Insanitary Conditions at Compounding Facilities – A Review of FDA's Guidance for Industry

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Background

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

Background

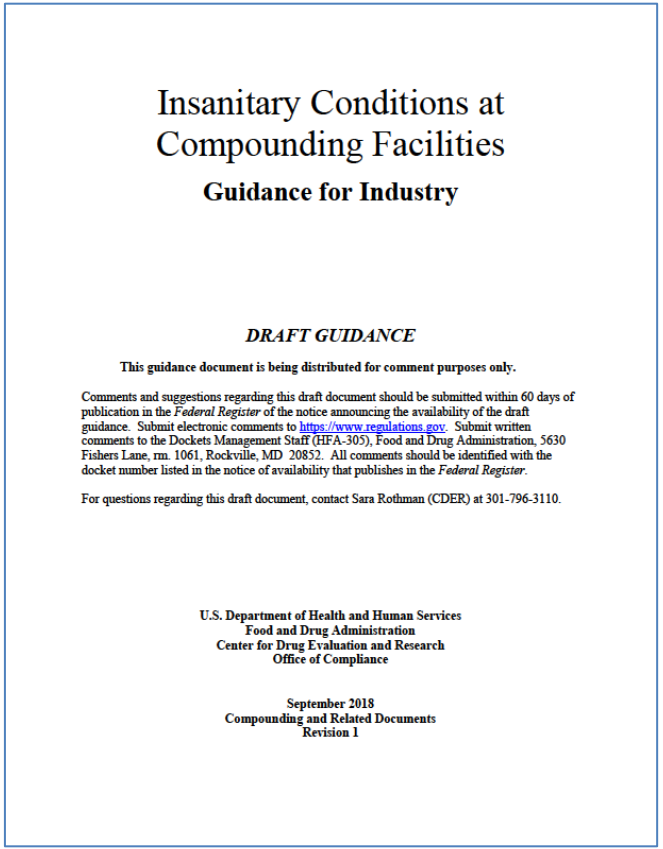
Section 501(a)(2)(A) applies to all drugs

There are no exemptions from Section 501(a)(2)(A) under 503A or 503B

Drug does not need to be contaminated to be deemed adulterated

Insanitary Conditions at Compounding Facilities Guidance for Industry

- Initial Draft Guidance published 8/4/2016
- Revised Draft Guidance published for comment on 9/25/2018
- Final Guidance is expected in 2020
- 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



Insanitary Conditions at Compounding Facilities

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Sara Rothman (CDER) at 301-796-3110.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance

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Compounding and Related Documents
Revision 1

Purpose of Draft Guidance

When finalized will represent FDA's current thinking on the insanitary conditions provision as it relates to compounding facilities

To provide examples of insanitary conditions that have been observed during FDA inspections

To help compounders identify these types of conditions within their facilities so they can implement corrective actions

Not intended to be an all encompassing list of insanitary conditions

For purposes of the Draft Guidance:

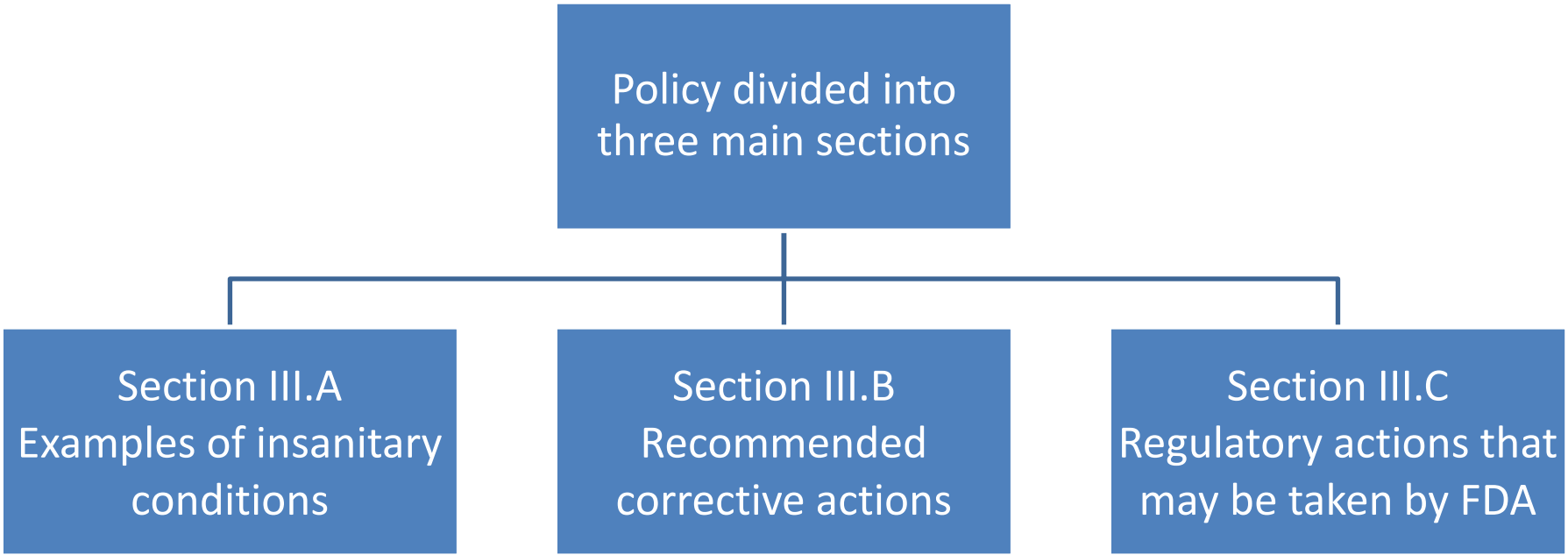
Insanitary Conditions: conditions that could cause a drug to become contaminated with filth or rendered injurious to health

Compounding facilities: pharmacies, federal facilities, and outsourcing facilities that compound or repackage drugs, or that mix, dilute, or repackage biological products

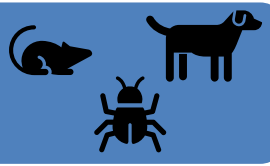
Production area: for sterile compounding, refers to any area classified under International Organization for Standardization (ISO) standards or SCA and for non-sterile compounding, as any room or area in which non-sterile compounding occurs

Critical area: an area designed to maintain sterility of sterilized materials; the ISO 5 area

Draft Guidance Content



Section III.A – Examples Applicable to the Production of Sterile and Non-Sterile Drugs

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

Section III.A – Examples Applicable to the Production of Sterile and Non-Sterile Drugs

- Sources of non-microbial contamination in production area
- Using ingredients that have or may have higher levels of impurities compared to compendial or pharmaceutical grade equivalents
- Handling hazardous, sensitizing, or highly potent drugs without adequate controls to prevent cross-contamination

Section III.A – Examples Applicable to Sterile Drugs

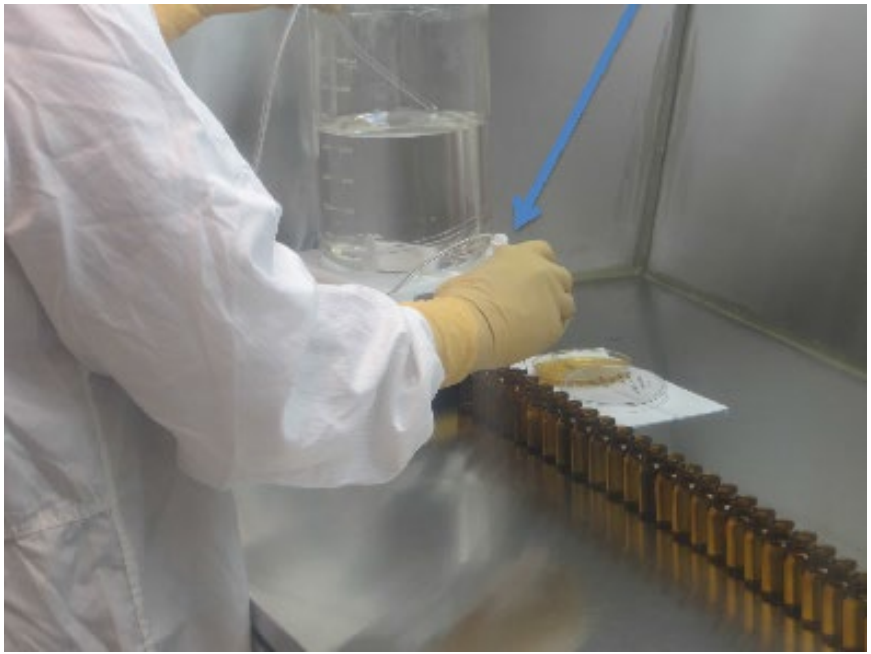
Gowning and Aseptic Practices

Section III.A – Examples Applicable to Sterile Drugs

- Non-sterile critical gown components
- Donning gowning in a way that may cause contamination
- Failing to change or disinfect gloves appropriately
- Engaging in aseptic processing after leaving cleanroom and re-entering production area from a non-classified area without replacing gowning
- Performing aseptic operations with exposed skin or hair
- Aseptic manipulations outside the ISO 5

Section III.A – Examples Applicable to Sterile Drugs

- Exposing sterile drugs and materials to lower than ISO 5 quality air
- Blocking or disrupting first air in the ISO 5
- Failure to disinfect containers of sterile components or supplies prior to opening
- Failure to use sterile containers and closures
- Using non-sterile tool or manually touching a product contact surface
- Quick movement in or immediately adjacent to a critical area that could disrupt airflow



Section III.A – Examples Applicable to Sterile Drugs

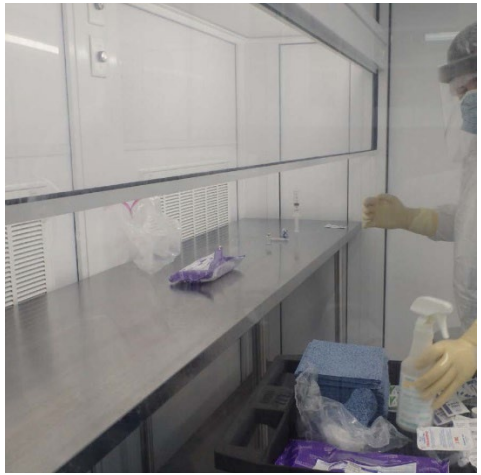
Equipment and Facilities

Section III.A – Examples Applicable to Sterile Drugs

- Actionable microbial contamination in the ISO 5
- Inadequate routine environmental monitoring
- No or infrequent measurement of pressure differentials during operations
- Unsealed HEPA filters; unsealed or loose ceiling tiles
- Difficult to clean equipment or surfaces in production areas
- Presence of water sources adjacent to ISO 5

Section III.A – Examples Applicable to Sterile Drugs

- Inadequate personnel sampling
- Lack of routine certification of the ISO 5 area, including dynamic smoke studies
- Facility design or operation that permits influx of lesser quality air into higher quality air areas
- Lack of HEPA-filtered air, or inadequate HEPA filter coverage over critical area
- Presence of unnecessary equipment in ISO 5
- Exposing sterile products to non-sterile or non-depyrogenated supplies

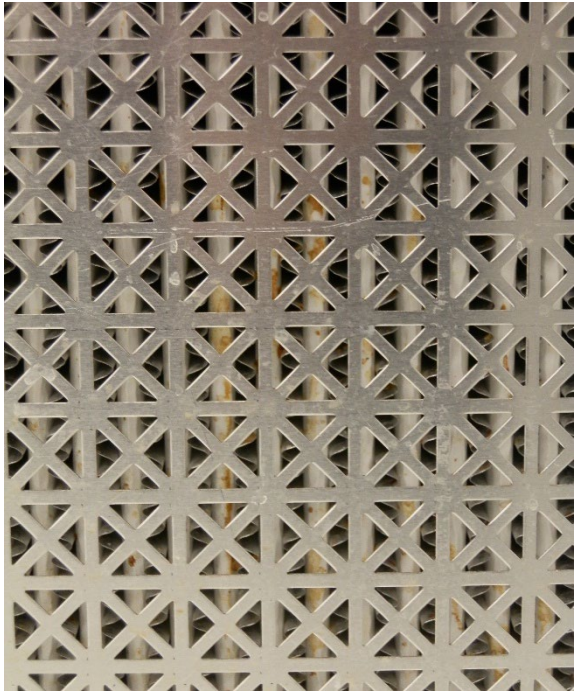


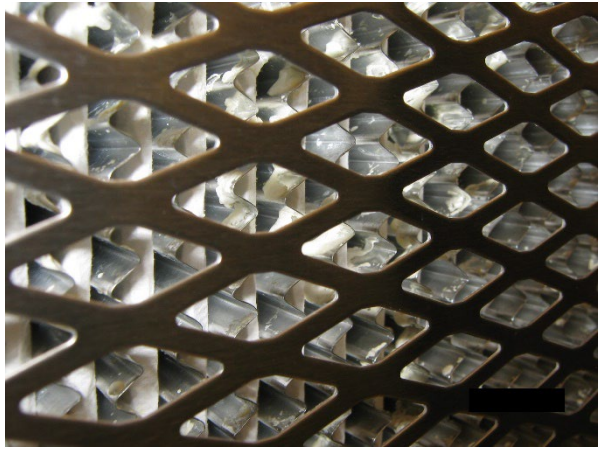
Section III.A – Examples Applicable to Sterile Drugs

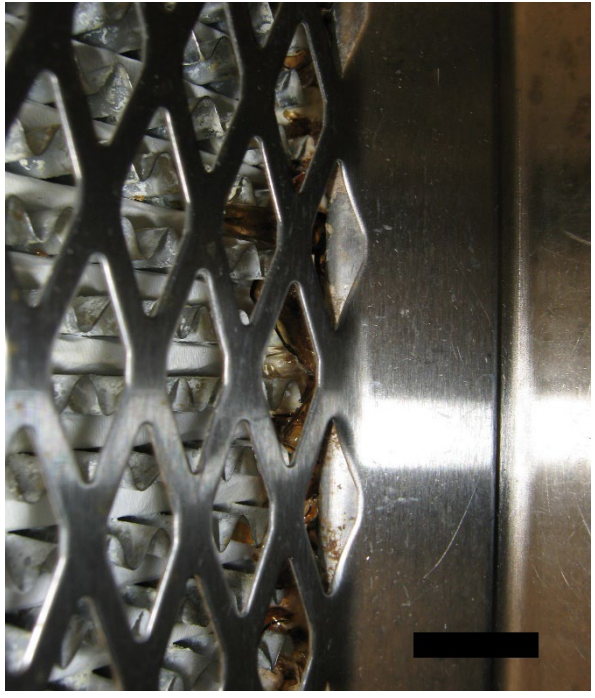
Cleaning and Disinfecting

Using non-sterile disinfecting agents and cleaning pads/wipes in ISO-classified areas
No, improper, or infrequent use of a sporicidal agent
Failure to clean and disinfect equipment in the ISO 5 area
Lack of disinfection of equipment or supplies at each transition to higher quality air
Using disinfectants in an insufficient manner
Using expired sterile cleaning and disinfecting agents
Using cleaning and disinfecting agents that may leave residues or not adequately rinsing such agents from product contact surfaces

Section III.A – Examples Applicable to Sterile Drugs







Section III.A – Examples Applicable to Sterile Drugs

Sterilization Practices
Using an inappropriate filter or using an appropriate filter improperly
Using a filter whose integrity is compromised or failing to conduct post-use filter integrity testing on sterilizing filters
Using a particle-shedding filter
Using parameters for sterilization that are not lethal to resistant microorganisms

Section III.A – Examples Applicable to Sterile Drugs

Other Insanitary Conditions

- Allowing operators with topical or respiratory infections or with open wounds to work within production operations
- Using components, containers, or other materials that have not been verified to assure that they do not contribute endotoxin contamination that may be objectionable given the product's intended use
- Production under conditions that offer insufficient assurance that the finished product will meet an endotoxin specification appropriate for its route of administration
- Failure to conduct media fills that closely simulate aseptic operations under the worst-case, most-challenging and stressful conditions

What do you see here?

Section III.B – Draft Guidance Recommendations Regarding Corrective Actions

Conduct Assessment of Insanitary Conditions

- Drug product impact
- Scope of the issue
- Duration
- Lots affected:
  - In house
  - Distributed

Consider if Recall and Cessation of Operations are appropriate

- Insanitary conditions considered to be particularly serious
- Do not rely upon or cite a passing sterility test result
- Insanitary conditions must be corrected
- Notification of Recall

Conduct a Comprehensive Evaluation of Operations

- Evaluation should include (as applicable):
  - Facility design
  - Procedures
  - Personnel
  - Processes
  - Materials
  - Systems
- Consider consulting a third party

Section III.C – Regulatory Actions

- Production of drugs under insanitary conditions may lead to regulatory actions by FDA, including, but not limited to:
  - Warning Letter
  - Seizure of Product
  - Injunction
- In addition, state regulatory agencies may also pursue regulatory action under applicable state authorities

Additional Notes

- Physician compounding or repackaging of drug products
- Insanitary conditions marked with an asterisk (*)
- Radiopharmaceuticals

One more time so we remember…

- **To whose drugs does the insanitary conditions provision apply?**
  A. Any type of facility preparing, packing, or holding drug products
  B. Only pharmacies compounding drugs under 503A
  C. Only facilities that compound drugs
  D. Only facilities that produce drugs subject to cGMP requirements

Where to find this Draft Guidance?

- FDA's website for Human Drug Compounding:

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding

- Searchable list of FDA Guidance Documents:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Thank you for your attention!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