Cleanrooms & Cleanroom Behaviors: Why they Matter

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Learning Objectives

- Identify the section of the Federal Food, Drug, and Cosmetic Act addressing drug products prepared under insanitary conditions.
- List different types of filth.
- Understand potential sources of filth.
- Understand how cleanrooms and cleanroom behaviors prevent/limit the introduction of filth.
- Discuss examples of 483 observations pertaining to insanitary conditions.

What Does the Law Say?

Section **501(a)(2)(A)** of the Federal Food, Drug, and Cosmetic Act (FD&C Act) states that a drug is deemed to be adulterated "if it has been prepared, packed, or held under **insanitary conditions**

(1) whereby it may have been **contaminated with filth**, or

(2) whereby it may have been rendered **injurious to health**."

Why Does it Matter?

Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including **death**.

NECC

- 2012 outbreak of fungal meningitis in multiple states
- Methylprednisolone acetate (intrathecal injection)
- 700+ infections with 60+ deaths

What is Filth?

- Non-microbial: dust, rust, glass, metal, rubber particles, hairs, fibers, paint chips, etc.
- Microbial: microbial contamination in or adjacent to the production areas
- Chemical: disinfectants, hazardous, sensitizing, or highly potent drugs, APIs or excipients with high levels of impurities (**non-compendial**; **not intended for pharmaceutical use**)
- Vermin: insects, rodents, or animals of any kind in or adjacent to the production areas

Filth: Non-microbial

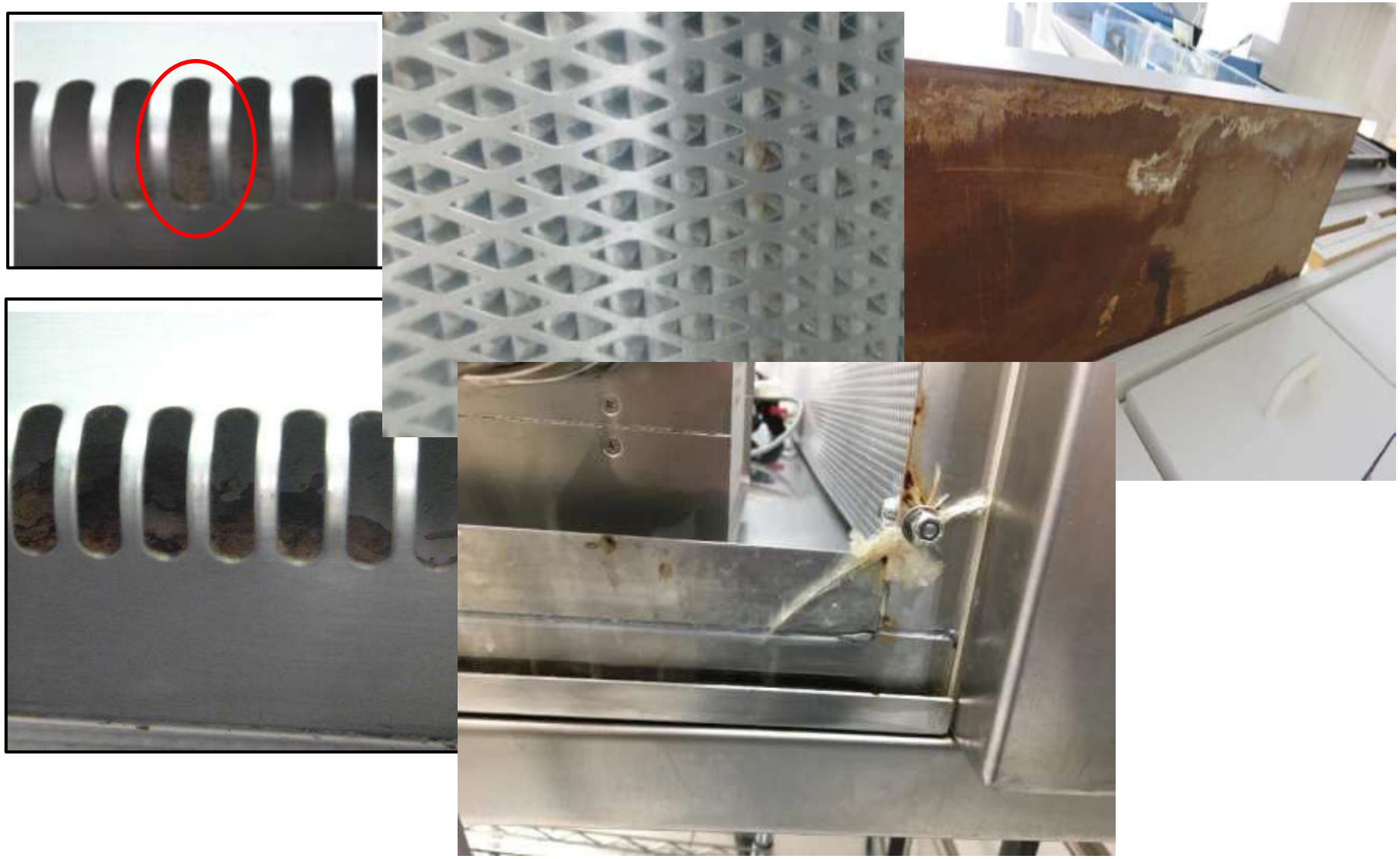
- Particles (dust, fibers, hairs, glass, rubber, etc.)
  - Air
  - Surfaces
  - Vehicles for Microbes
- Limits for sterile drugs
  - USP <788> Particulate Matter in Injections
  - USP <789> Particulate Matter in Ophthalmic Solutions
  - USP <790> Visible Particulates in Injections
  - USP <1790> Visual Inspection of Injections
- Considerations for non-sterile drugs

Where do particles come from?

- Materials of Construction
- Chemical residues
- Cardboard
- Cleaning supplies
- Gowning materials
- People
- Air handling units
- Space above the ceiling
- Space behind the walls
- Inadequate pressure cascade
- Other rooms (people, material transfer)

Materials of Construction – What could go wrong?

Filth in or near ISO 5 areas



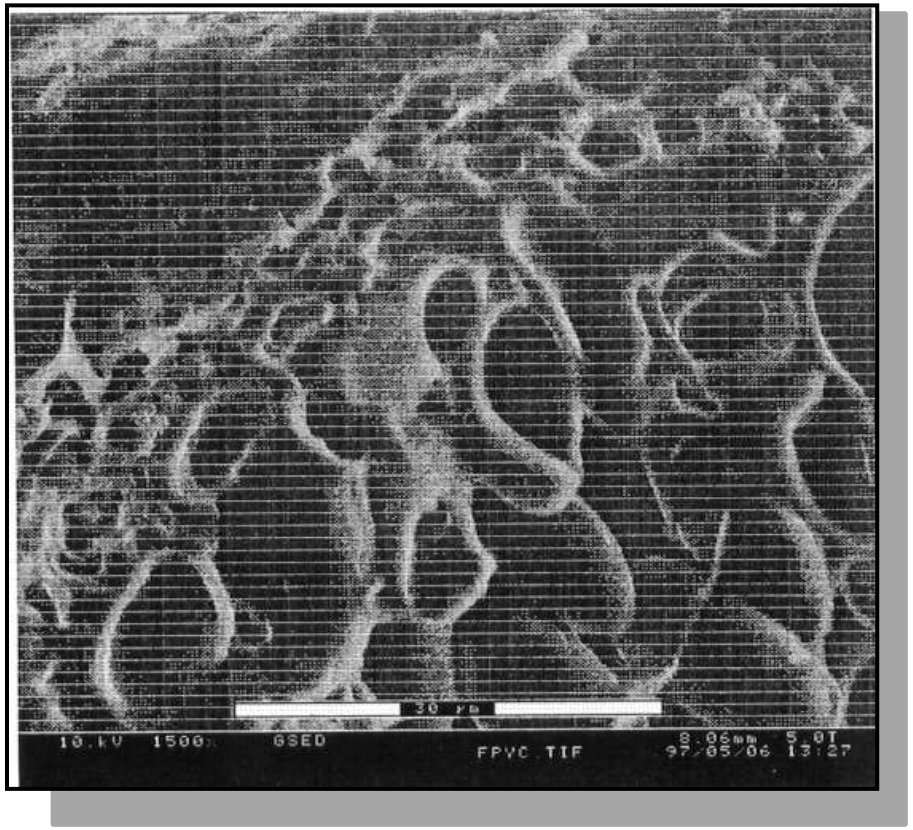
Which Types of Surfaces are Easier to Clean?

- Surfaces should be hard, smooth, resistant to disinfectants (stainless steel, plexiglass)

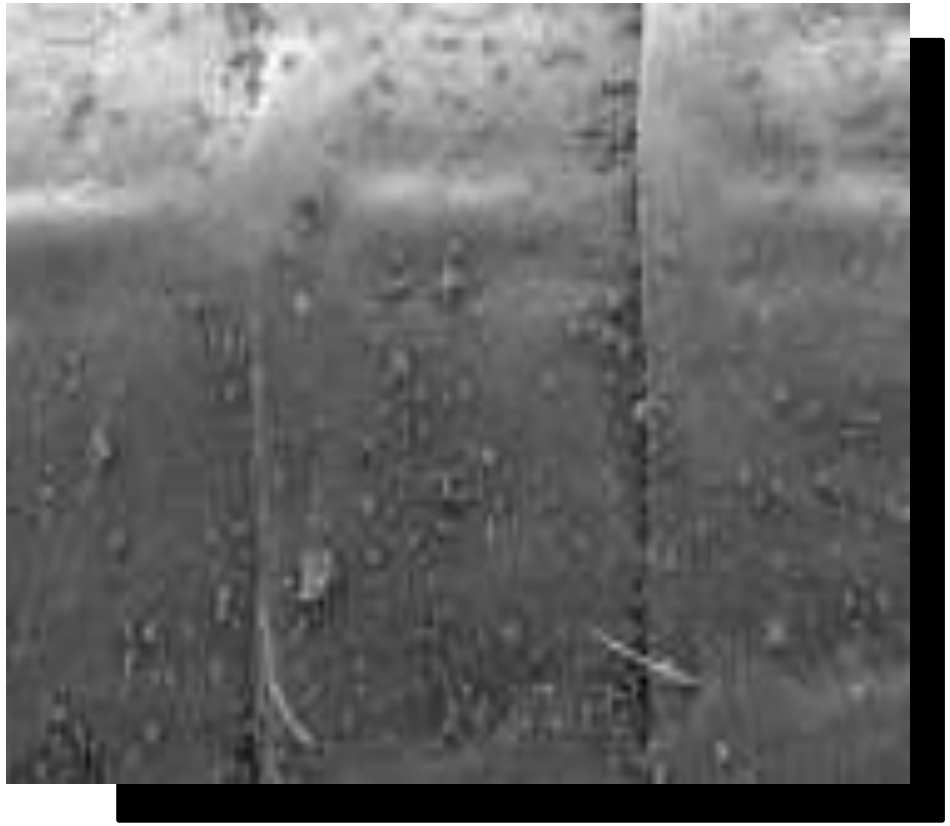
- Surfaces should not be rough, shedding, additive, or absorptive (wood, laminates)

Surfaces that are Difficult to Clean

Plastic Curtains

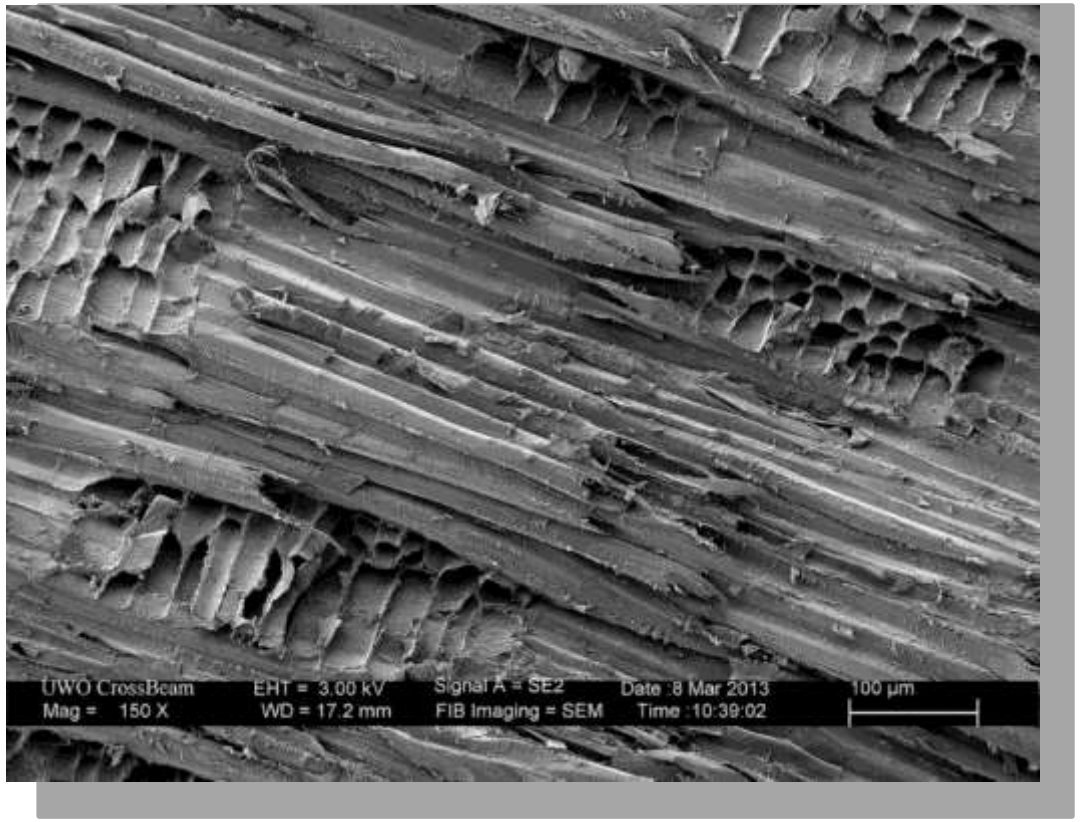


Vinyl Surface



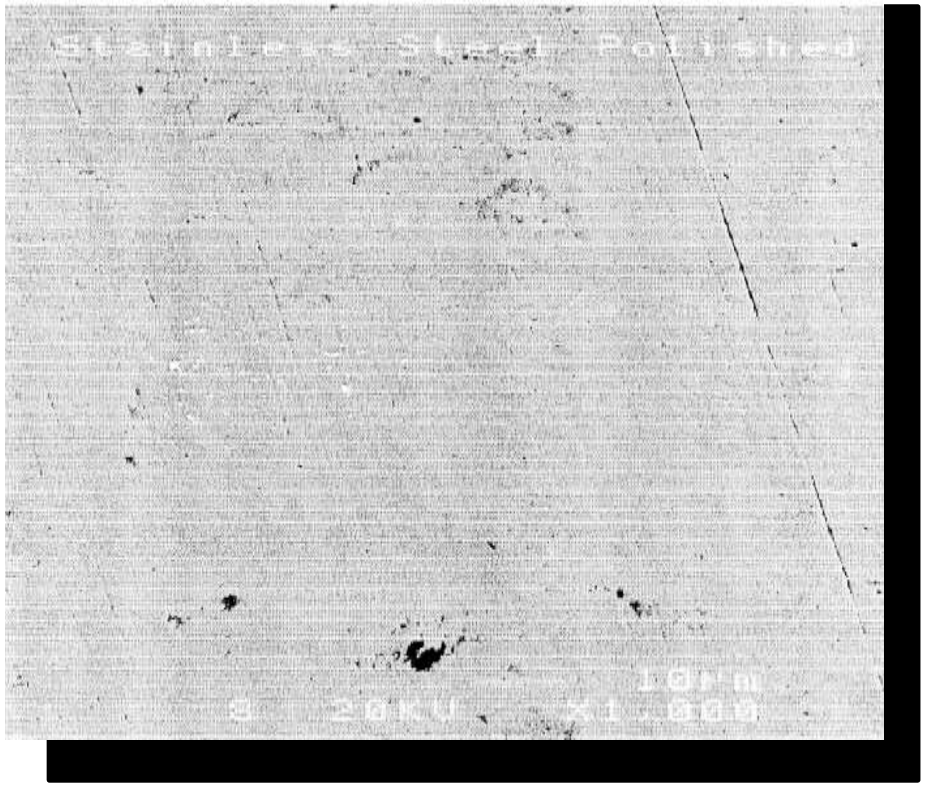
Surfaces that are Difficult to Clean

Wood Surface

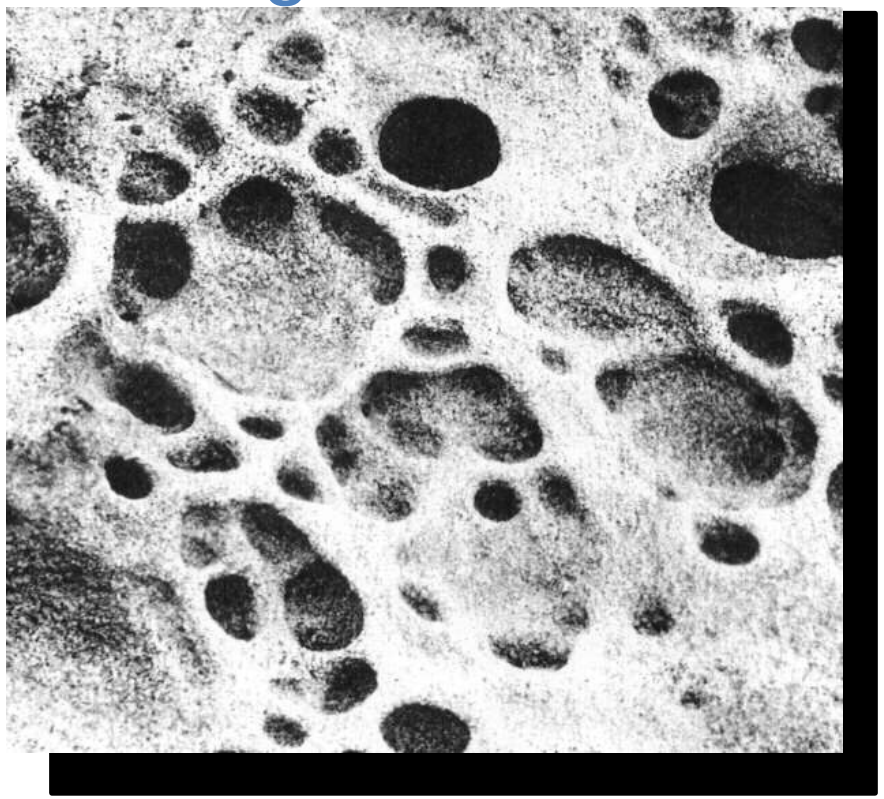


Surfaces Common to Cleanrooms

Stainless Steel Surface

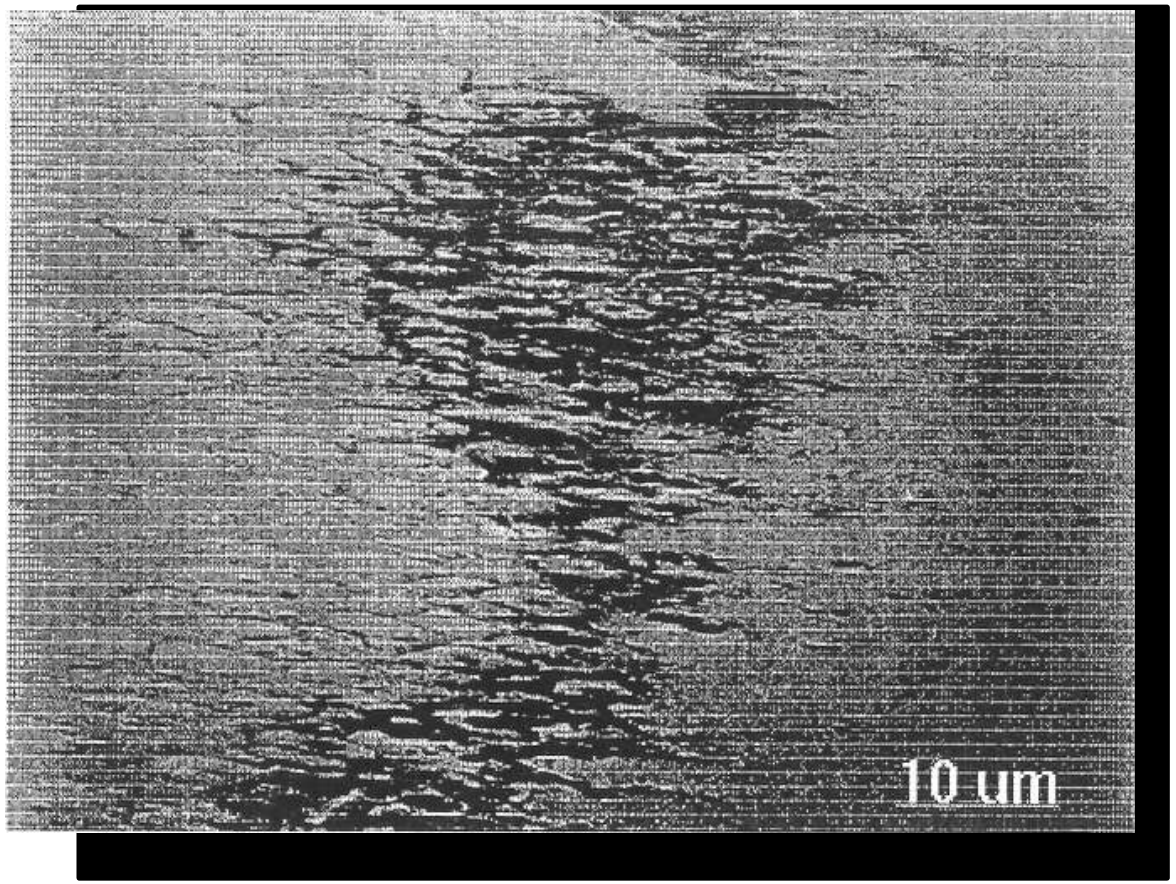


Plexiglass Surface



Surfaces Common to Cleanrooms

Epoxy Surface



483 Observation

OBSERVATION 2

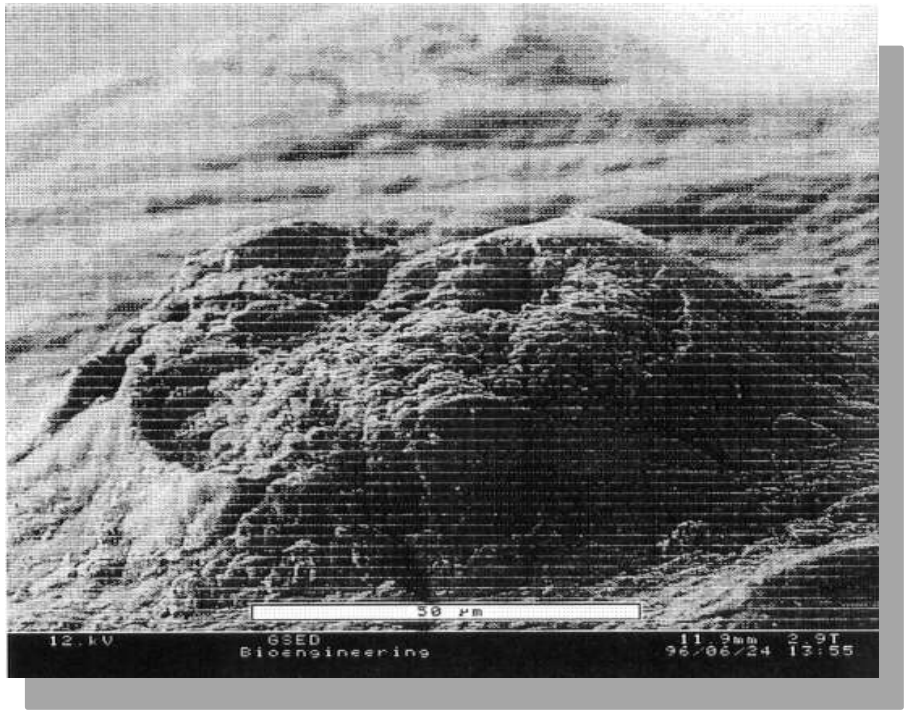
The ISO-classified have difficult to clean, particle-generating, or visibly dirty equipment or surfaces.

C. Dirt, debris, stains, and one strand of hair proximately 2 inches long was observed in the front recirculation vent immediately below the aseptic processing surface of the ISO 5 hood.

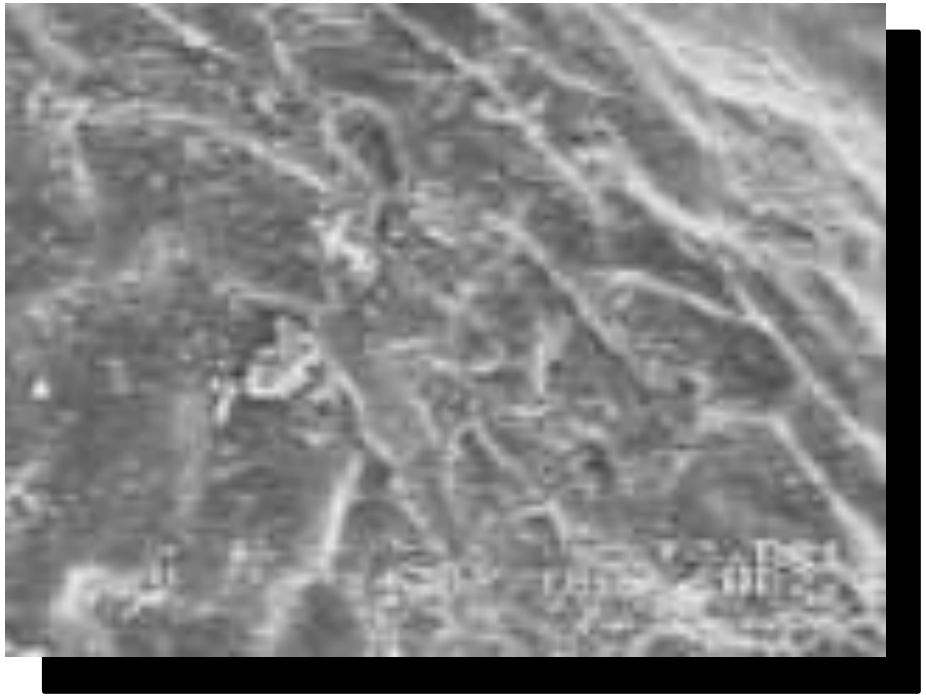
D. LAF Hood [redacted] is installed on a wood fiber board table with stainless steel, painted, and formica-type surfaces. This multi-surface table creates a difficult to sanitize surface in the clean room.

Disinfectant Residues

Phenol Residue

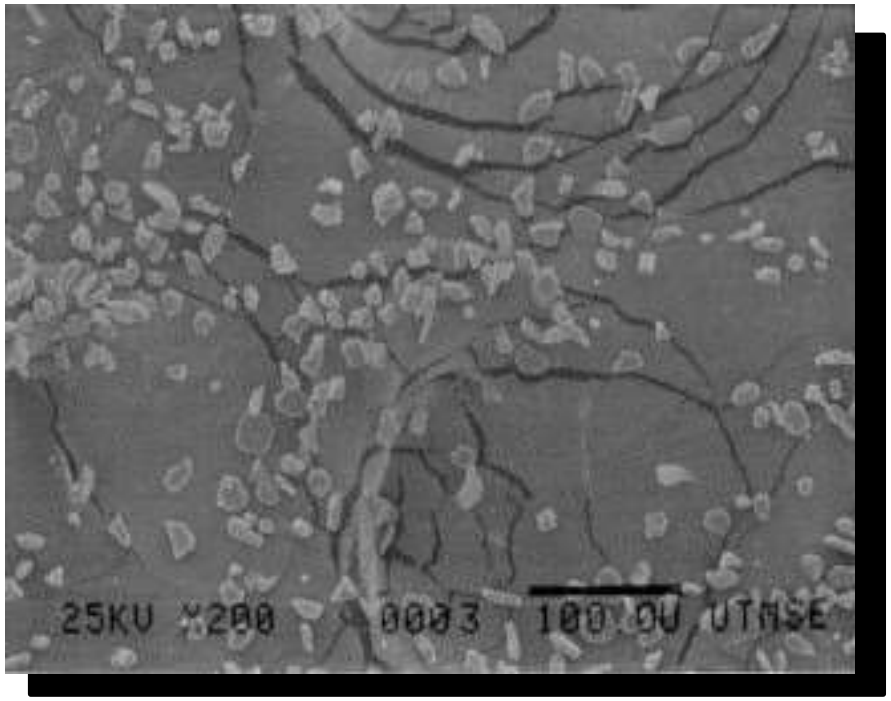


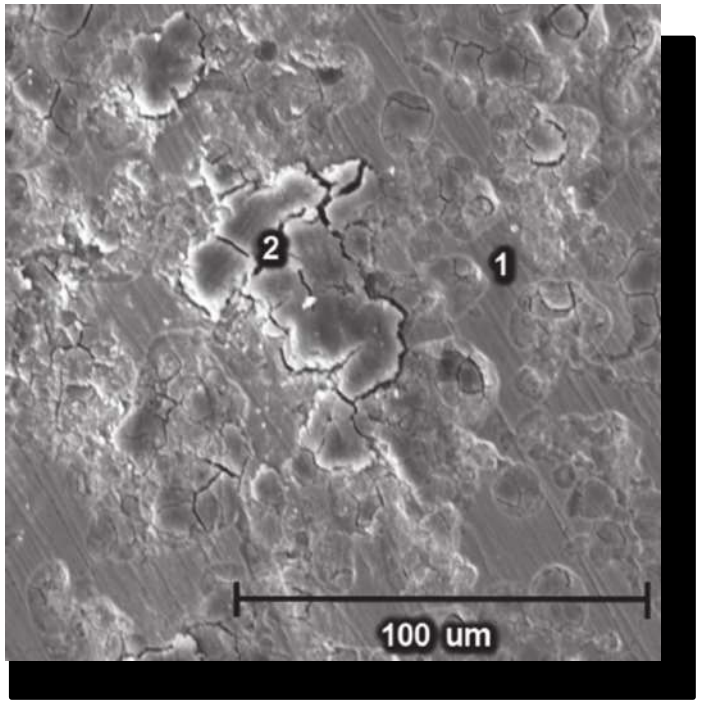
Quaternary NH_4 Residue



Disinfectant Residues

Bleach Residues





HEPA Filters, Air Returns, Ceiling Tiles

- Air supplied to cleanrooms should be HEPA filtered.
- Consider placement of air returns (low returns, not adjacent to HEPA).
- Airflow in cleanroom sweeps particles down and out.

HEPA Filters, Air Returns, Ceiling Tiles

- Loose/unsealed ceiling tiles or non-ducted air returns may permit introduction of particles (non-viable or viable) into the cleanroom.

Additional information can be found in self-guided training on Airflow and Cleanroom Design through FDA's Compounding Quality Center of Excellence.

483 Observations

OBSERVATION 6
Unsealed, loose ceiling tiles were observed in your cleanroom.

Specifically,

On 01/11/19, I observed that one of the ceiling tiles in your ISO 7 clean room is not sealed to the adjacent metal bracket along one of its short edges. This tile is located approximately 10' from the opening to the ISO 5 area of the LFH.

OBSERVATION 13
Unsealed, loose ceiling tiles were observed in your cleanroom.

Specifically, from 3/9-3/11/20, your firm's production area where ophthalmic Cyclosporin/Coconut Oil 2% eye drops for veterinary use are produced was observed to have unsealed, one cracked, and one visibly brown stained ceiling tile.

483 Observation – Preparing Drugs During Construction

OBSERVATION 1

Your firm produced drugs while construction was underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.
Specifically,

Your firm produced non-sterile and sterile drugs while construction was underway in an adjacent area to (b) (4) . Controls and cleaning frequency may not be adequate to prevent contamination of the production environment and product. Dust was observed in the ISO7 lab.

Materials Storage, Handling, and Transfer into the Cleanroom

Facility Design & Material Transfer

483 Observation

Observation 4

The facility design was observed to allow the influx of poor quality air into a higher classified area.

Specifically, the pass through (b) (4) windows located in between the buffer room ISO 7 and the unclassified room are not properly sealed to prevent the mixture of classified and unclassified air. In addition, these pass through windows directly open to the ISO 7 areas that are located in front of your ISO 5 laminar flow hoods (b) (4)

OBSERVATION 4

Equipment was not disinfected prior to entering the aseptic processing areas.

Specifically, equipment and materials and/or supplies were not disinfected prior to placing these items into to the ISO 5 aseptic processing area. For example, while conducting visual observations on 7/26/2018, 7/31/2018, and 8/1/2018, I observed your firm's pharmacy technician placing drug components into the cleanroom (b) (4) without disinfecting with sterile (b) (4) . Drug components were then transferred from your firm's ISO 7 to the ISO 5 aseptic processing area without disinfecting with sterile (b) (4) and used to aseptically process sterile patient-specific drug products.

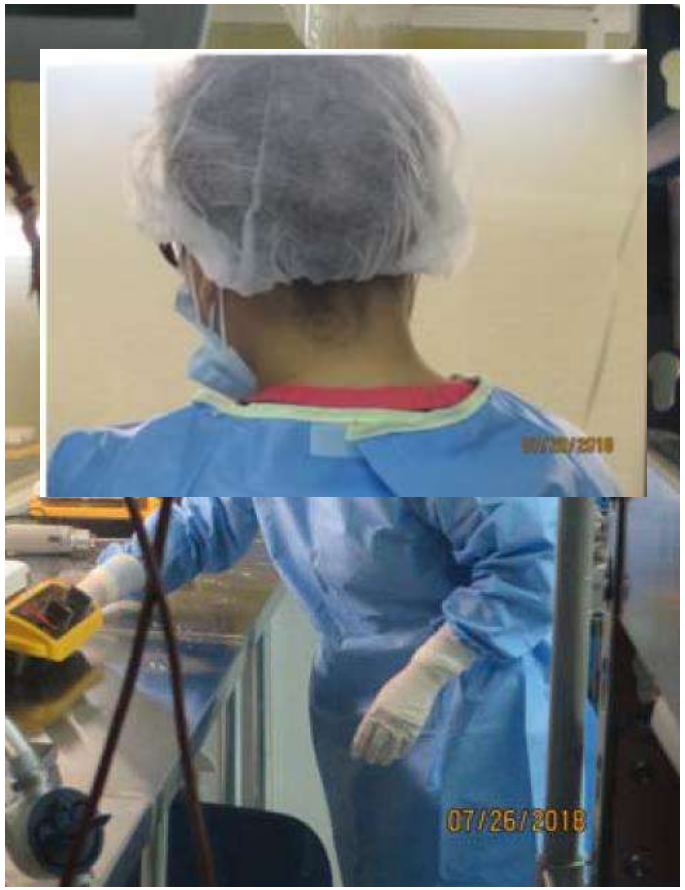
483 Observation

OBSERVATION 3

Aseptic practices in critical area are not adequate for sterile drug processing. On 25 July 2017, we observed:

A. The pharmacist touching item on floor and return to processing TPN products without changing gloves.
B. The pharmacist using a bar code scanner from outside hood and return to processing without sanitizing gloves.

Personnel and Gowning



483 Observations

OBSERVATION 2
Personnel engaged in aseptic processing were observed with exposed hair.

Specifically, on 7/26/2018 while observing your firm's pharmacy technician aseptically compounding 2 lots of sterile Tri-Mix Injection (Lot 07252018:91, BUD 1/21/2019; and Lot 07262018:52, BUD 1/22/2019), I observed your pharmacy technician hair sticking out from underneath the hairnet. On more than eight occurrences, your pharmacy technician entire head extended into your ISO 5 area while aseptically processing both sterile drug lots.

OBSERVATION #1

On 10/17/17, an operator engaged in aseptic processing was observed with his upper torso inside the ISO 5 area

Challenge Question #1

Non-microbial filth poses a contamination risk to:

A. Sterile drugs only
B. Sterile and non-sterile drugs
C. Non-sterile drugs only
D. Ophthalmic drugs only

Filth: Microbial

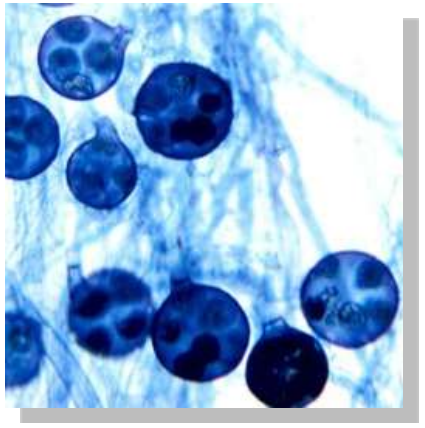
- Material transfer
- People
- Environment
- Water sources (sinks, drains)
- Standing water
- Air
- Surfaces
- Container/Closures
- APIs and excipients
  - Non-compendial
  - Non-pharmaceutical grade
  - Not suitable for the intended use

Basic Types of Microorganisms

- Bacteria
- Fungi (Yeast/Mold)

Bacteria (***Escherichia coli***)

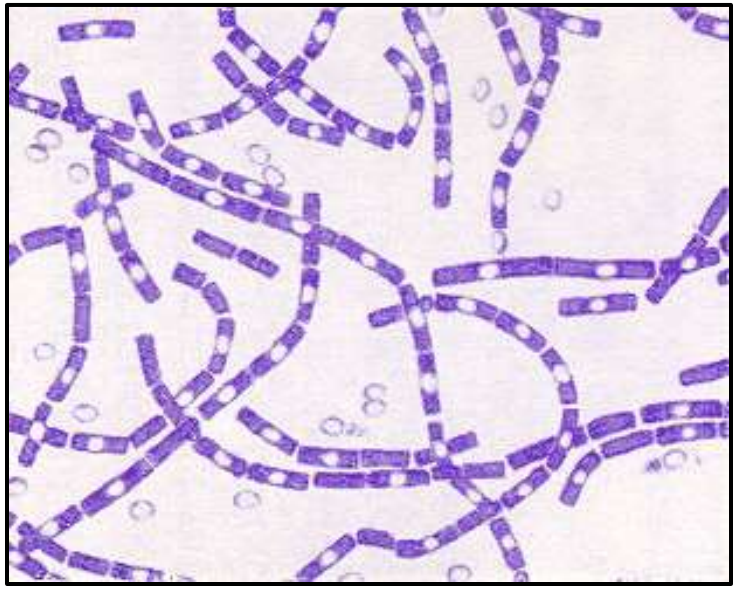
Yeast (***Tinea pedis***)



Mold (***Saprolegnia***)

Bacteria – most common cleanroom contaminant

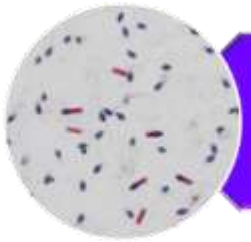
- Ubiquitous to every habitat on Earth (and beyond!)
- **0.2** µm – 20.0 µm (micron) in size
- Spore forming bacteria (gram positive rods)
- Endospore is a dormant, tough, non-reproductive structure
- Endospores (spores)
  - can survive without nutrients
  - Resistant to UV light
  - Resistant to desiccation
  - Resistant to high/low temperatures
  - Resistant to many disinfectants



- Yeasts/molds - less common
- Presence is cause for concern

Bacteria – Wide Range of Shapes

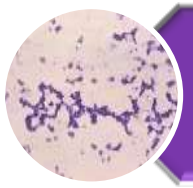
Bacilli (rods)



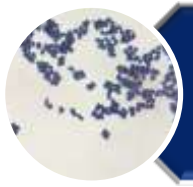
Bacillus (aerobic)

Clostridium (anaerobic)

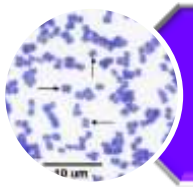
Cocci (spheres)



Streptococcus

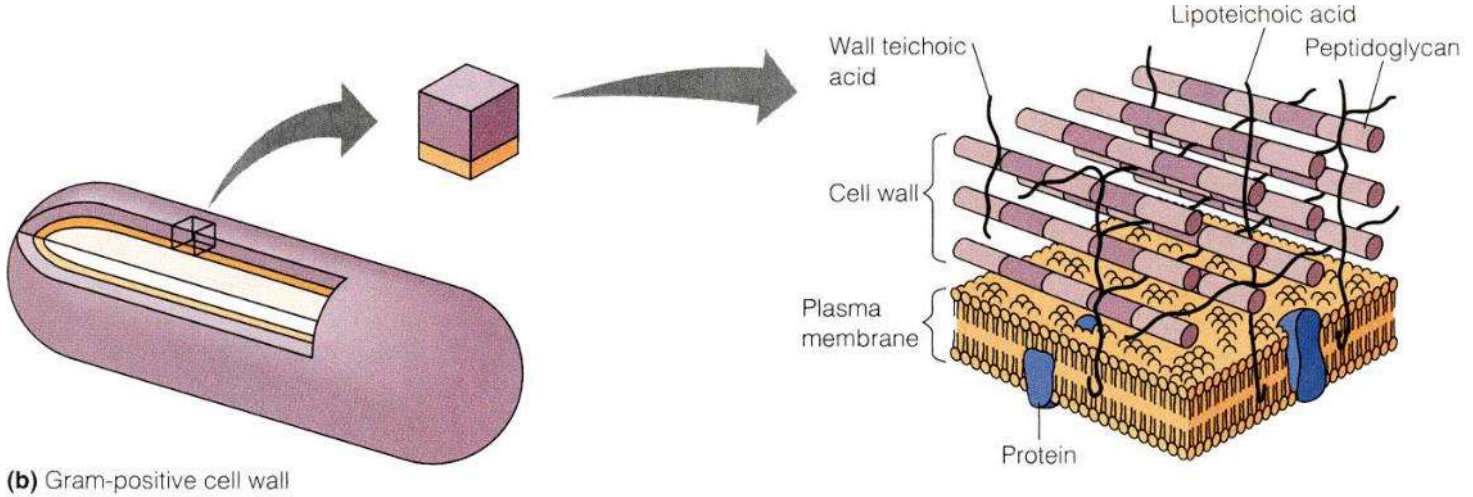


Staphylococcus

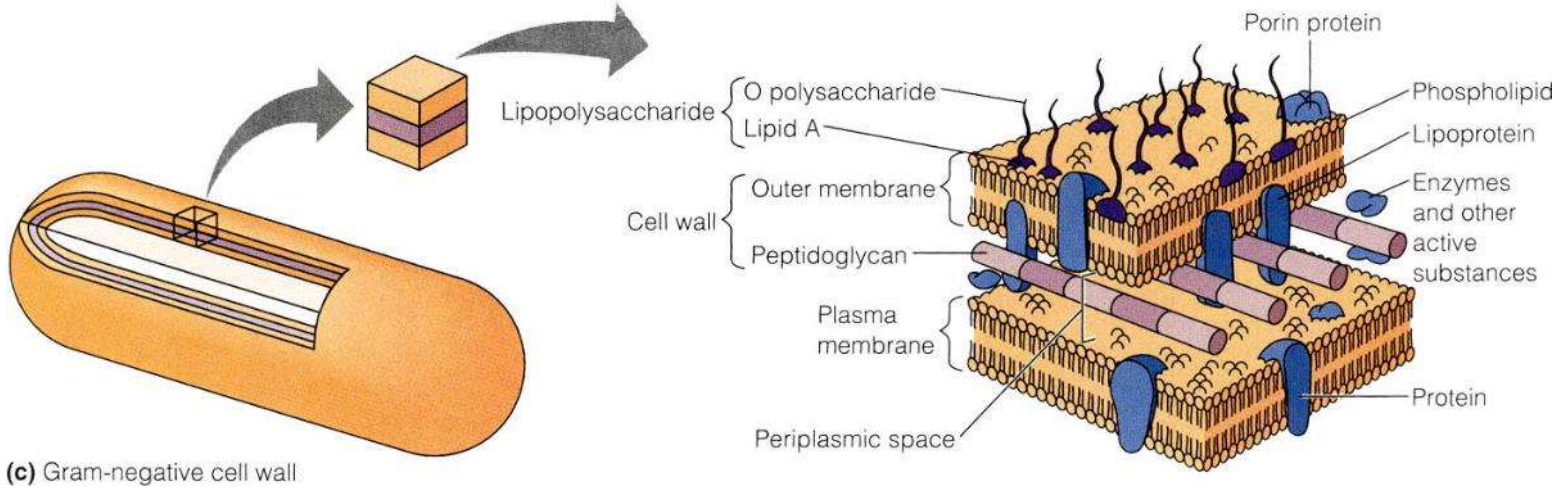


Micrococcus

Bacteria – Gram Positive or Gram Negative

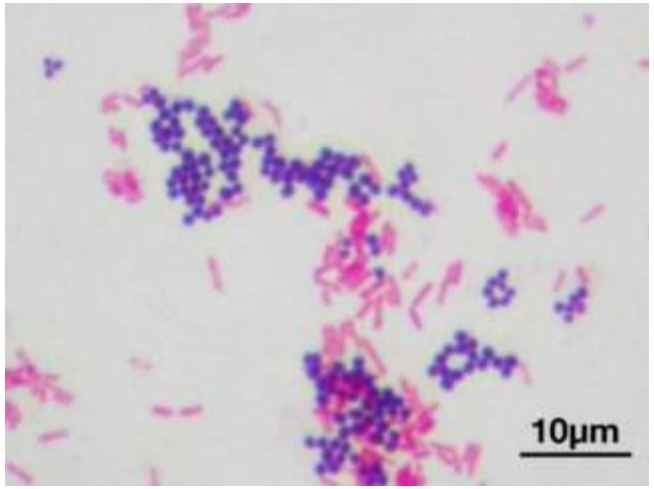


(b) Gram-positive cell wall



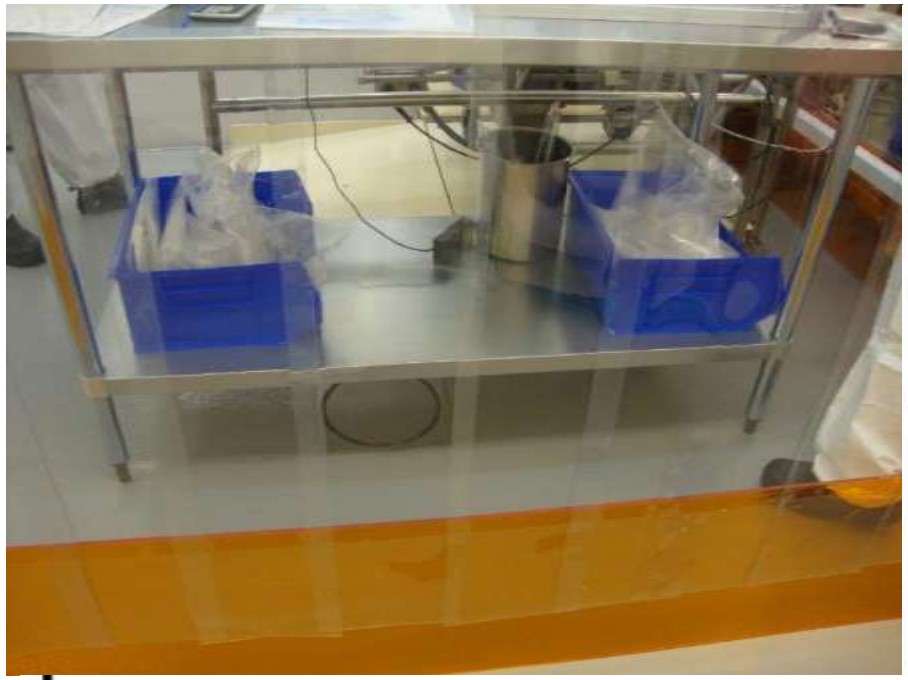
(c) Gram-negative cell wall

Bacteria – Gram Positive or Gram Negative



- Gram positive cocci are commonly found on **human skin**.
- Gram positive rods are commonly found in **environment** (soil, dirt) and may be spore-forming.
- Gram negative cocci are less common, may be associated with diseases (*Neisseria gonorrhea*)
- Gram negative bacteria produce **endotoxins**.
- Gram negative rods are isolated from **water** or may be shed by people suffering from illnesses (e.g., Salmonella infection).

Water and Water Sources



OBSERVATION #10

Sinks or drains are present in the cleanroom where the ISO 5 area is located. Specifically, in the ED satellite pharmacy, the sink is located right across from the ISO 5 (b) (4) hood in the unclassified ED satellite pharmacy.

Purified Water, USP

- Purified water as a component of non-sterile drugs.
- Purified water as final rinse for product contact surfaces (utensils, containers, closures).
- Refer to USP Monograph on Purified Water and USP <1231> for additional information.

Water for Injection, USP

- Sterile Water for injection (sWFI) as a component of sterile injectable drugs.
- Rinses with WFI can be used to reduce endotoxin levels on surfaces.
- Refer to USP Monograph and USP <1231> for additional information.

Microbial Contaminants – Drug Components & Drug Products

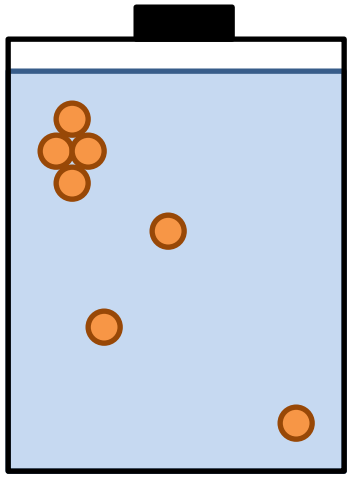
- Organism found in drug components: *Kocuria rosea*

Components should be suitable for their intended use

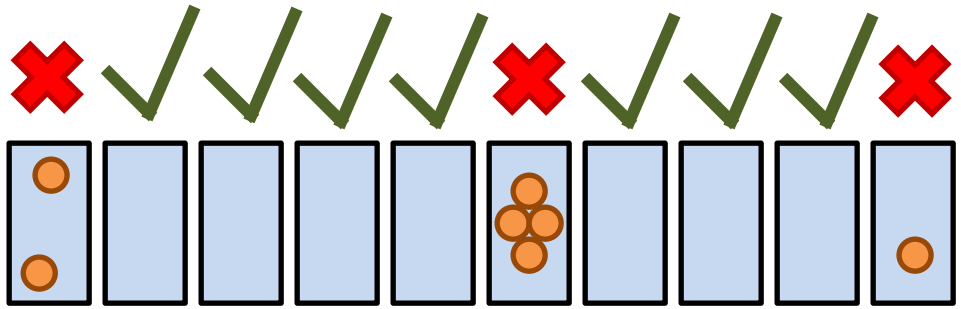
- Organisms recovered from finished products: *Exserohilum rostratum, Rhodotorula laryngis, Rhizopus stolonifer, Cladosporium cladosporioides*

Remember, passing sterility test is not proof of sterility of the lot!

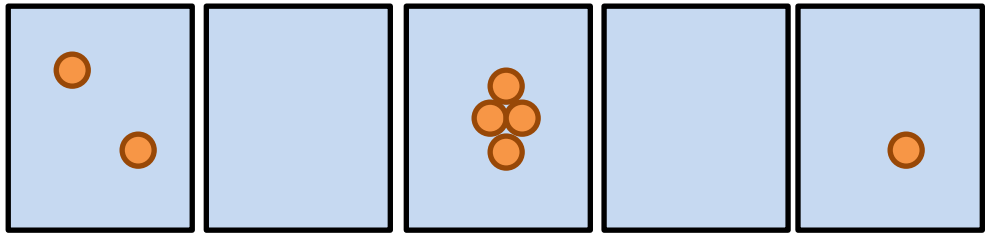
Microbial Contamination is not Uniform



100 ml



10 x 10 ml samples



5 x 20 ml samples

Endotoxin Contamination – Drug Components & Drug Products

- Drug components not intended for pharmaceutical use or for use in sterile drug preparations may have endotoxin levels that exceed safe limits.
- Refer to USP <85> for information on endotoxin safety limits. The limit differs depending on the route of administration (IV, intrathecal, ophthalmic).
- Compounding Risk Alert: FDA warns compounders not to use glutathione from Letco Medical to compound sterile drugs.

Endotoxin Contamination – Drug Components & Drug Products

- Know the allowable endotoxin limit for your dosage form.
- Consider using components that are intended for use in sterile drug preparations (APIs or sterile finished drugs).
- Endotoxin levels in the finished product may be calculated from results reported on the COA of drug components.
- Testing of drug components or finished drug product for endotoxin levels.
- Remember that container/closure can contribute to ET burden, so use suitable primary packaging components.

Endotoxin Contamination – Drug Components & Drug Products

- Endotoxins are not removed by sterile filtration.
- Endotoxins are not removed by autoclaving.
- Critical to establish endotoxin controls.

OBSERVATION 1

Your firm produces drug products intended for intrathecal use from non-sterile bulk active ingredients that are not controlled for endotoxin level. Therefore, you have no assurance that your final product is within allowable limits for bacterial endotoxins. Intrathecal (IT) drug products manufactured for use in pumps for pain management, such as various combinations of Baclofen, Clonidine, Dilaudid, Ketamine, Fentanyl, Morphine, Sufentanil, Methadone and Bupivacaine, are made with non-sterile bulk drug substances as starting materials e.g. (b) (6), (b) (7)(C) Hydromorphone/Fentanyl/Bupivacaine/Clonidine/Ketamine [hydro - (b) (4) , fenta - (b) (4) bupi (b) (4) , clonidine (b) (4) , and keta - (b) (4)]. Your firm lacks a mechanism for endotoxin control.

Filth: Chemical Contaminants

- Hazardous drug residues (e.g., cytotoxic drugs)
- Sensitizing drug residues (e.g., beta-lactams)
- Highly potent drug residues (e.g., hormones)
  - Appropriate containment
  - Clean with oxidizing/sporicidal agent

- Other drug residues
  - Use cleaning agent appropriate for pharmaceutical use (not dish detergent)

Filth: Chemical Contaminants

- Chemical components should be pharmaceutical grade/suited for intended their purpose; be used within expiry (impurities)
- Hazardous, sensitizing, potent, active residues pose potential cross-contamination risk
- Failure to adequately clean utensils, surfaces, glassware, balances, fume hoods, ISO 5 areas, etc. is considered an insanitary condition
- Know your suppliers

483 Observations

OBSERVATION 1
You produced hazardous drugs without providing adequate cleaning of work surfaces and cleaning of utensils to prevent cross-contamination.

Specifically,
The cleaning of hazardous drug product is not adequate. Your firm's cleaning between compounded products included only a wipe down of the compounding area/compounding hood with (b) (4). Your firm could not provide evidence that (b) (4) cleaned the hazardous drugs compounded at your firm. Additionally, you could provide no evidence that the detergents used to wash utensils and equipment remove the hazardous drug products you work with. The compounding area/compounding hood, utensils, and equipment are shared amongst all products (both hazardous drugs and non-hazardous drugs) at your pharmacy. Hazardous drugs compounded at your firm include

OBSERVATION 8
You produced beta-lactam drugs without providing adequate containment, segregation, and cleaning of work surfaces to prevent cross-contamination.

Specifically, beta-lactam drug products are produced in the same laminar flow hoods as other products separated only by a wipe down of hood surfaces with (b) (4) You do not have a specific process to deactivate and remove any beta-lactam product spillage that may occur within the laminar flow hoods or facility during handling, processing, or filling operations.

483 Observations

OBSERVATION 2

You used a non-pharmaceutical grade component in the formulation of a drug product.

Specifically, your pharmacy makes non-sterile prescription drug products using purchased (b) (4) (b) (4) including (b) (4) and (b) (4) /grocery store brands. You have never reviewed or collected certificates of analysis or established specifications to ensure that (b) (4) used is appropriate for pharmaceutical production operations. Examples of products produced with purchased (b) (4) include:

A. Triamcinolone 0.5% Oral Rinse liquid suspension, Rx (b) (6) made on 6/11/2019, (b) (4) BUD 6/25/2019

Challenge Question #2

The following method can effectively be used to remove endotoxin from container/closures:

A. Moist-Heat Sterilization
B. Irradiation
C. Dry-Heat Sterilization
D. Filtration

Cleaning and Disinfection

- Wipes used in ISO 5 area should be sterile, non-shedding
- Disinfectants used in ISO 5 area should be sterile
- Routine disinfection and cleaning following spills
- Routine application of sporicidal agent
- Disinfectant dwell times must be observed

USP <1072> Disinfectants and Antiseptics

483 Observations

OBSERVATION 4

Cleaning pads or wipes used in the ISO 5 aseptic processing areas are not sterile.

Specifically, the (b) (4) Wipes used in the cleaning and disinfection of the surfaces inside the ISO 5 laminar flow hoods and the biological safety cabinet are not sterile.

OBSERVATION 5

Sporicidal agents were not used in your facility's ISO 5 classified aseptic processing area.

Specifically, sporicidal agents are not used to clean the ISO 5 laminar flow hoods and the biological safety cabinet. Additionally, expired (b) (4) Sterile, Sporicidal Disinfectant and Cleaner (Exp. 11/2017) is currently being used to clean the ISO 7 and ISO 8 areas.

THIS IS A REPEAT OBSERVATION

OBSERVATION 6

Disinfectant contact time (also known as "dwell time") and coverage of the item being disinfected were insufficient to achieve adequate levels of disinfection.

Specifically, on 8/1/2018, I observed the pharmacy technician mopping the floor one minute after application of the (b) (4) Disinfectant. The manufacturer's direction of use for (b) (4) Disinfectant indicate that a (b) (4) contact time is required to achieve efficacy.

Filth: Vermin

- Pests (living or dead), urine, fecal matter
- Pets, support animals
- Facility design - prevent ingress of pests
- Pest control program - control for insects, rodents
- Routine trash collection and disposal - remove potential nesting/hiding places for pests

483 Observation

OBSERVATION 1

Vermin was observed present in areas immediately adjacent to your production area.

A dead spider was observed in HEPA filter located in the ceiling of the ISO 7 clean room, approximately 10 feet from the ISO 5 laminar air flow (LAF) hood used for sterile drug processing.

Keeping the Filth Out…

"The patient in the next bed is highly infectious. Thank God for these curtains."

Barrier Technologies

Cleanrooms – ISO 8, ISO 7, ISO 5 areas

Cleanrooms are harsh environments:

- controlled (low) temperature
- controlled (low) humidity
- low nutrients
- frequent cleaning and disinfection
- surfaces and materials are easy to clean & non-shedding
- pressure cascade to prevent ingress of lower quality air
- limits for viable and total particle counts

Particle Action and Alert Levels

TABLE 1- Air Classifications[a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)

USP <797> Viable Particle Levels in Air

Table 2. Recommended Action Levels for Microbial Contamination*† (cfu per cubic meter [1000 liters] of air per plate)

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

USP <797> Viable Particle Levels on Surfaces

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

* Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-6, 5 April 2007.

Cleanroom/HEPA Filter Certification

- HEPA filter integrity testing
- Air velocity measurements
- Total particle counts (to meet ISO classification)
- Airflow pattern studies (smoke studies) performed under dynamic conditions
- Differential pressure cascade
- Environmental monitoring (air, surface, personnel)

483 Observations

OBSERVATION 9
Inadequate pressure differentials between higher quality air rooms and lower quality air rooms were observed. .

Specifically,

a. Sterile drug filling is conducted inside the ISO 5 core of Laminar Air Flow Hood (LAFH). The evaluation of unidirectional airflow (e.g., smoke studies) for microbiological contamination was not performed under dynamic conditions in the ISO 5 LAFH, which is located in an ISO 7 environment.

b. During filling operations, we observed that the doors from the ISO 8 compounding room to the ISO 7 Ante room, and the door from the ISO 7Ante-Room to the ISO 7 aseptic filling room, did not stay consistently closed. We heard multiple alarms during the aseptic filling due to loss in pressure. The firm cannot assure continuous positive pressure during filling operations.

OBSERVATION 4
You did not have a HEPA filter over the area to which sterile product was exposed.

Specifically, your firm's unclassified (b) (4) hoods fail to contain HEPA filters. Instead, your firm is currently utilizing household air filters that can potentially shed particulates. On 3/10/20, your firm produced ophthalmic Cyclosporin/Coconut Oil 2% eye drops for veterinary use (firm used (b) (4)), lot (b) (4) (Rx (b) (6) within the (b) (4) hood.

483 Observations

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

The ISO 5 classified aseptic processing area was located within a non-classified room (segregated production area).

Specifically, your firm's ISO 5 (b) (4), which is used to produce mitomycin and cyclosporine drug products, is located in a non-classified room. The following Lots were produced in the (b) (4) between 05/14/18-08/14/18:

1. Mitomycin Opth 0.02%, Lot 06152018@13
2. Cyclosporin Aqueous 0.5% solution, Lot 06132018@43
3. Cyclosporin Aqueous 1% solution, Lot 06252018@45
4. Cyclosporin Aqueous 1% solution, Lot 07262018@7

People and their Particles

Activity	Number of particles generated (0.5 micron and larger per minute)
Sitting or standing still	100,000
Sitting, small movement of arms or head	500,000
Sitting, moving arms, legs or head	1,000,000
Standing Up	2,500,000
Walking slowly	5,000,000
Walking normally	7,500,000
Walking ~ 5.5 MPH	10,000,000
Performing a workout	15,000,000 - 30,000,000

Source: Encyclopedia of Cleanrooms, Bio-Cleanrooms, and Aseptic Areas, July 2000, Philip R. Austin

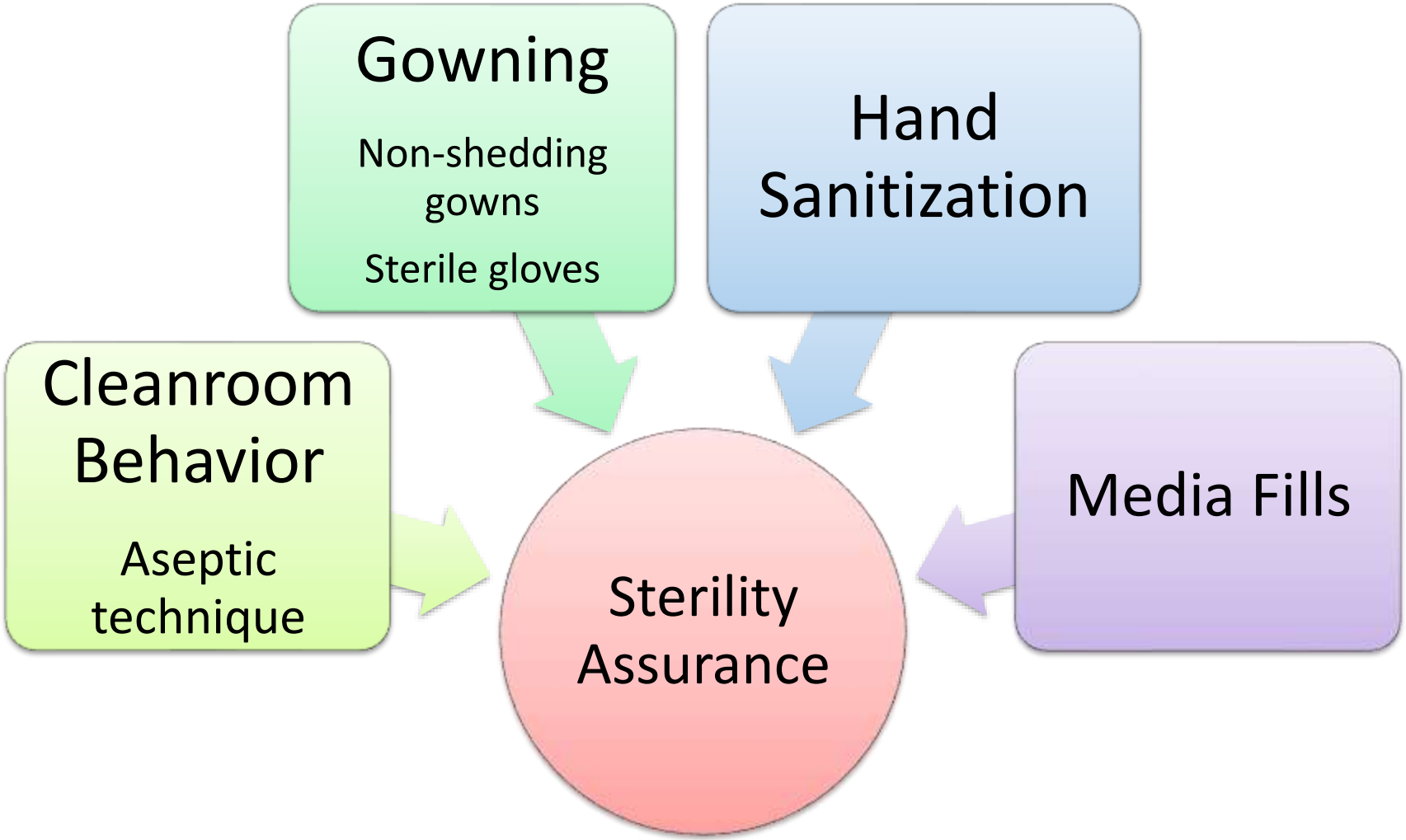
How Dirty are We?

"There are billions of germs, bacteria, and microbes living on my body...but I still get lonely sometimes."

AREA	NUMBER OF MICROORGANISMS/cm^2
Scalp	1 million
Saliva and nasal fluid	10 million/gram
Back	100
Groin	1 – 20 million
Forehead	100 – 1000
Hand	10,000 – 100,000
Armpit	1 – 10 million
Feet	1 million

Source: Clean Room Primer, 1985, J.J. Nappi Jr. Liberty Industries Inc. USA.

Particle Control – Personnel



483 Observations

OBSERVATION 4
Personnel engaged in aseptic processing were observed with exposed hands.

Specifically, an operator was observed donning sterile gloves inside the ISO 5 LAFW prior to the media fill on 08/06/18.

OBSERVATION 9
Personnel engaged in aseptic processing were observed wearing non-sterile gloves.

Specifically, on 3/10/20, during the production of ophthalmic Cyclosporin/Coconut Oil 2% eye drops for veterinary use (firm used (b) (4)), lot (b) (4) (Rx (b) (6)) your firm's Pharmacist was observed wearing non-sterile gloves.

Observation 7: Media fills were not performed that closely simulate aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

Specifically, your firm's media fills fail to demonstrate your current compounding process. For example, there is no documentation of the simulated filling and (b) (4) process. In addition, (b) (4) units were filled, but only 60 units were incubated and inspected for growth and turbidity. Your firm failed to provide scientific justification for not incubating and inspecting all units. Your firm also lacks documentation of growth promotion testing for the media used.

Challenge Question #3

What is the dirtiest thing in the cleanroom?

A. Cardboard
B. People
C. Gowning materials
D. Drug ingredients

Summary

- A drug product shall be deemed to be adulterated if it is prepared, packaged, or held under insanitary conditions whereby it becomes contaminated with filth or is rendered injurious to health.

- Employ various controls to limit or eliminate filth (non-microbial, microbial, chemical, or vermin).

- Independently, sterility testing, finished product testing, media fills, environmental monitoring do not establish or ensure product quality.

References

- FDA Draft Guidance for Industry – Insanitary Conditions at Compounding Facilities
- FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
- FDA Compounding Risk Alerts
- FDA Compounding Quality Center of Excellence
- For online courses on Insanitary Conditions and Sterility Assurance, Investigations and CAPAs, Airflow, and others

Questions?