

CONTAMINATION CONTROL STRATEGIES: CASE STUDIES

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Agenda

- Contamination Control: Why?
- Microbiology 101
- Sources of Contamination
- Control & Prevention
- Case Studies
 - 3 Key Concepts
 - Techniques & Solutions for Success



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Contamination Control: Why?

- Producing Safe, Pure, Efficacious Drug Products
- Prevention of Objectionable Microorganisms (bacteria, molds, yeasts, viruses)
- Meeting industry regulations: CFR, Draft Annex I, and FDA Aseptic Processing Guide Regulations
- Operational Success
 - "Right First Time"



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Microbiology 101

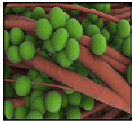
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Bacteria...what are they?

Bacteria are:

- Single celled microorganisms
- Sub visible – require magnification
- Most abundant form of life on earth
- Trillions of bacterial cells, account for 1-3% of our body mass
- Outnumber human cells by a factor of 1.3
- Our microbiome is genetically more diverse than ourselves
- Different regions of the body harbor different species of bacteria (skin, hair, mouth, gut, etc.)
- Thousands of different species occupy the human ecosystem

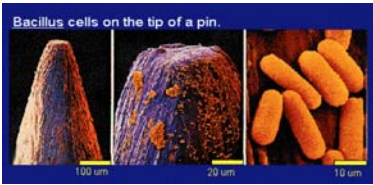


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Size Matters

Bacillus cells on the tip of a pin.



100 μ m 20 μ m 10 μ m

© 2018 James A. Sullivan, Cells Alive

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Aspergillus brasiliensis





Conidiospores


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Microorganism Resistance Hierarchy

	Microorganism	Examples
↑	Prions	Spongiform encephalitis, Chronic wasting disease
↑	Bacterial Spores	Bacillus, Clostridium, Geobacillus, Clostridium
↑	Protozoan Cysts	Cyclospora
↑	Helminth Eggs	Ascari, Enterobius
↑	Mycobacteria	Mycobacterium tuberculosis, M. avium, M. chelonae
↑	Small, Non-Enveloped Viruses	Poliovirus, Parvovirus, Papilloma virus
↑	Protozoan Cysts	Giardia, Amoebae
↑	Fungal Spores	Aspergillus, Penicillium
↑	Gram negative bacteria	Pseudomonas, Pseudomonas, Escherichia
↑	Vegetative Fungi and Algae	Aspergillus, Fusarium, Candida, Chlamydomonas
↑	Vegetative Helminths and Protozoa	Ascari, Cyclospora, Giardia
↑	Large, non-enveloped viruses	Adenovirus, Rotavirus
↑	Gram positive bacteria	Staphylococcus, Streptococcus, Enterococcus
↓	Enveloped viruses	HIV, Hepatitis B virus, Herpes Simplex virus

↑ **Bacillus cereus / sphaericus**
 ↑ **Bacillus subtilis / G. stearothermophilus**
 ↑ **Clostridium spp.**


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Sources of Contamination


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Contamination Sources

Facility

- Poor design
- Aging facility
- Maintenance
- Cleaning and disinfection



Materials

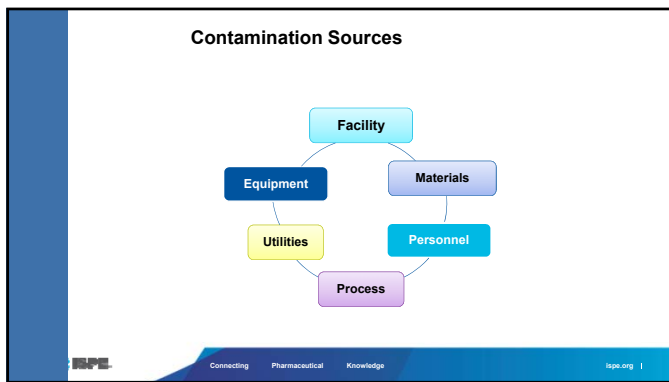
- Pass through sterilizers (autoclaves, dry heat ovens, depyrogenation tunnels, etc.)
- Decontamination chambers (EO, VHP, UV, etc.)
- Material handling airlocks



People

- Gowning rooms
- Attire (clothing, shoe covers, hoods, face masks, goggles, etc)
- Conduct
- Standard Operating Procedures


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Chemical types



Disinfectants and sanitizers

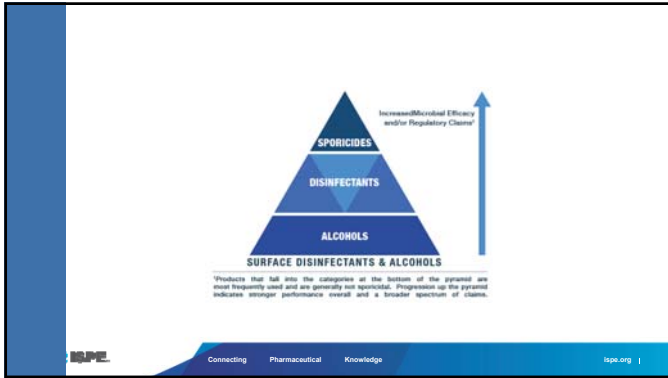
- Phenolics
- Quats
- Alcohols
- Hydrogen Peroxide 3%

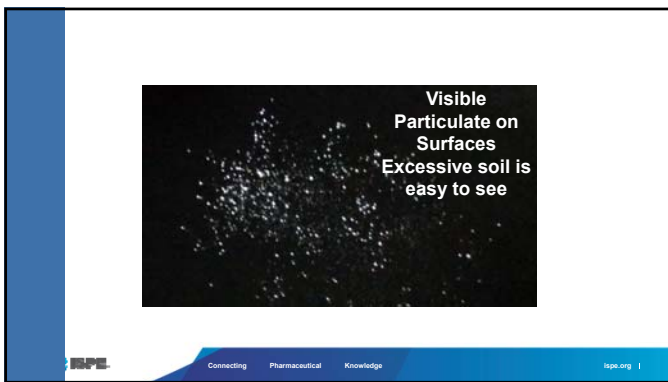
Sterilants and sporicides (potentially)

- Sodium hypochlorite
- Chlorine dioxide
- Hydrogen peroxide 6%
- Peracetic acid
- Peracetic acid/hydrogen peroxide blends
- Glutaraldehyde/formaldehyde
- Ozone
- Nitrogen Dioxide
- Vaporized Peracetic Acid and VHP

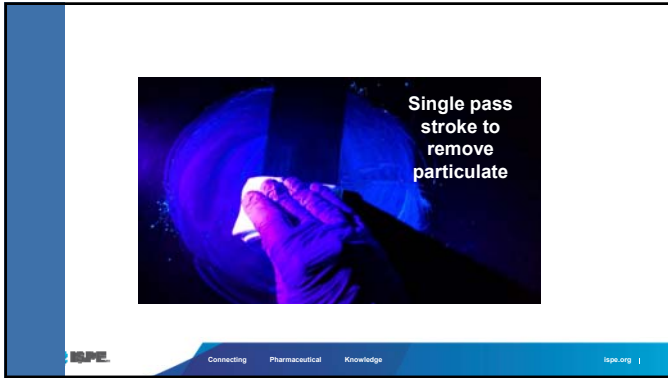


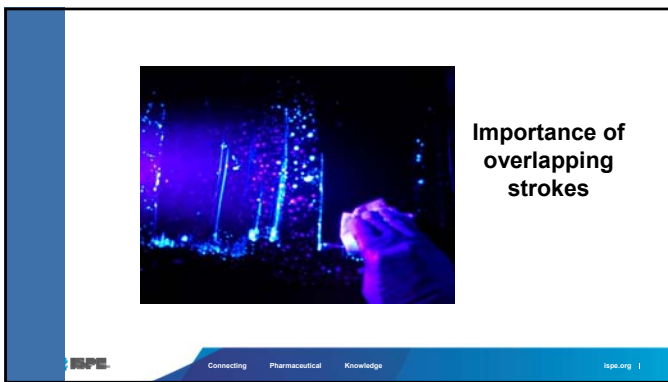

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Molds common to cleanrooms and cold rooms

- *Aspergillus* spp.
- *Penicillium* spp.
- *Stachybotrys* spp.
- *Cladosporium* spp.
- *Mucor* spp.
- *Scopulariopsis* spp.
- *Trichophyton* spp.
- *Chaetomium* spp.
- *Acremonium*
- *Candida albicans* (yeast)


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Aspergillus Case Study

- **ISO-5 Cleanroom**
 - Source
 - > High Impingement Spraying Device
 - > Broken Pipes
 - > HVAC Shut Down
 - > Honeycomb Doors
- **Exceeding Limits in ISO-7 areas**
 - Dock Doors proximal to ISO-7 cleanroom
 - Storage room with limited control
 - No limits for mold spores (Establish Limits)
 - Limited control for incoming and outgoing items

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High Pressure Impingement Sprayers



Holes in Walls

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Sources of Aspergillus



Black Sharpie Marker Tip

Behind Cleanroom Door Kickplate

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Cleanroom Fungi



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Aspergillus Investigation

- Sporicidal usage in pass-through
- Clean and dirty area on the dock
- Better control of gowning area
- Cart Wheel control methods
- Better gowning control



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NECC Fungal Contamination

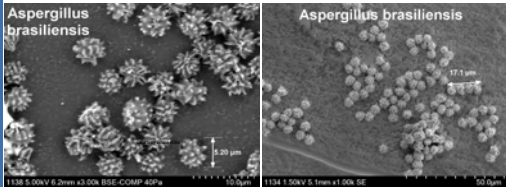
- > There was no investigation by the firm when levels exceeded the action limits and no identification of isolates. No documented corrective actions were taken to remove microbial contamination (bacterial and fungal) from the facility. (FDA WL October 2, 2012)
- > 83 out of 321 vials of methylprednisolone acetate contaminated (fungal contamination found)
- > 64 deaths and 750 illnesses



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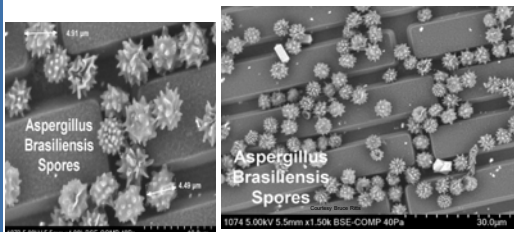
Aspergillus brasiliensis



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Aspergillus brasiliensis



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Penicillium Case Study



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Recent 483


- "Cleaning agents used to disinfect, clean, sanitize equipment, and or production areas of non-sterile product are not suitable for use. I observed your firm using expired sterile disinfectants to clean and sanitize."
- FDA 483 2/26/2020
- <https://www.fda.gov/media/136443/download>



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Recent 483

- "In addition, the following complaints were received due to the presence of **observed mold**:"
- a..... Lot, complaint received due to the product having mold. Approximately lots of have been distributed over the last two years.
- b....., Lot, customer complaint was received due to **moldy cap line**. However, the investigation did not include evaluation of the drug product's stability and reasoning as to why microbiological testing of retention samples was not applicable. Approximately lots of have been distributed over the last two years."
- GMP Trends July 1, 2019



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Penicillium

- **Two ISO-7 Cleanrooms**
- **Action Levels of 10 and picking up >100 Fungal Spores**
 - Engineering Investigating
 - HVAC
 - Duct Work
 - HEPA Filters
 - Cooling Coils (two hits)
 - Wall Coverings
 - Airflow Vents
 - Cold Room Environments

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Penicillium Investigation

- **Entry and Exit Procedures**
- **Gowning Procedures (Triple Gowning)**
- **Cart Wheels**
- **Construction (Current Maintenance Log)**
 - Further Investigation
 - Use of Sporicides and Frequency
 - Plastic Containers in the Cleanroom
 - Coldroom Cleaning Procedures (0-5° Celsius)
 - Documentation of Cleaning Process
 - Designate Assignable Causes


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Penicillium Investigation

Cleanroom Cooling Coils


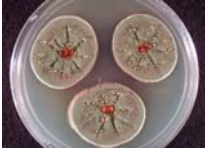


Plywood made up the sliding door



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Penicillium

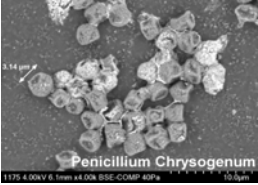
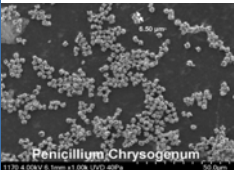


Courtesy Ann Larson

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Penicillium Spores

Courtesy Bruce Ritts



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Acremonium Case Study

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Acremonium Investigation

- Establishing Realistic Limits
- Finding one mold spore in a filled product
- One hit found near a pump on ultrafiltration skid
- Using a proactive science-based approach
- Chases with water
- Is Zero Mold possible?
- CAPA investigation



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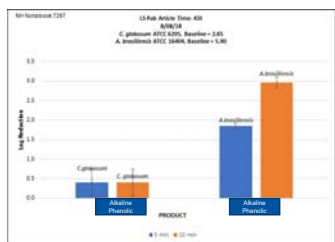
Fungal Spore DE Testing



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Chaetomium Testing



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Summary Slide:


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 - ✓ Techniques & Solutions for Success



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Industry References

- USP 43 <1072> Disinfectants and Antiseptics
- Draft Annex 5 v. 12 (Draft 2020) and MHRA Orange Guide (2017)
- FDA Aseptic Processing Guide (2004)
- FDA, MHRA, HPRA, CFDA, ANSM, ANVISA, FDAHA, ANMAT, Swissmedic, & EMA Expectations
- Industry Articles (Ex. Dr. Scott Sutton, Jose Martinez, Dr. Tim Sandle, Richard Prince, Rebecca Smith, Jeanne Moldenhauer, Crystal Booth)
- PDA Cleaning and Disinfection TR No. 70 (October, 2015)
- PDA TR No. 69 on Biofilms (2015)
- The CDC Handbook - A Guide to Cleaning & Disinfecting Cleanrooms (Dr. Tim Sandle 2016)
- A Guide to Disinfectants and their use in the Pharmaceutical Industry (Pharmig 2017)
- USP 43 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
- USP 43 <1115> Bioburden Control of Non-Sterile Drug Substances and Products
- PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (2014)
- WHO Annex 6
- PIC / S PI 007-6
- FDA's Aseptic Processing Guide (2004)
- Japanese and Chinese Pharmacopoeia
- PHSS Technical Monograph #20 "Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas"
- IEST-RIIP-CC018.4 Cleanroom Cleaning and Sanitization: Operating & Monitoring Procedures (June, 2020)



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Thank You!

Q&A

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