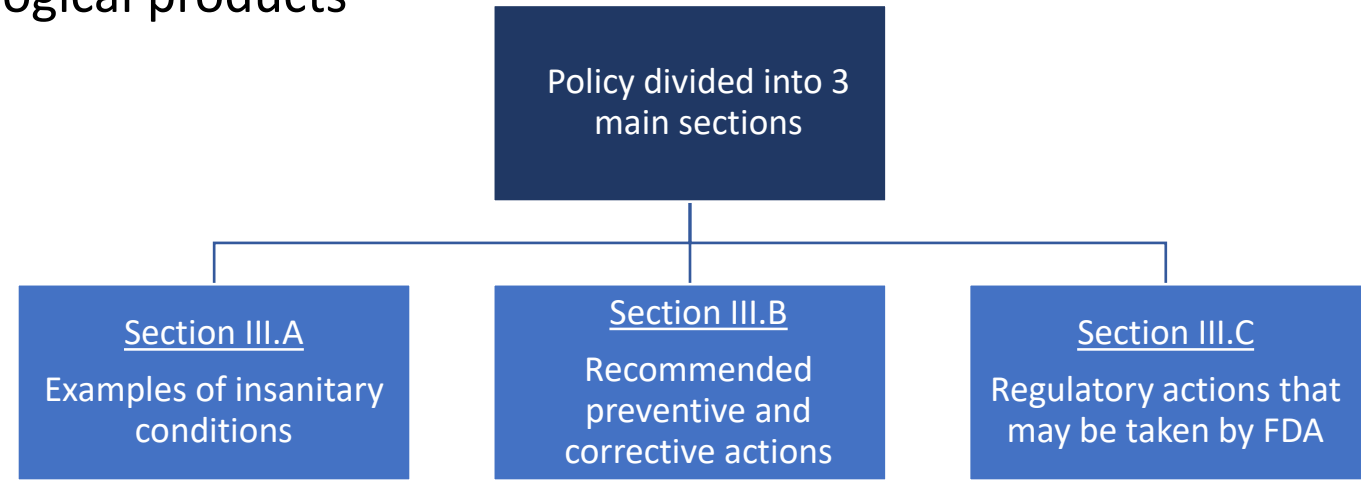
- Section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that a drug is deemed to be adulterated if:
  - It has been prepared, packed, or held under insanitary conditions whereby it may become contaminated with filth or rendered injurious to health
- The drug itself need 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



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.

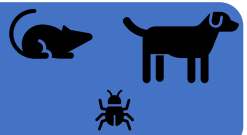
Insanitary Conditions at Compounding Facilities: Overview of Revisions

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

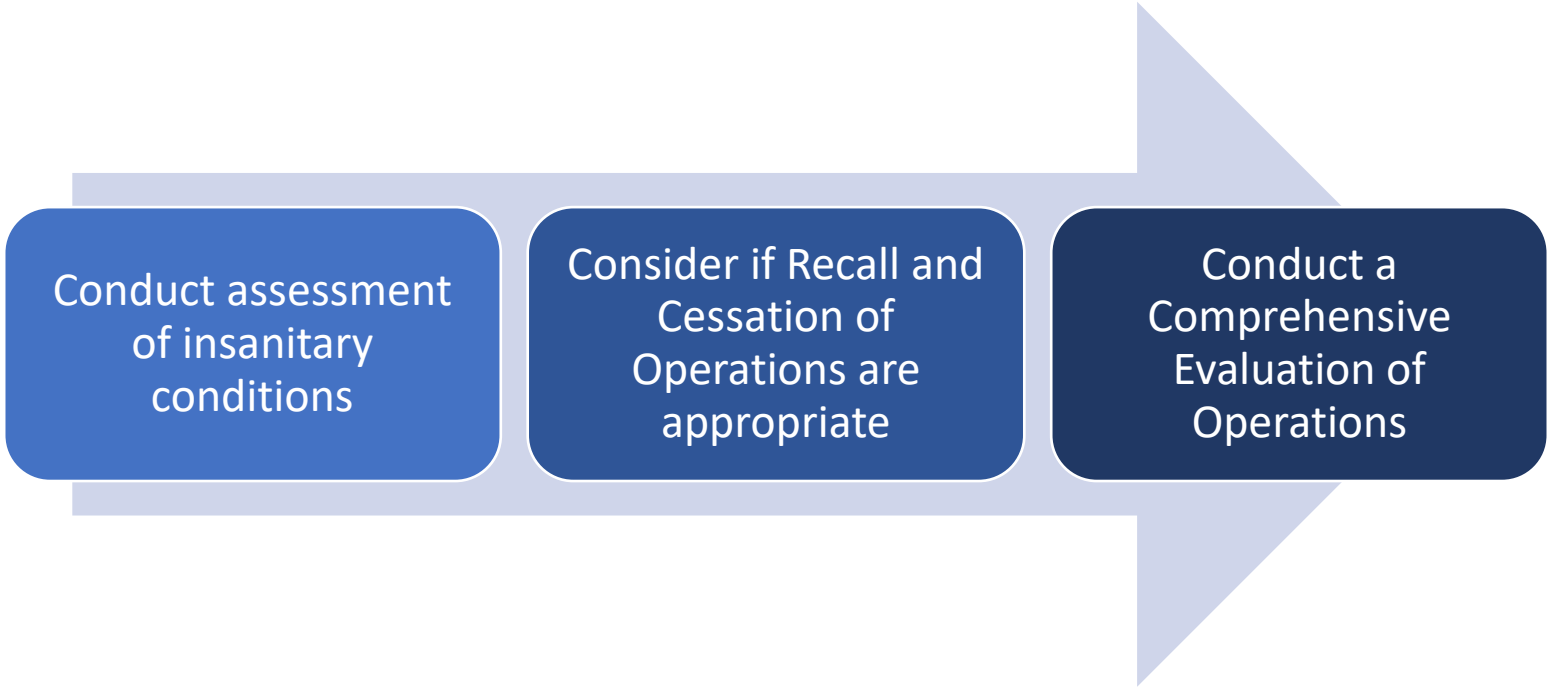


- Visible microbial contamination
- Production during construction without adequate controls
- Standing water or evidence of water leakage

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



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

503B Bulks List: Statutory Framework

- 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

503B Bulks List: Statutory Framework

- 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

March 2021 Federal Register Notice Regarding 5 Bulk Drug Substances and 503B List

- 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)

Include	Not to Include

- Diphenylcyclopropenone (P)
- Glycolic acid (P)
- Squaric acid dibutyl ester (P)
- Trichloroacetic acid (P)
- Quinacrine HCl (FDA nominated) (P)

- **Nicardipine hydrochloride (F)**
- **Vasopressin (F)**
- Bromfenac sodium (P)
- Bumetanide (P)
- Diazepam (P)
- Dipyridamole (P)
- Dobutamine HCl (P)
- Dopamine HCl (P)
- Edetate calcium disodium (P)
- Ephedrine sulfate (P)
- Famotidine (P)
- Folic acid (P)
- Glycopyrrolate (P)
- Hydralazine HCl (P)
- Hydroxychloroquine sulfate (P)
- Hydroxyzine HCl (P)
- Ketorolac tromethamine (P)
- Labetalol HCl (P)
- Mannitol (P)
- Methacholine chloride (P)
- Metoclopramide HCl (P)
- Mitomycin – C (P)
- Moxifloxacin HCl (P)
- Nalbuphine HCl (P)
- Nepafenac (P)
- Polidocanol (P)
- Potassium acetate (P)
- Procainamide HCl (P)
- Sodium bicarbonate (P)
- Sodium nitroprusside (P)
- Sodium tetradecyl sulfate (P)
- Sodium thiosulfate (P)
- Trypan blue (P)
- Vecuronium bromide (P)
- Verapamil HCl (P)

P: Proposed; F: Final

Questions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