Hot Topics in Aseptic Behaviors

PDA Missouri Valley Chapter

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Speaker Introduction

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Background Aseptic Processing

Aseptic processing is a manufacturing method that can produce product that is absent of bacteria without subjecting the product to terminal sterilization processes.

Many products degrade and become ineffective when subjected to the harsh conditions of terminal sterilization.

Aseptic process manufacturing allows these products to be produced in a sterile environment, allowing them to maintain their effectiveness while being safe to inject into patients.

Aseptic Processing

- In aseptic processing of sterile drug and biological products, the drug product, container and closure are first sterilized separately and then brought together.
  - Glass containers – dry heat
  - Rubber closures – moist heat
  - Liquid dosage forms – filtration
    - Each of these processes requires validation and control
- The environment for bringing these parts together (filling and sealing) must be extremely high quality
- Aseptic processing has more variables than terminal sterilization
- Careful control during processing is required
- An error in any part could lead to distribution of contaminated product
- Controlling risk of contamination

Aseptic Processing

Product should have minimal exposure to people since people are the major source of microbial contamination in aseptic processing

Critical that workers understand the purpose of their work

Workers must develop the skills for aseptic technique required to assemble drug product/containers closures or perform aseptic technique

Manufacture of Sterile Products – EU Annex 1

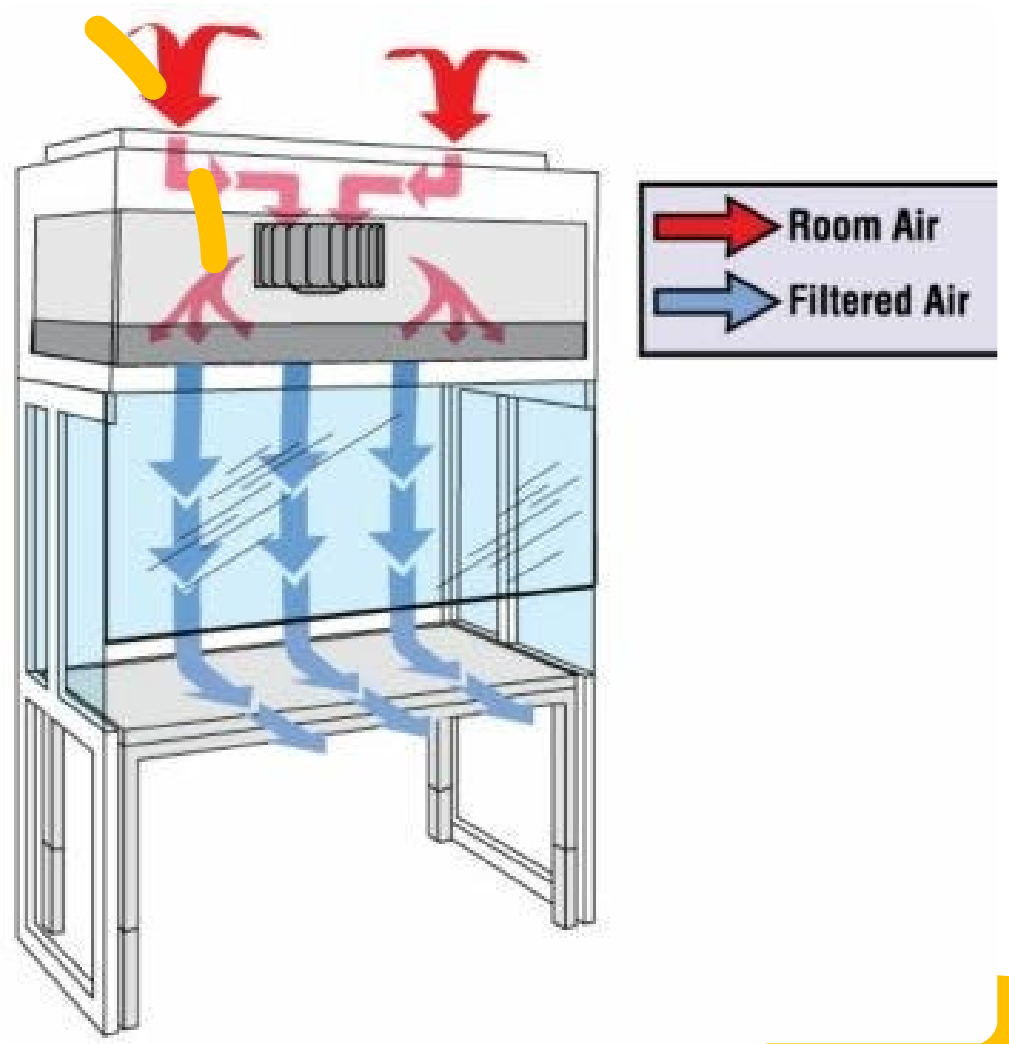
- Facility, equipment and process should be appropriately designed, qualified/validated according to cGMPs.
- RABS, isolators, robotic systems and rapid/alternative methods should be considered to increase the protection of product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination.
- Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles.

CCS – EU Annex 1

- A contamination control strategy should be implemented across the facility in order to define all critical control points and assess the effectiveness of the controls and monitoring measures employed to manage risks to medicinal product quality and safety.

Aseptic Processing – First Air

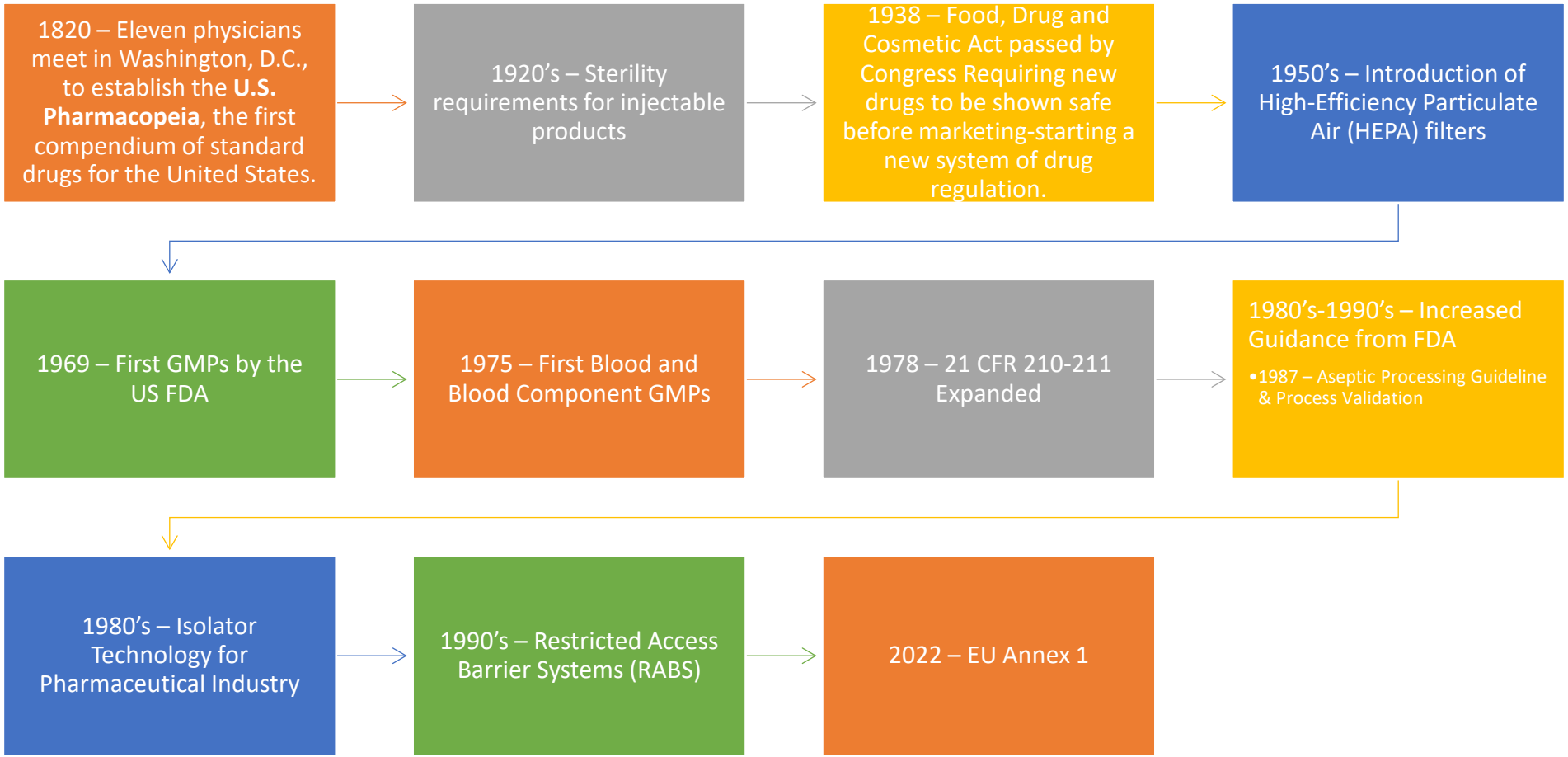
- The undisturbed, unidirectional air that comes from a HEPA filter and impacts open products
- Reaching over items disrupts first air
  - Air turbulence moves contamination
- HEPA – High Efficiency Particulate Air
  - HEPA filters were developed in the 1940s by the US Army
- Air Visualization Studies (AVS) ensure design and practice is adequate



Aseptic Processing – First Air

- Annex 1 reinforces the importance of AVS (Clauses 4.15, Qualification, 4.31, EM locations and 7.18, Operator Training)
- The FDA guidance on aseptic processing from 2004 has always been very clear on this subject: “ it is crucial that airflow patterns be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants (e.g., from an adjoining lower classified area). In situ, air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.

cGMP Timeline/History



Basics of Microbiology

People carry a large amount of bioburden load on our bodies

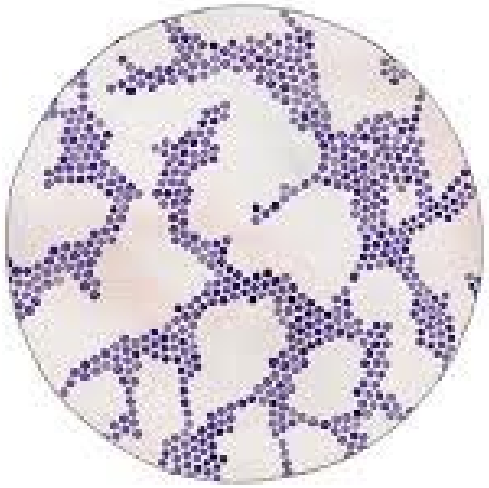
We are the largest source of contamination inside the cleanrooms

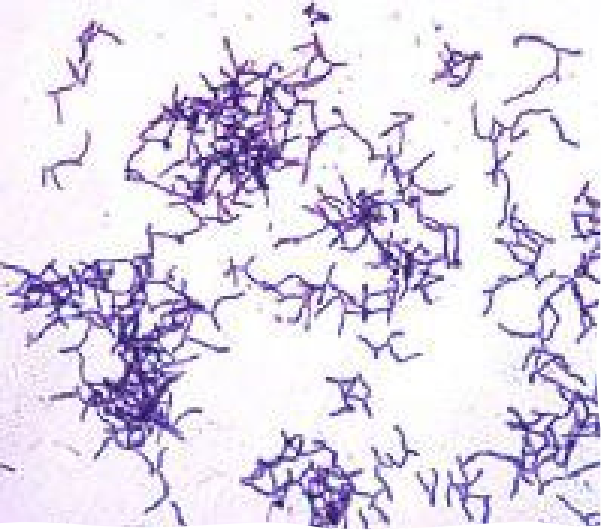
So what is bioburden?????

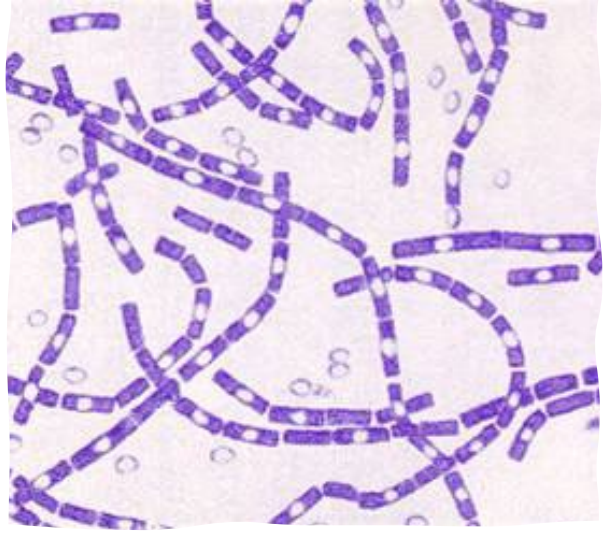
Bacteria

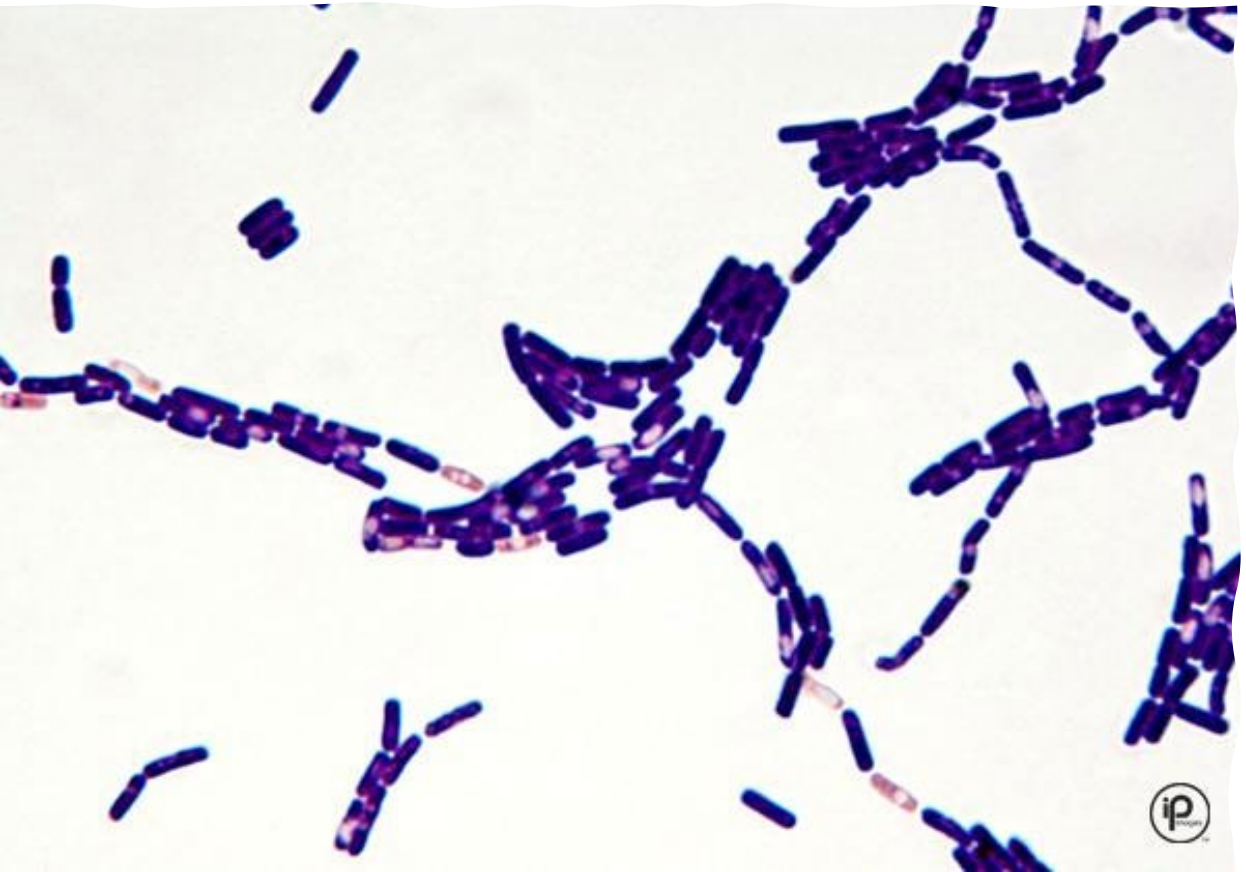
Gram Positive Cocci

- Skin organisms
- Shed off in clean rooms
- Most prevalent microbe









Bacteria

Gram Positive Rods

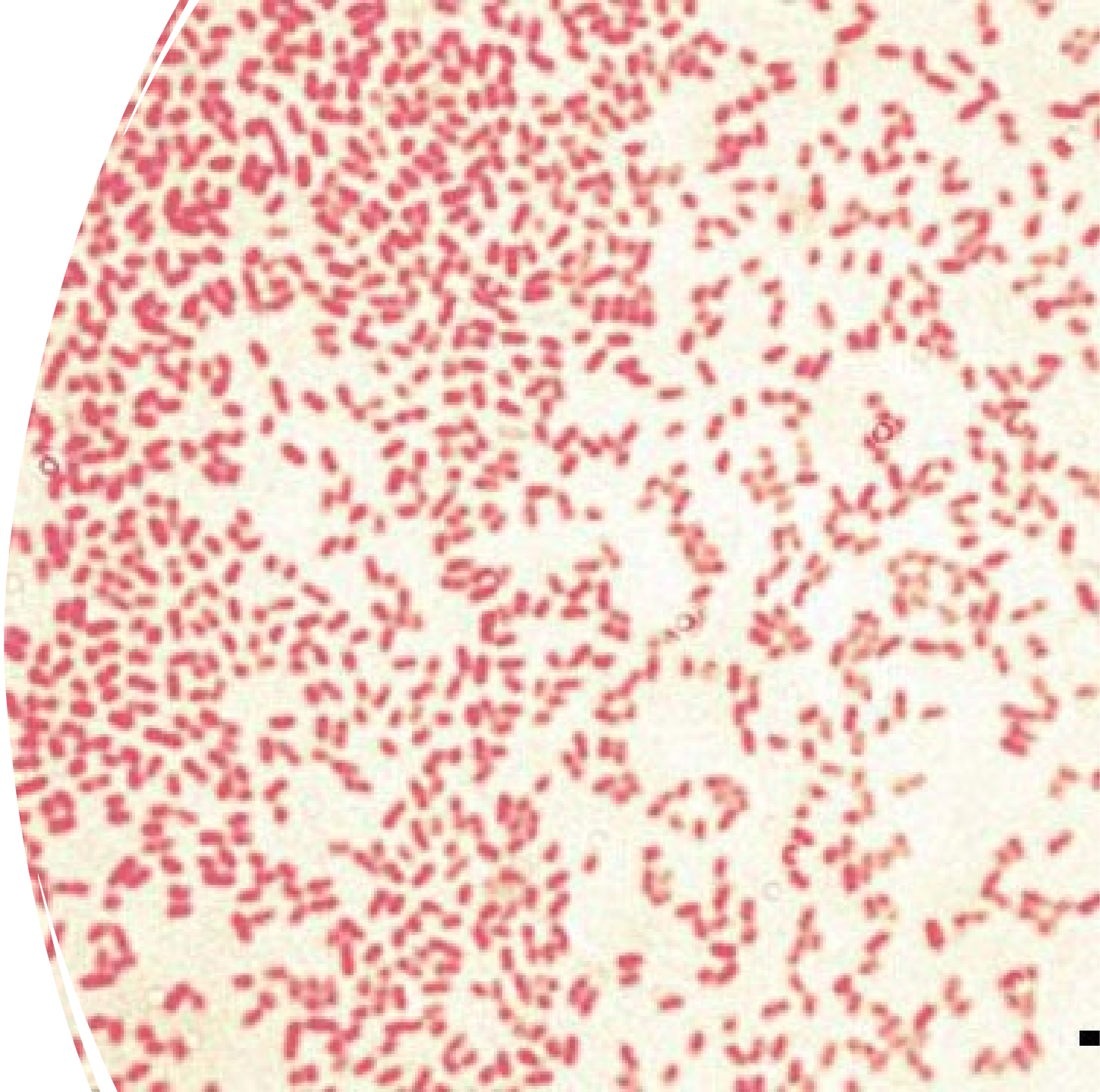
- Soil Organism
- Environmental isolates
- Spore Forming

Require consideration when selecting cleaning agents

Bacteria

Gram Negative Rods

- Water organisms
- Gastrointestinal



Fungal

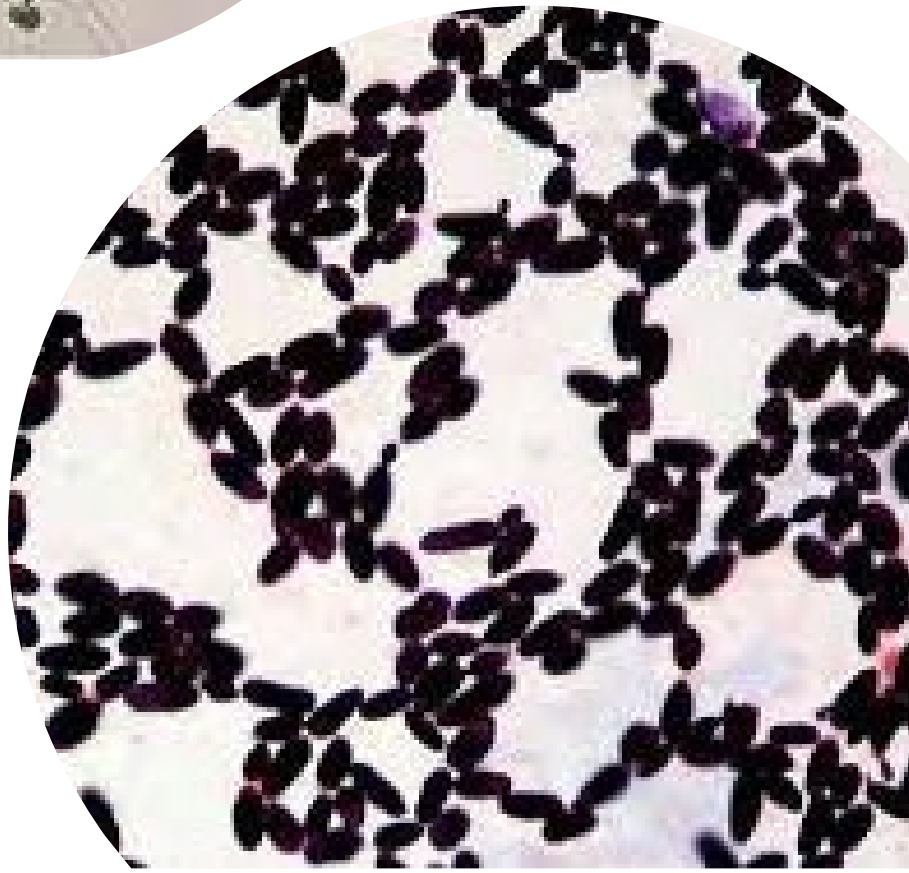
Yeast and Molds

Yeasts

- Small, single celled plants
- Feed on sugars and starches
- *Candida*

Molds

- Plants
- Grow in air, moisture
- Produce spores, abundant in the air
- *Aspergillus*
- *Penicillium*



Pathogenic Microorganisms

Aseptic = absence of the potential to cause infection

In aseptic processing, we are concerned with any microbial contamination

Trying to avoid pathogenic organisms from harming patients

Non-pathogenic – most common, non disease causing

Opportunistic pathogens – cause disease under appropriate conditions

- Need a path of entry (open wound, weak immune system)

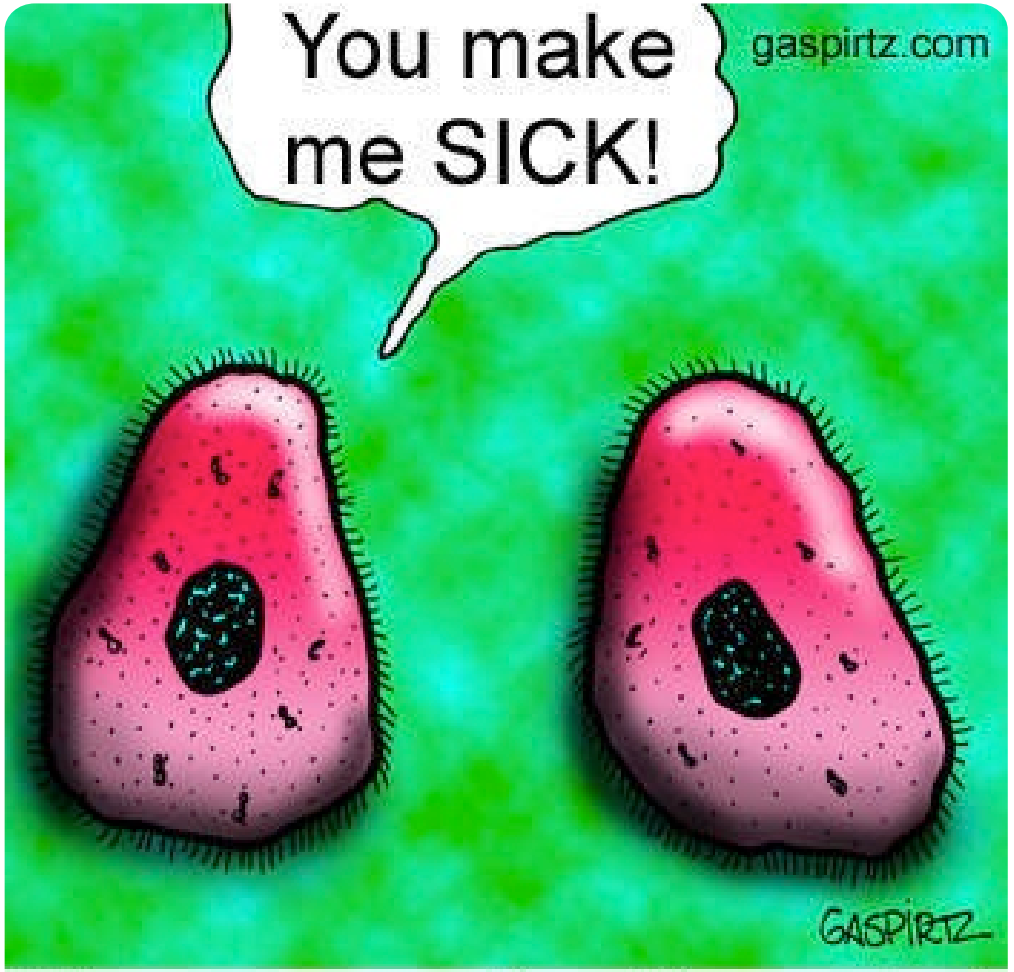
Obligate pathogens – cause disease on their own, bacteria must infect a host to survive

Sterile = free of microorganisms

Human Flora

The amounts and types of bacteria each person carries varies:

- How much hair on body
- Skin type – oily, dry, normal
- Lotions used
- Genetics
- Hygiene
- Amount of natural shedding



Transmission of Microorganisms

- Modes of transmission:
- Breathing
- Talking
- Droplet Transmission
  - Sneezing/Coughing
- Moving
- Direct or In-direct contact
  - Direct – touching, hugging, kissing
  - In-direct – touching object microbe has landed on
- Body Fluids
- Food, Water, Insects

Prevention of Transmission in Clean Rooms

Do not enter clean rooms if sick

1

Do not enter clean rooms with open wounds

2

Gown appropriately every time you enter a clean room

- Check for gloves tears, exposed skin

Gowning for Aseptic Processing

- Cleanroom personnel are the greatest risk for sterile product manufacturing
- Extensive gowning is required to keep microbial contamination away from the products
  - In collaboration with uni-directional air flow to sweep contamination away from the products and sterile processing area
- Sterile outer garments made of synthetic materials
- Non-particle shedding (or low)
- Laundered and sterile (Gamma irradiation)
  - Disposable, sterile for small operations
- Gowns keep your contaminants from reaching the cleanroom environment and sterile drugs

Gowning for Aseptic Processing

- Laundered scrubs
- Dedicated plant shoes/shoe covers
- Bouffant/Beard cover
- Sterile mask
- Bunny suit/full body gown
- Sterile hood
- Gloves and Sterile Gloves
- Sterile googles
- Sterile sleeves
- Sterile boots

Gowning Training and Qualification

- Documented and Approved Procedures are needed for:
- Gowning
- De-gowning
- Hygiene
- Qualification
- Disqualification
- Requalification

Gowning Training

Very important to train very well on how to act/move in a cleanroom

Training and qualification required for anyone working in the aseptic processing core area

- Manufacturing personnel – operators
- Maintenance staff
- Engineers
- Microbiology/Quality Control staff
- Quality Assurance staff

Training should include:

- Basics of Micro/Aseptic
- Gowning demonstration
- Gowning attempts with critique

Gowning Qualification

RISK ASSESSMENT NEEDED

- Takes place inside the clean room
- Microbial sampling
- Must pass three consecutive
- Video recording may be helpful if having trouble passing

Facility Design

Separate and defined areas of operation for aseptic processing facility required by regulations (21 CFR 211.42)

Need to be appropriately controlled to achieve correct degrees of air quality

Must satisfy microbiological and particle criteria

Room Classification

ISO 14644 assigns ISO classification levels to be used for the specification of air cleanliness in cleanrooms and associated controlled environments

Classification – defined per ISO 14644-1

level (or the process of specifying or determining the level) of airborne particulate cleanliness applicable to a cleanroom or clean zone, expressed in terms of an ISO Class *N*, which represents maximum allowable concentrations (in particles per cubic meter of air) for considered sizes of particles

ISO 5 Critical Area

- Where the sterilized drug product, containers and closure are exposed to the environment
- Product is vulnerable to contamination
- Environment must be controlled and maintained
- Appropriately designed air handling system to minimize particles in this zone
- Particle counts taken not more than 1 foot away from critical work
  - Remote counting systems, continuous
- HEPA air supplied at velocity to sweep particles away from filling line
- Airflow patterns must be designed to prevent turbulence
  - Smoke studies to evaluate eddy's or turbulence required

Support Areas

- Classified according to level of activity
- Background to filling line must at least meet ISO 7 under dynamic conditions
- ISO 8 appropriate for less critical activities (i.e., equipment cleaning)
- Must have proper airflow from areas of higher cleanliness to ones of lower cleanliness
  - Cleaner have higher positive pressure
  - Pressure differentials must be monitored continuously each shift and recorded – alarms for deviations
- Air Changes per Hour of 20 for ISO 8, more for ISO 5 & 7

HEPA Filtered Air

Twice per year HEPA leak tests and clean room certification HEPA efficiency testing

Aerosol challenges – DOP or PAO leak test aerosols

Uniformity to velocity across the filter (and relative to adjacent filters) – variations in velocity cause turbulence which increases the possibility of contamination

Layout and Flow

- Personnel and material flow must be design to prevent unnecessary activities and cause contamination
- One way flow
  - Gown in one room
  - De-gown separate room
  - Material pass separate
- Minimize number of personnel allowed in aseptic processing room
- Limit frequency of room entry and exits
- Number of transfers to the critical area should be minimized

Aseptic Technique

Minimize **motion**

- Slow deliberate, well thought out movements

Avoid **fatigue**

Do not place body in between **airflow** and product/product contact surface

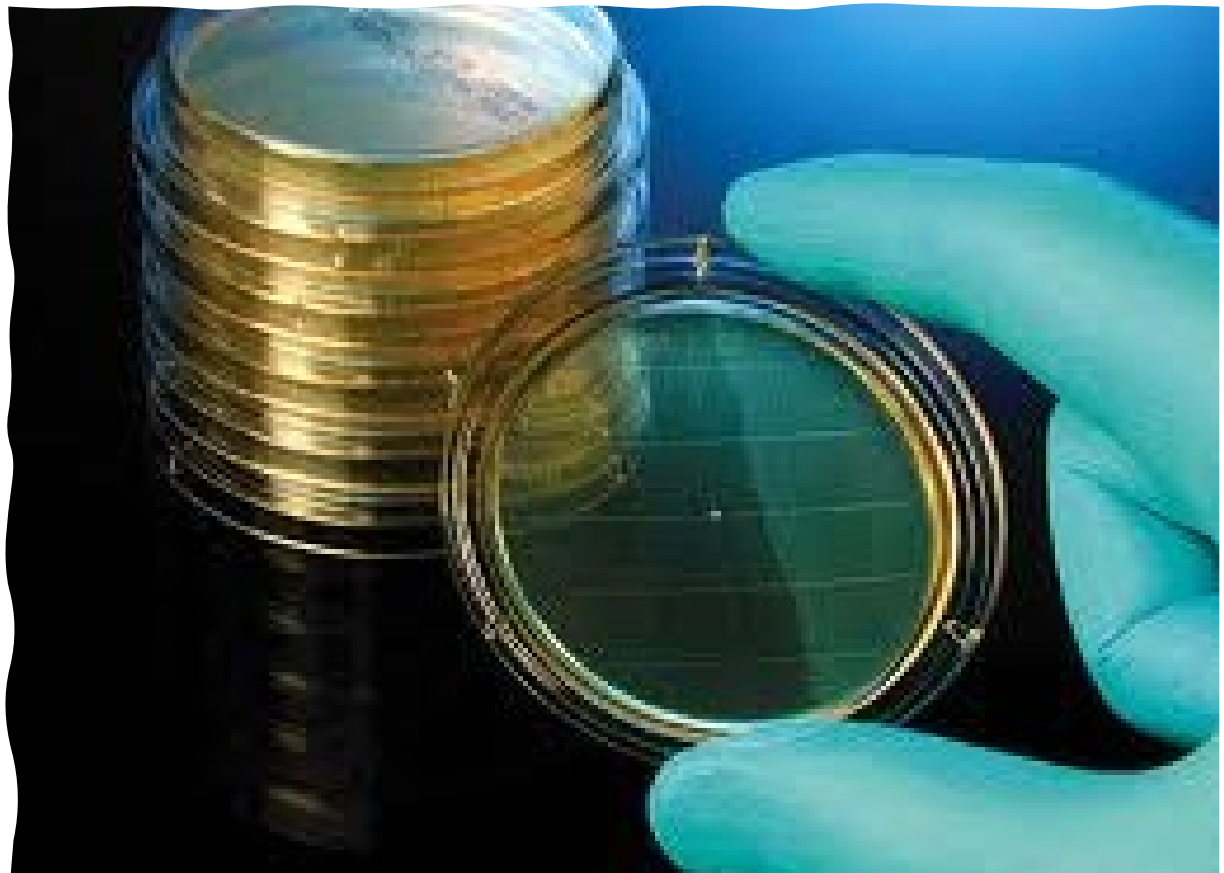
Do not **touch** product contact surfaces/components

Rinse and/or **change** gloves frequently

Use sterilized **utensils**, rather than hands

What is Environmental Monitoring?

- Sampling of controlled environments for non-viable and viable air particulates as well as surface viables
- Allows for assessment of effectiveness of cleaning/disinfection
- Allows for identification of trends
- Facilitate early detection of potential problems



Cleaning and Sanitization of Rooms

- The qualification of the cleaning and disinfectants agents is required
  - Disinfectant efficacy
  - Coupons walls/floors/SS/glass
- The qualification of the sanitization processes will need to be done in conjunction with a documented process and trained personnel
- Development of the expiration dates for the formulated sanitization solutions
- The cleanroom sanitization process requires full sterile gowning and all of the required aseptic techniques that would be utilized during the aseptic filling
- The cleanroom sanitization process requires documentation, personnel training and qualification

Cleaning Agents

- Some of the common disinfectants and sterilants:
  - Phenolics
  - Sterile Alcohol – 70% IPA
  - Hydrogen Peroxide
  - Quaternary Ammonium
  - Sodium Hypochlorite
- Annex 1 – Disinfectants and detergents used in Grade A & B should be sterile prior to use. Grade C and D as per your own CCS.

Annex 1 Regulations on Material Transfer

- 4.7 Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.

Annex 1 Regulations on Material Transfer

- 4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.

Define your controls in your CCS

Application of Risk Management

- Application of risk to all parts of life cycle
- Commercial production Stage 3
- Risk Based EM
- Risk Based Intervention Selection
- Risk Based Sample Selection
  - Critical Quality Attributes Determination
- Microbial HACCP – Hazard Analysis and Critical Control Points

Regulatory Findings

REGULATORY OBSERVATIONS

Regulatory Findings

483 OBSERVATIONS – FDA Warning Letter Database

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the sterilization process.

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b))

Regulatory Findings

483 OBSERVATIONS – FDA Warning Letter Database

Poor Aseptic Practices

During the inspection of your facility, we observed poor practices and behaviors in ISO 5 areas during the manufacturing of sterile (b)(4) drug products. These poor practices included, but were not limited to:

Operators blocked first air by placing their gloved hands directly over open sterilized bottles without clearing them from the aseptic filling line.

Operators used their gloved hands instead of using appropriate sterile tools to remove jammed bottles.

Operator movements in the critical areas were not always slow and deliberate.

- Your smoke studies did not adequately demonstrate unidirectional air flow in the ISO 5 classified areas used for the aseptic filling of …

Regulatory Findings

483 OBSERVATIONS – FDA Warning Letter Database

3. We reviewed your **(b)(4)** validation for sterilizing the stopper sorting bowl, supply hopper, and insertion station and acknowledge your process improvements. In your response you stated that, “XXX has also implemented a **(b)(4)** schedule for the stopper sorting bowl and associated components to improve sterility assurance while awaiting additional spare parts.” It is unclear how you determined the adequacy of “a **(b)(4)** schedule” to ensure the equipment remains sterile. We remain concerned with your continued injectable drug production while lacking assurance that equipment, which comes into contact with product contact components, is sterile.

Regulatory Findings

483 OBSERVATIONS – FDA Warning Letter Database

Regarding your established environmental monitoring alert and action levels, your response states that your ISO 5 surface sampling action level will remain at greater than or equal to **(b)(4)** CFU. Please note that any microbial contamination in the ISO 5 area is a serious concern and considered an insanitary condition. If any recovery occurs within the critical aseptic processing area, you should immediately assess the impact on drug products produced. This assessment should include a thorough evaluation of how contamination could have entered this critical area, and over what period of time the contamination could have existed, as well as drug products that remain on the market that could have been affected.

Aseptic Behaviors Training

Critical to have **GOOD** aseptic behaviors training

- Operators
- QA
- QC Microbiology

Isolators – It Is NOT a Magic Box

STEED MicroBio

THANK YOU

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