Draft Guidance for Industry Insanitary Conditions at Compounding Facilities

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Background

- **Statutory Prohibition**: 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 whereby it may have been rendered injurious to health. FD&C Act 501(a)(2)(A)
- There are no exemptions from 501(a)(2)(A) in either section 503A or 503B – drug products prepared, packed, or held under insanitary conditions by compounding facilities are adulterated under the Act regardless of whether they qualify for the exemptions in section 503A or 503B of the Act
- Drugs need not be actually contaminated to be deemed adulterated (different provision applies to products that are contaminated)

Insanitary Conditions Draft Guidance

- Action Item #5 from 2015 50-State Meeting: FDA will consider publishing a guidance on insanitary conditions at facilities that engage in compounding
  - Desire for clarity regarding insanitary conditions
- Draft guidance published August 3, 2016; Comment period closes October 3, 2016
- Purpose of Draft Guidance
  - Assist compounding facilities in identifying insanitary conditions so they can implement appropriate corrective actions
  - Assist State regulatory agencies in understanding some examples of what FDA considers to be insanitary conditions

Content of Draft Guidance

- Examples of insanitary conditions
  - examples are all conditions actually observed during FDA inspections
  - non-exhaustive list – other conditions not described in the draft guidance may be insanitary conditions

- Identifying insanitary conditions
  - non-exhaustive list of procedures critical to help ensure compounding facilities do not have insanitary conditions and can produce sterile products

In general, insanitary conditions described in draft guidance consistent with standards for sterile compounding in USP chapter <797>

Content of Draft Guidance – Con't

- Corrective actions
  - assess the impact of insanitary condition on drug products produced (how widespread and over what period of time)
  - determine whether to cease production until conditions have been corrected and initiate recall of potentially affected lots
    - draft guidance includes list of particularly serious conditions, which, if any one exists, FDA strongly recommends that the facility recall and cease sterile operations until corrected
  - conduct comprehensive assessment of operations (facility design, procedures, personnel, processes, materials, and systems) and implement appropriate corrective actions; consider using third party expert
- Note: passing sterility test should not be relied on as an indication of sterility assurance

Content of Draft Guidance – Con't

- Regulatory action
  - Federal regulatory action for compounding facilities and responsible individuals producing drugs under insanitary conditions include, but are not limited to: warning letter; seizure, and/or injunction
  - FDA may recommend compounding facility initiate recall of some or all products and/or cease operations until insanitary conditions have been adequately addressed
  - Some conditions may be actionable under applicable State authorities, and we encourage States to pursue their own regulatory action
    - Model Act includes prohibition on insanitary conditions that mirrors FD&C Act and could serve as basis of state regulatory action
    - States that have adopted USP <797> standards may be able to bring action given similarities between insanitary conditions and USP <797>

Insanitary Condition Example

- Visible microbial contamination

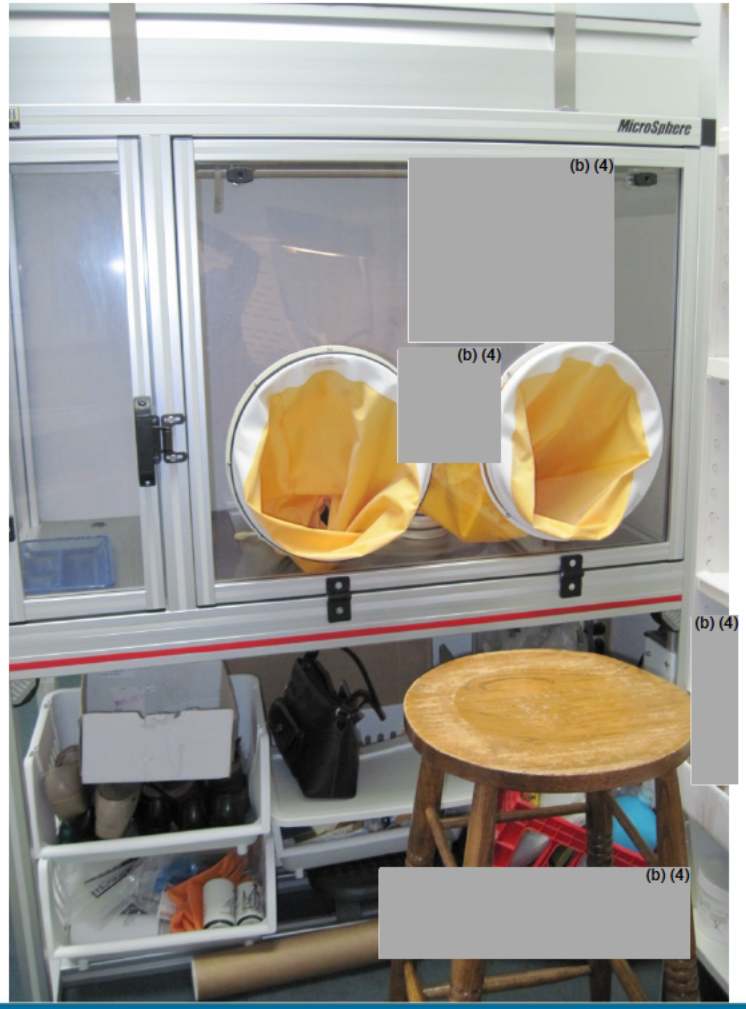
Insanitary Condition Example

- Insects (vermin) dead or alive

Insanitary Condition Example

Filth under the hood including multiple pieces of medical supply waste and dust build up in the pre-filter for the ISO 5 hood.

Insanitary Condition Example



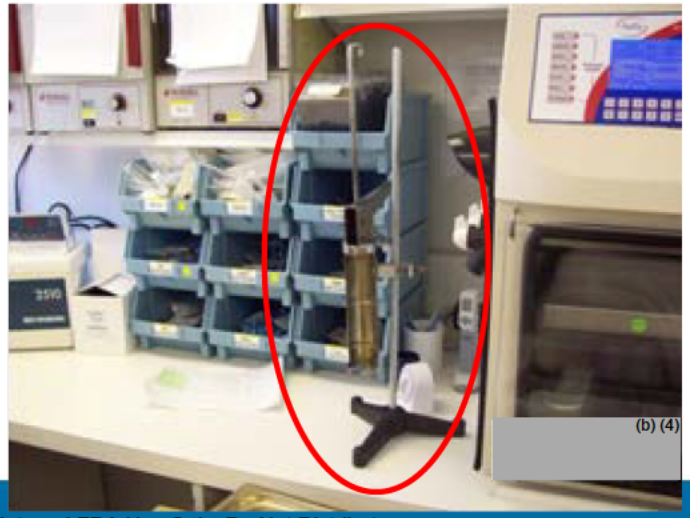
The glove box that provides ISO 5 conditions where aseptic processing operations occur, was located in an unclassified carpeted room where the room air was not HEPA filtered. Note the wooden stool.

Insanitary Condition Example

Gowned employee working in the cleanroom, exposing legs

Insanitary Condition Example

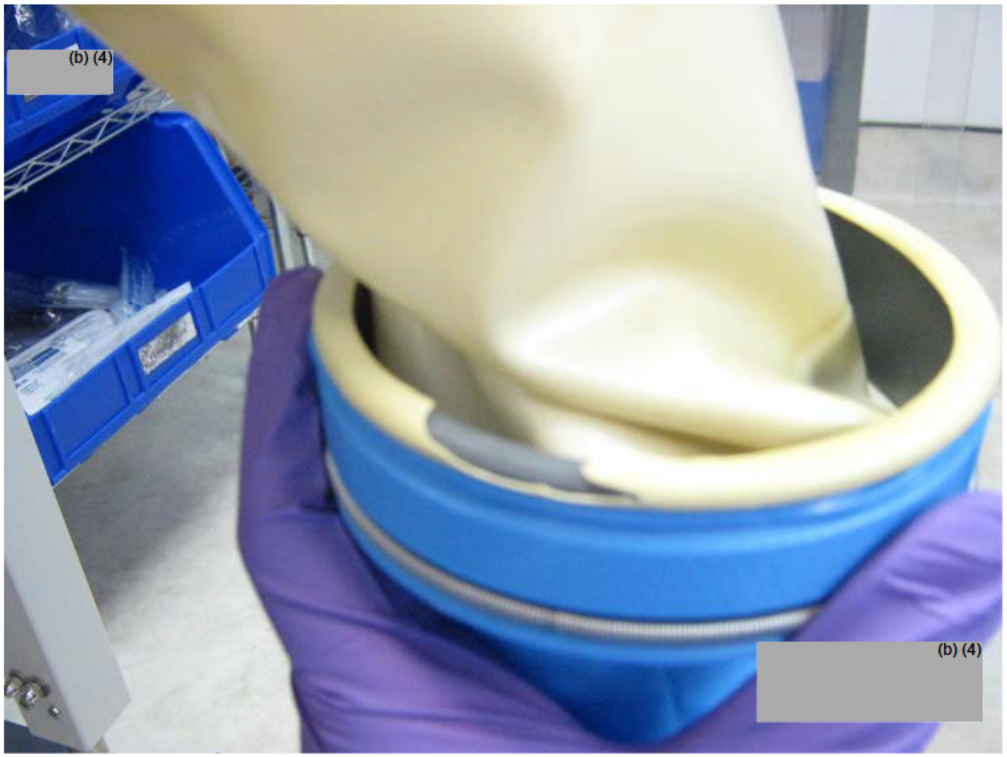
The HEPA filter located immediately above the ISO 5 workbench was observed to have been stained on the filter surface



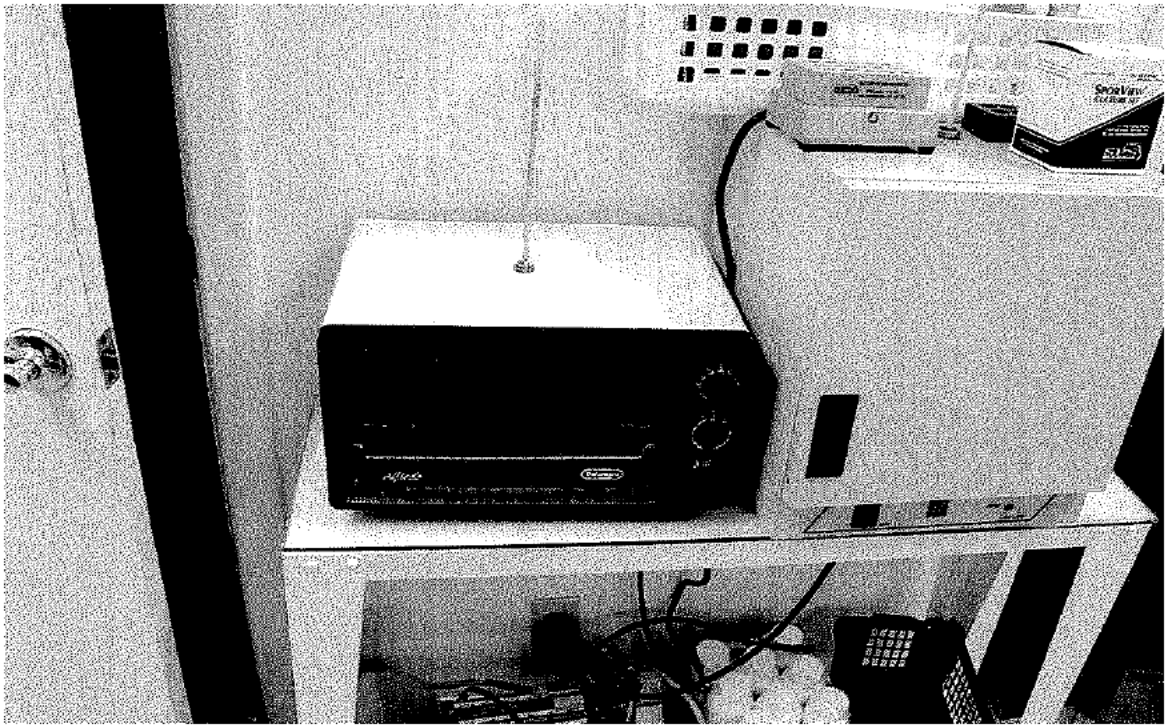
The HEPA filter stain was due to drug product which had exploded due to excessive pressure applied when forcing non-sterile product through a sterilizing filter. The device used to force the product sterilizing filter was a stainless steel caulking gun that was not sterilized.

Insanitary Condition Example

Sleeve used in the glove box used for aseptic manipulations is damaged.

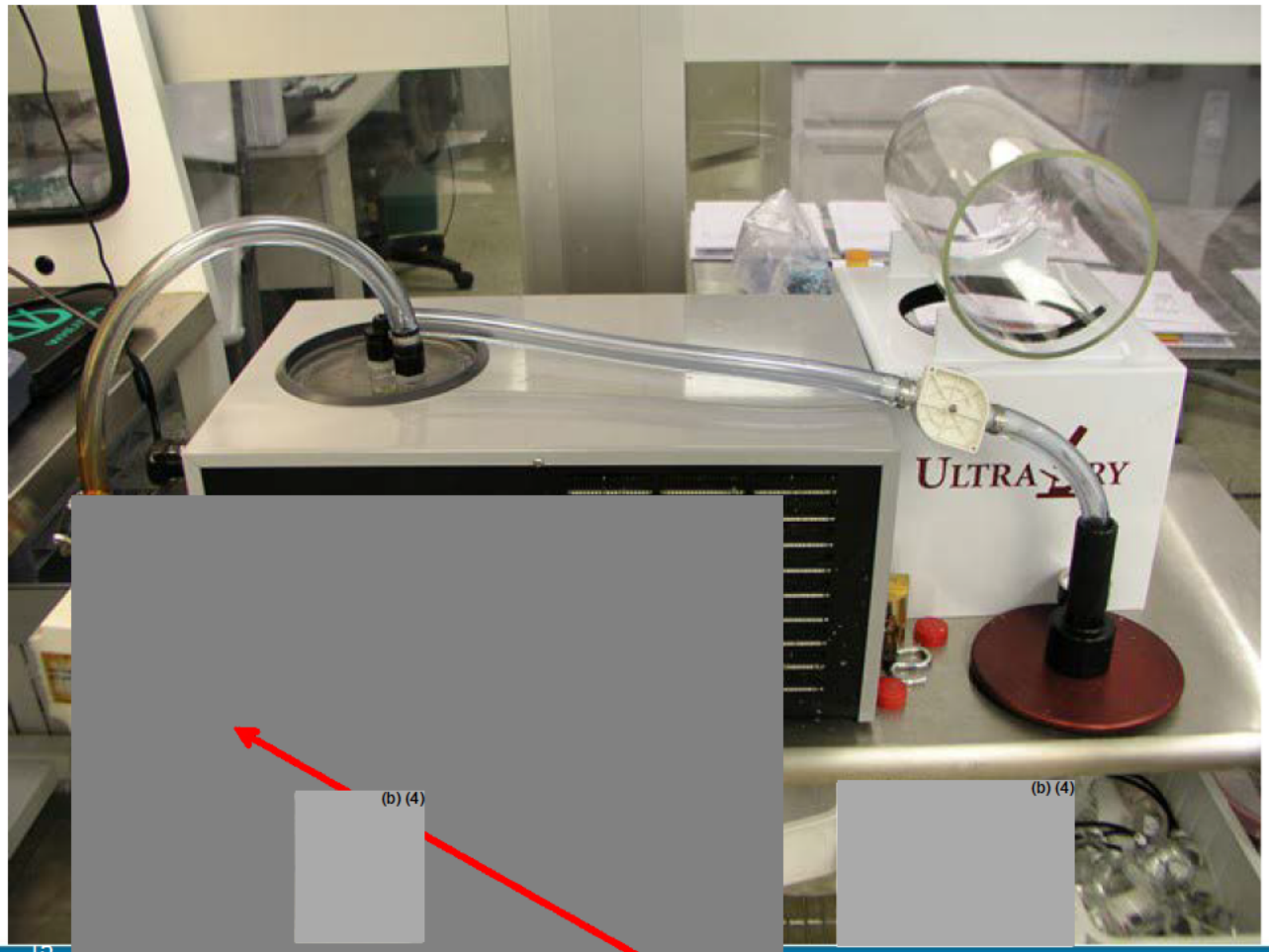


Insanitary Condition Example



Toaster oven used to dry heat sterilize and depyrogenate glassware; however, oven was not capable of reaching high enough temperature to be effective

Insanitary Condition Example



Lyophilization unit located in the cleanroom. Oil leaked from the pump and a paper towel is used to absorb the oil (bottom left portion of the photo)

Insanitary Condition Example

Ceiling above the doorway to cleanroom with exposed insulation

Insanitary Condition Example

Kitchen home dishwasher (supplied with tap water) and Cascade brand detergent used to clean equipment and utensils that comes in contact with product intended to be sterile – no subsequent cleaning step

Insanitary Condition Example

- Failure to routinely use a sporicidal agent, *correctly*
- Review label claim
- See *USP* <1072> - *Disinfectants and Antiseptics*

Insanitary Condition Example

- Non-sterile wipes used to clean "aseptic" surfaces

- FDA analysis of these wipes – presence of:
- ***Bacillus* sp. and other spore-formers**
- Gram negative bacteria

Insanitary Condition Examples

- Not all insanitary conditions are readily discernable. For example:
  - Most microbial contamination not visible
  - ISO-5 devices (e.g. laminar flow hood, biosafety cabinets, etc.) not fully functional
  - Sterilizing grade filter malfunction

Environmental monitoring (EM)

- Actionable EM results (from *USP* <797>):

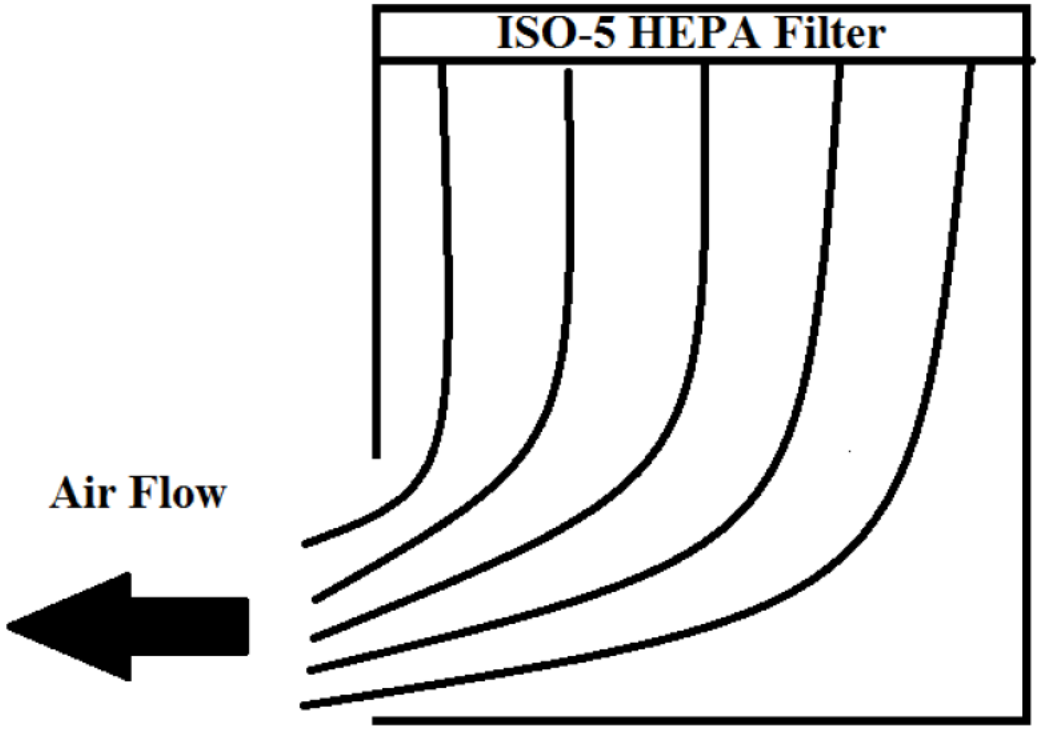
Table 2. Recommended Action Levels for Microbial Contamination

Classification	Air Sample
ISO Class 5	> 1
ISO Class 7	> 10
ISO Class 8 or worse	> 100

Table 4. Recommended Action Levels for Microbial Contamination

Classification	Fingertip Sample	Surface Sample (Contact Plate) (cfu per plate)
ISO Class 5	> 3	> 3
ISO Class 7	N/A	> 5
ISO Class 8 or worse	N/A	> 100

Smoke Studies of the ISO-5



Functionality of sterilizing membrane

- Insanitary condition: *"The "sterilizing filter" is not adequate to accomplish sterilization…"*
  - How do you determine adequacy of filter?
    - Filter manufacturer "Certificate of Suitability"
    - Post-filtration integrity test (in accordance with filter manufacturer instruction)
      - Determines whether individual filter is free from defects
  - Baxter Healthcare Corp – August 26, 2016 – Letter to Pharmacies
    - Issuing a voluntary recall of 50 mm 0.2 micron "sterilizing" filter
      - Missing membrane layer
        - » No longer capable of filtering any microbial contaminants
      - Releases particles