A Risk Based Cleaning and Disinfection Program

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SoCal PDA Chapter
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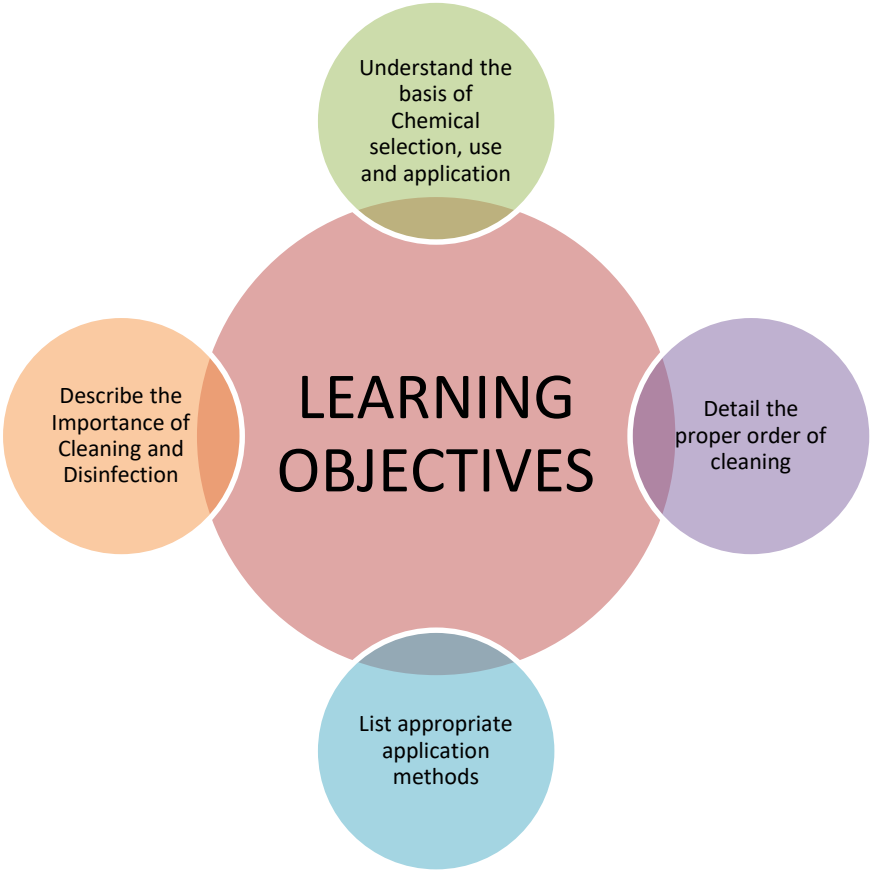

Topics Covered

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- Regulatory Requirements
- Cleaning and Disinfecting Technologies
- Cleaning and Disinfection Techniques
- Rotation and Residues

Regulatory Requirement

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USP 42 <1072> Disinfectants and Antiseptics*:*

"A sound cleaning and sanitization program is needed for controlled environments used in the manufacture of Pharmacopeial articles to prevent the microbial contamination of these articles. Sterile drug products may be contaminated via their pharmaceutical ingredients, process water, packaging components, manufacturing environment, processing equipment, and manufacturing operators"

Industry Guidance

PDA TECHICAL REPORT #70 “Cleaning and Disinfection Programs from Aseptic Manufacturing Facilities”:

“The purpose of the cleaning and disinfection program is not only to control microbial contamination but also to serve as a corrective action for the loss of control for viable excursions contamination. While the destruction of viable cells are an integral part of the cleaning and disinfection program, the use of disinfection as a singular focus without efforts to control contamination from entering the area is without technical merit. Environmental monitoring (EM) evaluates the efficacy of controls on the manufacturing environment. It is through control of bioburden levels entering the area, along with cleaning and disinfection, that acceptable viable control of the manufacturing or appropriate testing environment is achieved. “

Draft of Annex I: Disinfection

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Disinfection

568

569 5.31 The disinfection of clean areas is particularly important. They should be cleaned and
570 disinfected thoroughly in accordance with a written programme (for disinfection to be
571 effective, cleaning to remove surface contamination must be performed first)., More than one
572 type of disinfecting agent should be employed, and should include the periodic use of a
573 sporicidal agent. Disinfectants should be shown to be effective for the duration of their in use
574 shelf-life taking into consideration appropriate contact time and the manner in and surfaces
575 on which they are utilized. Monitoring should be undertaken regularly in order to show the
576 effectiveness of the disinfection program and to detect the development of resistant and/or
577 spore forming strains. Cleaning programs should be effective in the removal of disinfectant
578 residues.

579

580 5.32 Disinfectants and detergents should be monitored for microbial contamination;
581 dilutions should be kept in previously cleaned containers and should only be stored for
582 defined periods. Disinfectants and detergents used in grade A and B areas should be sterile
583 prior to use.

584

585 5.33 Disinfectants should be shown to be effective when used on the specific facilities,
586 equipment and processes that they are used in.

587

588 5.34 Fumigation or vapour disinfection of clean areas such as Vapour Hydrogen Peroxide
589 (VHP) may be useful for reducing microbiological contamination in inaccessible places.

Recent FDA WL

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"Your firm used a broad-spectrum hard surface disinfectant that was not labeled as sporicidal or sterile as the sole sanitizing agent for sanitizing the ISO 5 classified area."

FDA WL 2/11/19.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2019/ucm631353.htm

FDA 483 (5/9/19)

- Specifically, your firm failed to use sterile cleaning agents in the routine cleaning of ISO 5 LAFW and BSC hoods and the nuclear and pain medicine ISO 7 clean rooms. Examples of non-sterile cleaning agents include, but are not limited to the following:
- (b) ___ does not appear to be high enough to be sporicidal (made with non-sterile water).

https://www.fda.gov/media/129281/download

Recent FDA 483 (5/16/2019)

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- Disinfecting agents and cleaning pacts or wipes used in the ISO 5 area are not sterile.
- Specifically, Your firm uses (b) (4) J and:(1)) in your ISO 5 area. Neither of those products is considered self-sterilizing and you do not use sterile versions,or perform sterilization actions on these cleaners. This could result in contamination of your sterile production area by microorganisms and thus risk contamination of your product.

https://www.fda.gov/media/128970/download

Recent FDA WL: Cleaning and Disinfection

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"A. (b)(4) and (b)(4) cleaning and disinfecting solutions used in the critical processing zones and direct support zones are made with non-sterile tap water and held in non-sterile bottles that are used at (b)(4) per the cleaning procedure (FRAN-SOP002).

B. your firm's preparation and use of a (b)(4) solution during (b)(4) cleaning and disinfecting of the Class 10,000 cleanrooms and Class 100 laminar flow hoods where sterile saline/heparin filled syringes are manufactured has not been validated.

C. the adequate removal of residues of disinfecting and cleaning solutions in the Class 100 laminar flow hoods has not been validated."

FDA WL 9/14/18

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm622651.htm

Recent WL on Cleaning and Disinfection

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"1. Your firm failed to use adequate contact times for sporicidal agents used as part of your disinfection program for the aseptic processing area.

1. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions. 21 CFR 211.42(c)(10)(v)

1. Your response did not include any supporting documentation related to the review and revision of your cleaning procedure to address the inadequate contact time you use for sporicidal agents."

FDA WL March 1, 2018

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2018/ucm602078.htm

Cleanroom Contamination Control

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"Your firm used non-pharmaceutical grade drinking water, obtained from a bottled water dispenser located in the break room of your facility, in the production of non-sterile stock solutions and non-sterile drug products. Our investigators determined that the water was used in the production of dozens of drug products. During the inspection, our investigators collected a sample of the water obtained from the dispenser. FDA analysis of the **(b)(4)** identified the presence of *Burkholderia cepacia*, which is considered an objectionable microorganism."

FDA WL May 9, 2018

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2018/ucm607912.htm

Cleanroom Behavior

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"Investigators observed an operator sitting with her upper body leaning into the ISO-5 classified area with the sleeves of her non-sterile gown resting directly on the work surface of the ISO-5 classified area, thereby providing a potential source of contamination"

FDA WL July 10, 2018

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2018/ucm613879.htm

Recent WL

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"no use of sporicidal disinfectant on surfaces inside aseptic filling room **(b)(4)**, although your environmental monitoring detected spore-forming organisms there; and"

FDA WL 1/19/17.

Cleaning and Disinfection: Product Selection

- EPA Classifications
  - Sanitizer
  - Disinfectant
  - Sterilizer (Sporicide)

When germ relationships go bad

Cleaning and Disinfection: Product Selection

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- Sanitizer
  - Proper use results in bacteria reduction of >99.9%
  - 3-Log reduction
  - Used on precleaned surfaces unless tested with serum load

Cleaning and Disinfection: Product Selection

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- Disinfectant
  - Proper use results in 100% kill of vegetative bacteria, target viruses and target fungi
  - https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-810-product-performance-test-guidelines
  - 4 Log reduction
  - May or may not require pre-cleaning
    - Serum efficacy - 5% BSA and EN methods differ example: skimmed milk as a soil load

Cleaning and Disinfection: Product Selection

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- Sterilant
  - Proper use results in 100% kill of all microorganisms, including bacterial endospores (*B. subtilis*, *C. sporogenes*)
  - 6 Log reduction-complete kill
  - Always requires pre-cleaning
    - Water quality is important

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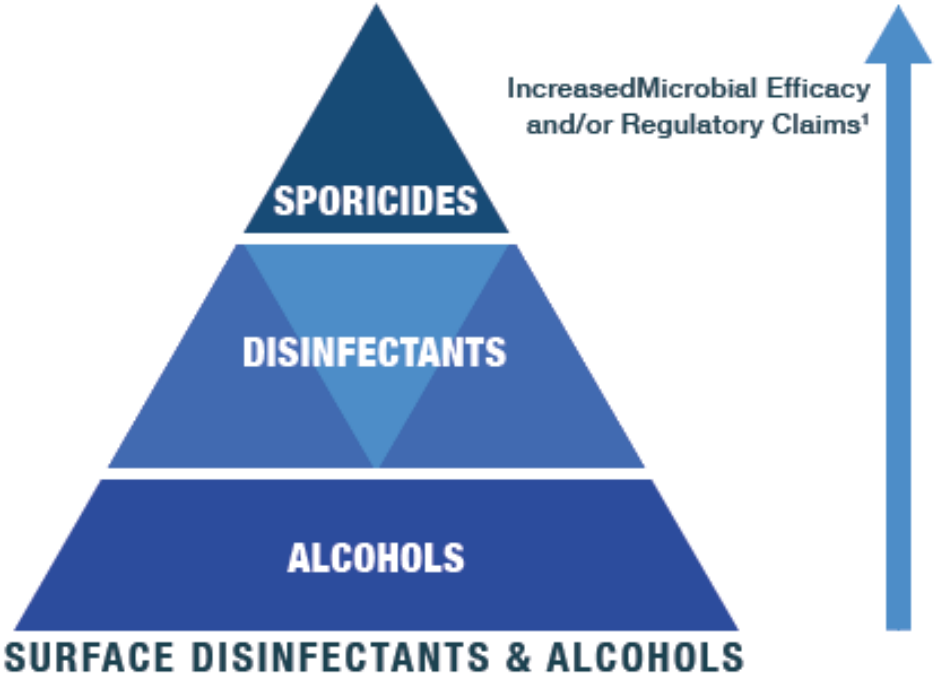

[1]Products that fall into the categories at the bottom of the pyramid are most frequently used and are generally not sporicidal. Progression up the pyramid indicates stronger performance overall and a broader spectrum of claims.

Review - Microflora in Cleanrooms (U.K.)

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- Tim Sandle
- PDA J Pharm Sci and Tech 2011, 65:392-403
- **A Review of Cleanroom Microflora: Types, Trends, and Patterns**

- Examined isolates from 2000-2009 in U.K.
- Grade A/B and C/D

Review - Microflora in Cleanrooms (U.K.)

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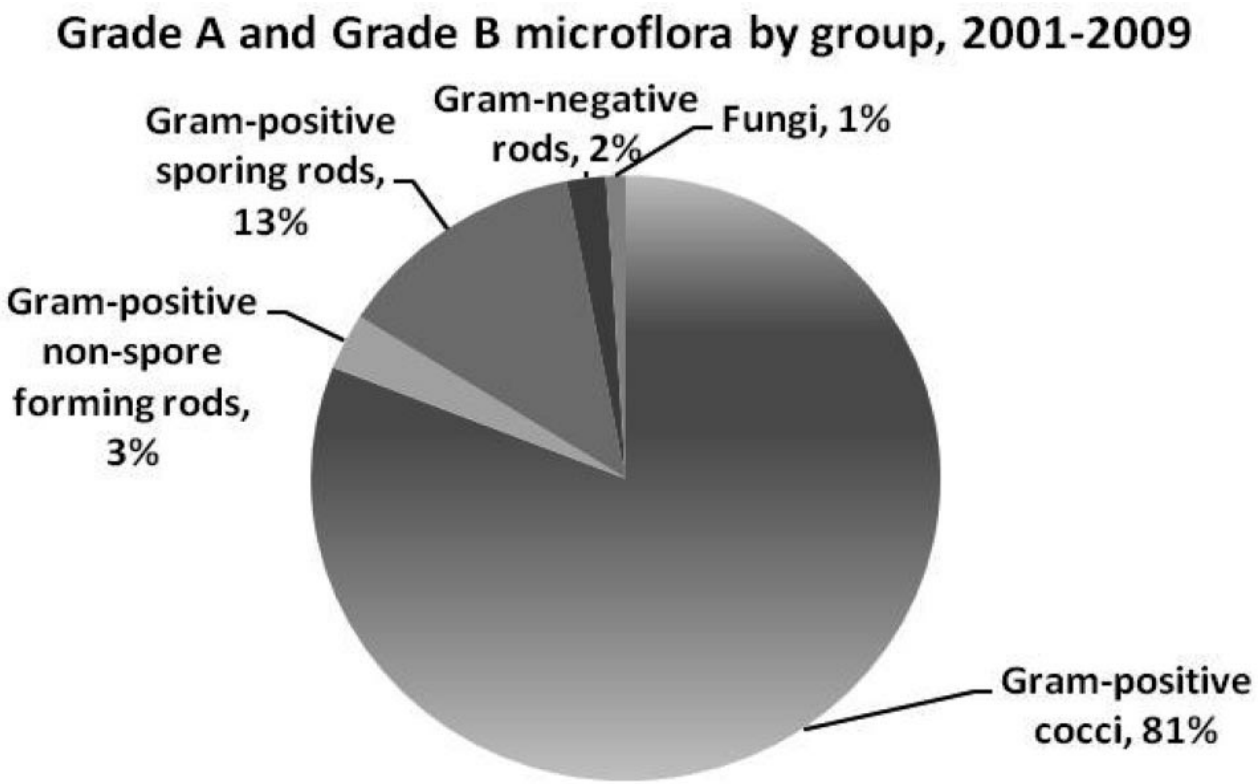

Review - Microflora in Cleanrooms (U.K.)

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Genus	A/B (6729)	C/D (2500)
Micrococci (and related)	38%	40%
Staphylococci	21%	11%
Bacillus (and related)	13%	10%
Pseudomonas (and related)	<1%	8%
Corynebacterium (and related)	3%	5%
Rhodococci	<1%	N/A
Fungi	N/A	3%

Microorganism Resistance Hierarchy

	Microorganism	Examples
More Resistant	Prions	Scrapie, Creutzfeld-Jacob disease, Chronic wasting disease
	Bacterial Spores	*Bacillus, Geobacillus, Clostridium*
	Protozoal Oocysts	*Cryptosporidium*
	Helminth Eggs	*Ascaris, Enterobius*
	Mycobacteria	*Mycobacterium tuberculosis, M. terrae, M. chelonae*
	Small, Non-Enveloped Viruses	Poliovirus, Parvoviruses, Papilloma viruses
	Protozoal Cysts	*Giardia, Acanthamoeba*
	Fungal Spores	*Aspergillus, Penicillium*
	Gram negative bacteria	*Pseudomonas, Providencia, Escherichia*
	Vegetative Fungi and Algae	*Aspergillus, Trichophyton, Candida, Chlamydomonas*
	Vegetative Helminths and Protozoa	*Ascaris, Cryptosporidium, Giardia*
	Large, non-enveloped viruses	Adenoviruses, Rotaviruses
	Gram positive bacteria	*Staphylococcus, Streptococcus, Enterococcus*
Less Resistant	Enveloped viruses	HIV, Hepatitis B virus, Herpes Simplex virus

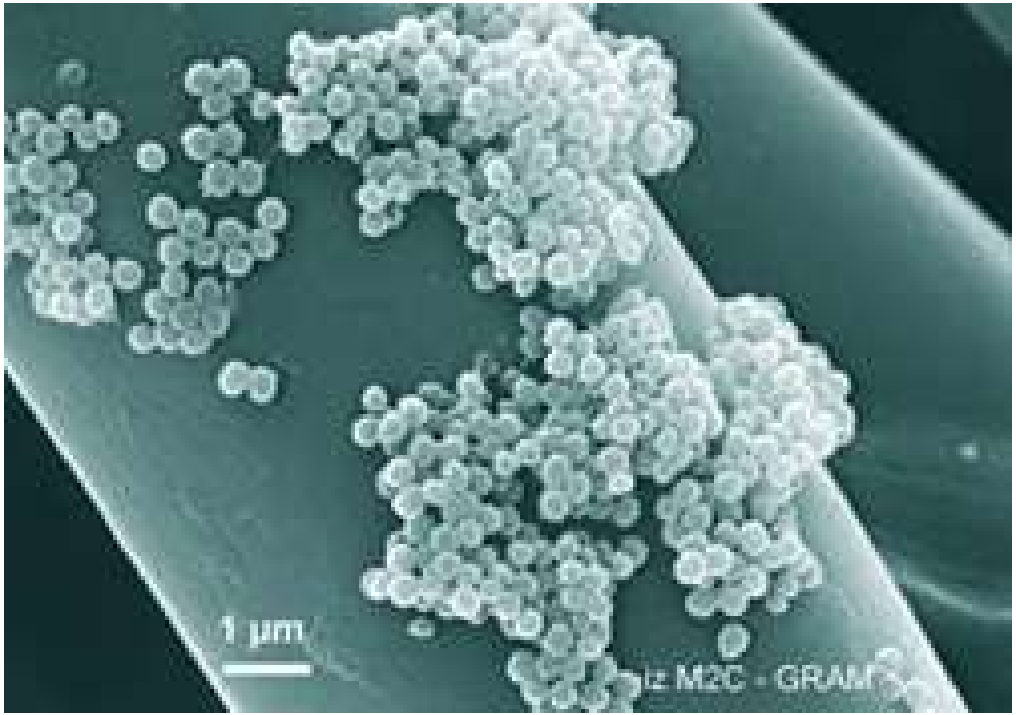
Bacillus cereus / sphaericus

Bacillus subtilis / G. stearothermophilus

Clostridium spp

From McDonnell, "Antisepsis, Disinfection, and Sterilization: Types, Action, and Resistance" 2007, ASM Press

Staphylococcus haemolyticus



Courtesy Grace Thornhill

Aspergillus Spores

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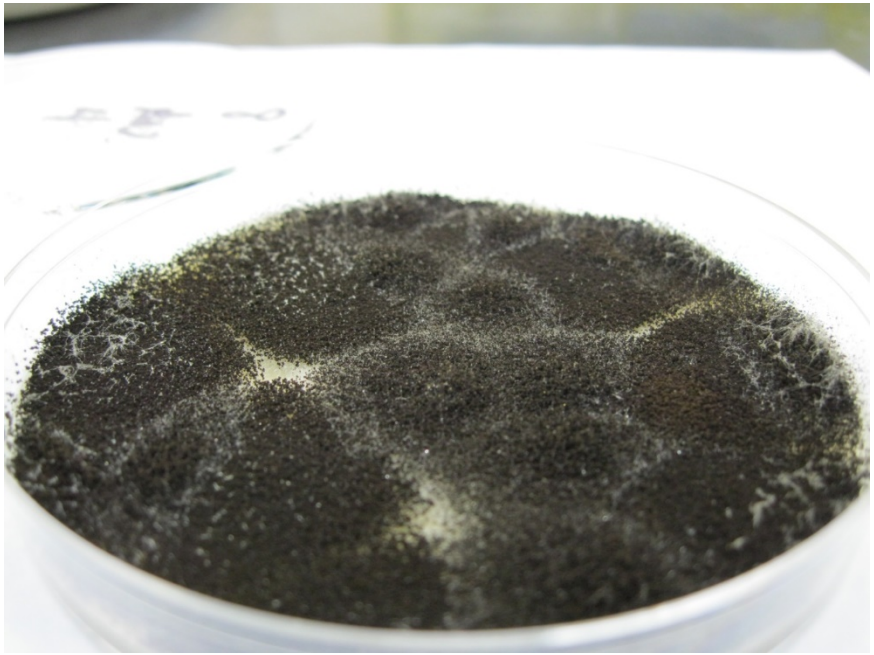

Cleanroom Fungi

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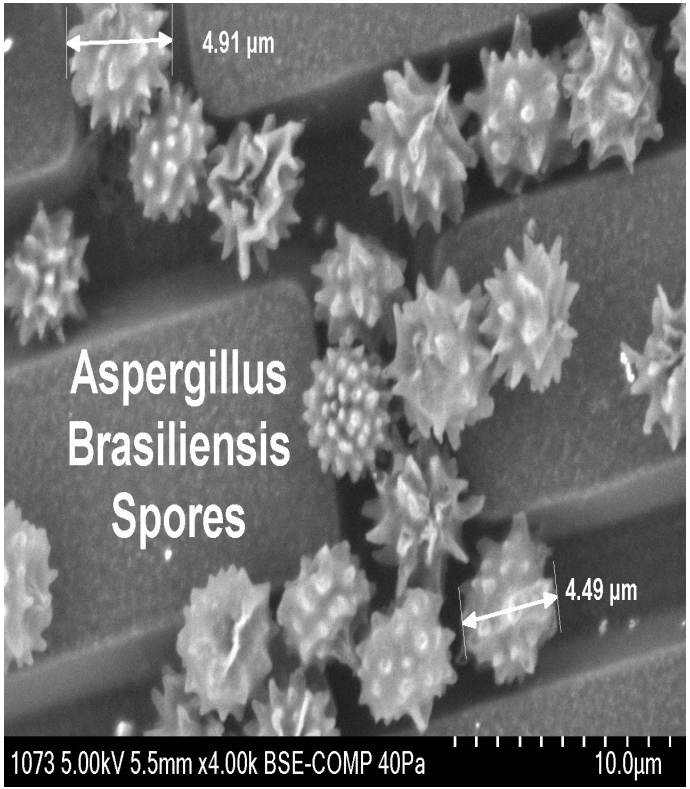
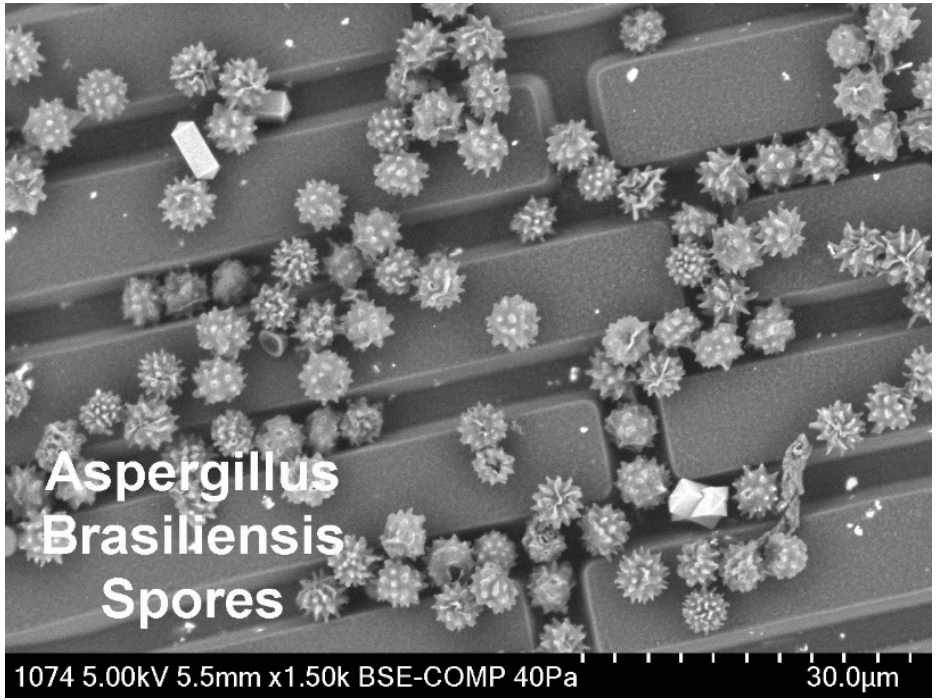
Courtesy Dan Klein

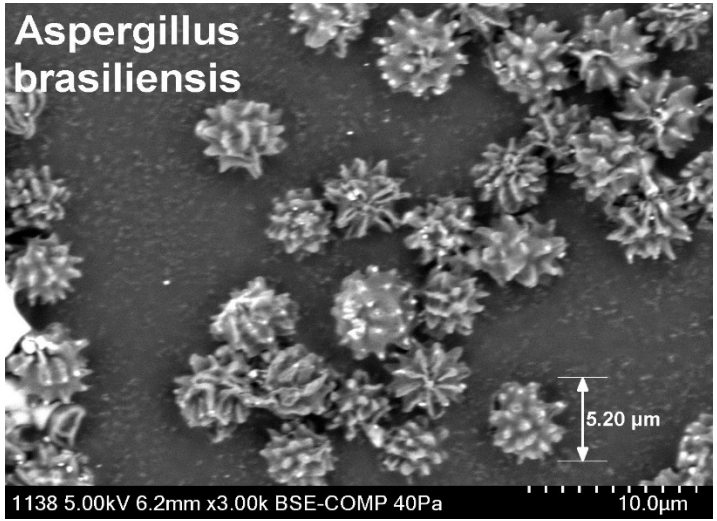
Aspergillus Spores

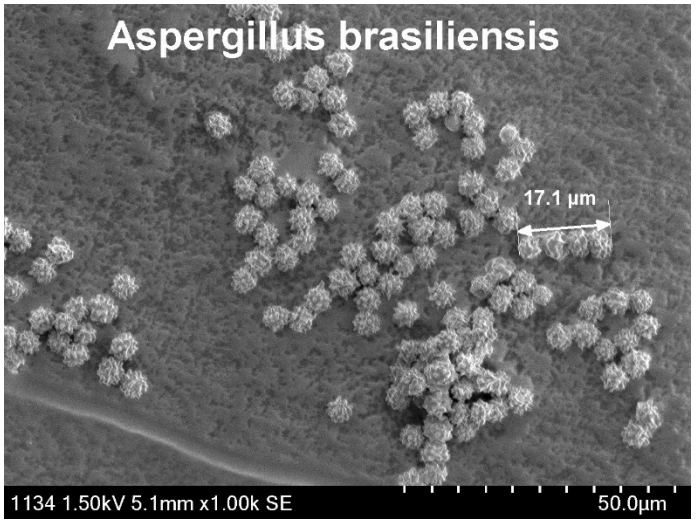




Courtesy Bruce Ritts

Aspergillus brasiliensis





Courtesy Bruce Ritts

SEM: Pseudomonas 5,000X magnification

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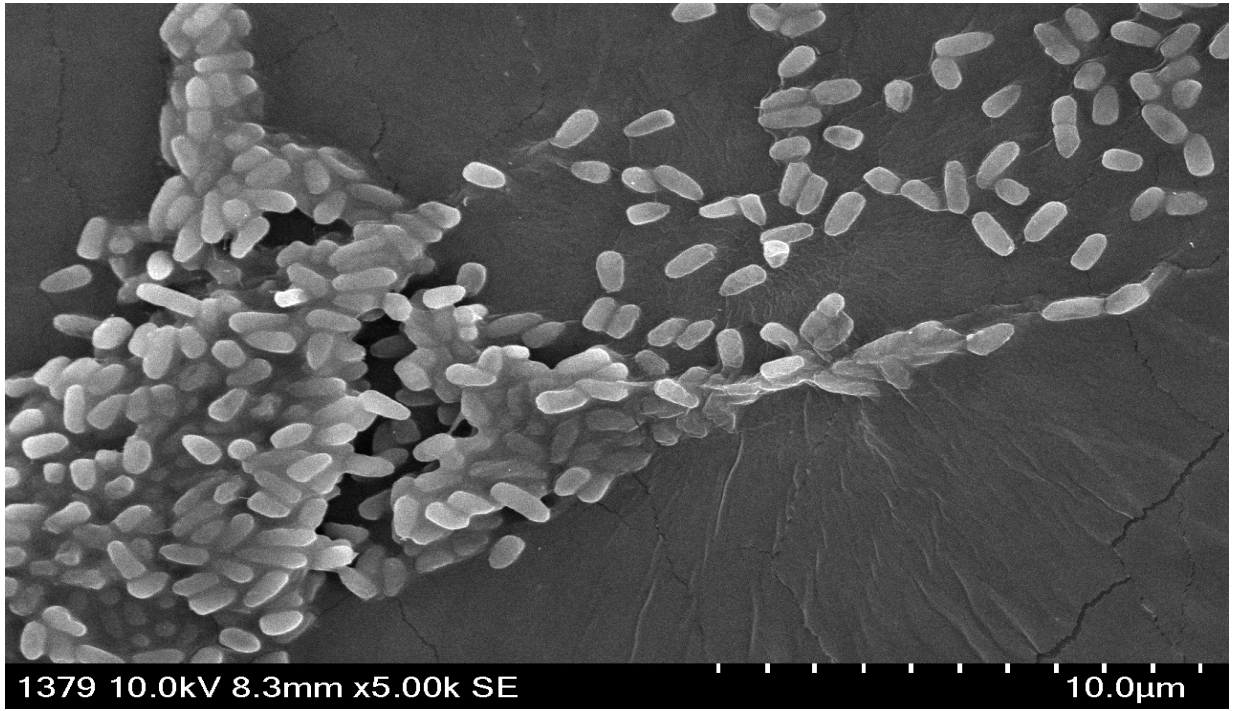
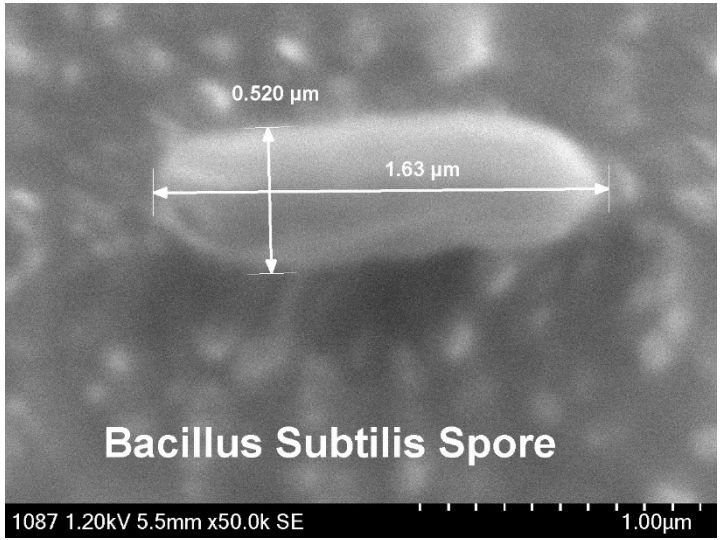


Bacillus Subtilis



Courtesy Bruce Ritts

Biofilms

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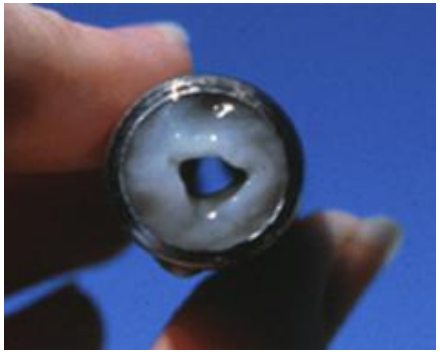

Courtesy Dan Klein

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Chemistries & Frequency

Purpose of Cleaning and Disinfection

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Control microbial contamination

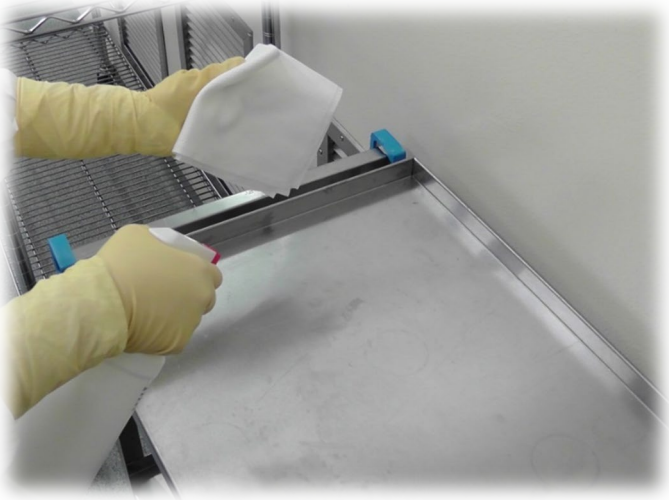
- Destruction of viable cells

Corrective action for loss of control

- Viable and non-viable excursions

Disinfection used in conjunction with contamination control program

- Prevent contamination from entering the room



Cleaning and Disinfection

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- **Hospital Grade Disinfectants are formulated with surfactants, dispersants, builders, and chelants to provide a moderate level of cleaning and microbial kill in cleanrooms.**

- **Post construction and after worst case events either a triple cleaning or a double cleaning with a neutral or acidic cleaner would be recommended.**

Disinfectant Components

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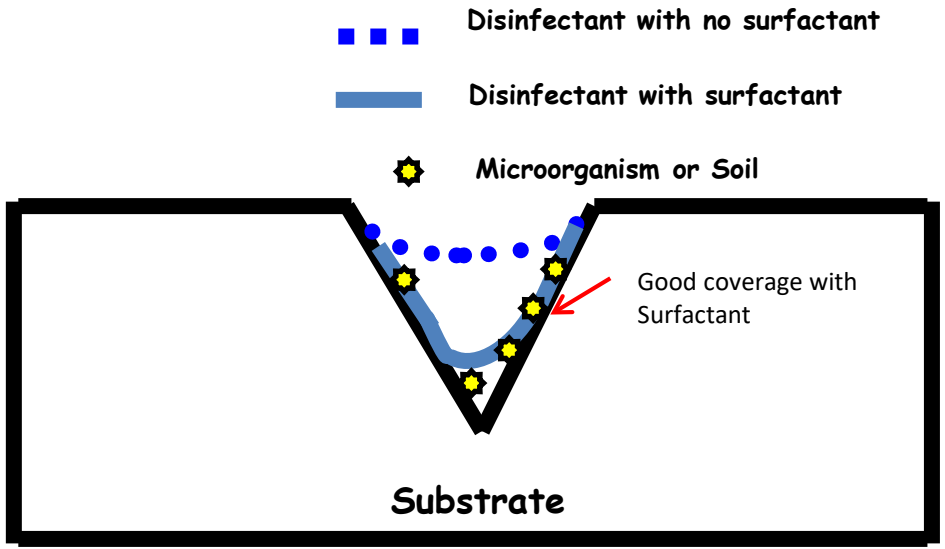
Component	Function in Disinfectant
Water	Solvent
Antimicrobial	Kill, reduce microbes
Oxidants	Oxidize, kill microbes
Chelants	Tie up calcium, iron, stabilize oxidants, potentiates antimicrobial action
Solvents	Solubilization and stabilization of formula
Bases	Alkalinity source, hydrolysis (KOH)
Acids	Acidity source, hydrolysis (H3PO4)
Surfactants	Emulsification, Wetting

Effect of Surfactants

- Influence of Surfactants on Wetting
  - Ability to displace particles
  - Penetrate soil and surface irregularities
  - Better contact

Wetting Surface Tension and Penetration



Contamination Control

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Control what enters your environment

- Viable and non-viable

Begin with items transferred into facility

- Components, carts, personnel, tanks, tools, etc.
- Defined entrance procedures

Good control leads to less

- Excursions
- Investigations
- Down time

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All items cleaned, sterilized or disinfected

Highest level of decon possible

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®

Factors in Performance

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- pH
- Temperature
- Contact time
- Concentration
- Surface
- Presence of organic matter
- Water Quality (hardness)

Phenolics - Features & Limitations

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- Features
  - TB effective and broad spectrum
  - EPA registered
  - Anionic / Neutral surfactants provide good cleaning ability
  - Alkaline or acidic formulas available
- Limitations:
  - Not sporicidal
  - Residues
  - Activity affected by incompatible chemical agents

Quats - Features & Limitations

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- Features
  - Broad spectrum activity
  - EPA registered alkaline (and acidic)
  - Cationic surfactancy provides excellent cleaning
- Limitations:
  - Not sporicidal
  - Not always TB effective
  - Activity affected by incompatible chemical agents

H2O2/PAA RTU

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- Blend of 0.8% hydrogen peroxide, 5% Acetic Acid and 0.06% peracetic acid
  - Sterility Tested per USP 42 <71> sterility test method
  - Broad spectrum and sporicidal efficacy
    - Sporicide 30 minutes (AOAC Testing)
    - Several viruses including Polio Virus type I, HIV-1, MVM, Mouse Hepatitis, Sendai Virus, Mouse Parvo, Noro virus and others.
    - *Aspergillus brasiliensis* 5 minutes
  - Ready to use
    - Disinfects in 10 minutes
    - 96-day open container stability – 14-day re-use stability
    - 12 months stability

Hydrogen Peroxides - Features & Limitations

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- Features
  - Broad spectrum activity (including spores at 6%)
  - Stable
  - Decomposes to oxygen and water
  - Solution or vapor effective
- Limitations
  - High concentration for spores
  - Inactivated by heat and organic material
  - Slow rate of kill

Peracetic Acid - Features & Limitations

- Features
  - Broad spectrum activity (including spores)
  - Effective in the presence of organic material
  - Decomposition products are non-hazardous
  - Solution or vapor effective
- Limitations
  - Unstable at higher temperatures
  - Irritant
  - Corrosive to soft metals

Bleach - Features & Limitations

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- Features
  - High level of disinfectant efficacy
  - Sporicidal at 800ppm - 5,000ppm
- Limitations:
  - Pre-cleaning required
  - Temperature and light sensitive
  - May only be a disinfectant, not a sterilant
  - Safety concern with chlorine gas
  - Corrosive to eyes and skin
  - Corrosive to soft metals and stainless steel
  - May produce THM in presence of organic material
  - Generally not EPA registered

Sodium Hypochlorite

$$OCl^- + H_2O \rightleftharpoons HOCl + OH^-$$

Hypochlorite Ion	Hypochlorous Acid
pH	% Hypochlorous acid
4.0	Almost 100
5.0	99.6
6.0	95.8
7.0	69.7
8.0	18.7
9.0	2.2
10.0	0.2

Reference: Holweida (1928)

Chlorine Dioxide - Features

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- High level disinfectant efficacy
- Efficacy against non-enveloped viruses
- EPA Registered

Chlorine Dioxide - Limitations

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- Corrosive to metals
- Activation of dilution required
- Precleaning required
- Temperature sensitive
- May only be a disinfectant, not a sterilant
- Safety concerns with chlorine dioxide and chlorine gas
- 0.1ppm Permissible Exposure Limit (PEL)
- Limited use after dilution
- Offensive odor

Aldehydes – Features & Benefits

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- Features
  - Broad spectrum activity (including spores)
  - Non-corrosive
  - May be used in fogging applications
- Limits
  - Requires activation
  - Unstable and inactivated by organic material
  - Requires long contact time
  - Safety (toxicity)
  - May have to neutralize residues

Halogens - Features & Benefits

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- Features
  - Broad spectrum disinfectant
  - Stable and less irritating
  - Non-corrosive
- Benefits
  - Not sporicidal (unless higher concentration validated)
  - Safety
  - Possible Staining
  - Mainly used as antiseptics

Alcohol Features & Limitations

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- Features
  - No residue & Evaporates readily
  - Broad spectrum
  - Excellent at removing residues
- Limitations
  - Not sporicidal
  - Poor cleaner
  - Flammable Risk
  - Limited contact time
  - Not EPA registered
  - Volatile Organic Carbons (VOC) emissions
  - Isopropyl Alcohol (IPA) (Threshold Limit Value (TLV) 200ppm)

Isopropyl Alcohol (IPA) - Aerosol, Trigger Spray, Squeeze Bottles

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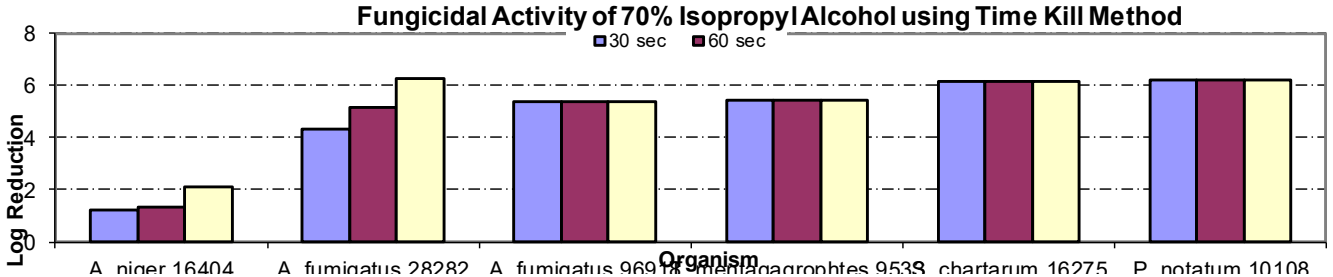
70% IPA Efficacy Against Molds



Tanks, Carts and Equipment

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Tank/Vessel

- If interior sterile, only address exterior

Special attention to wheels

- Increased contact time
- Manual wiping

Note: *Captive carts (or commodity transfer in pass through) is HIGHLY preferred*

Cleaning Supplies

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Chemicals

- Sterilizing filtration (.2 u)
- Gamma Radiation
- Autoclaving
- Pre-purchased sterile

Mop heads/Sponges – Sterilized

Other equipment

- Mops, buckets, squeegees, carts
- Sterilized (disinfected at a minimum)

Manufacturing Components and Supplies

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Sterile components used in process

- Packaged in container that can be sanitized

Disinfectant Application

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Spraying

- More wetting, no cleaning

Mopping

- Mechanical action cleaning, less wetting

Wiping

- For smaller surfaces, less wetting

Fogging/Gassing

- Excellent efficacy, high residues, no cleaning

Application Techniques

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- Most critical areas to least critical areas
- Apply disinfectant to wiper or spray on the surface (garden variety sprayer)
- Changing out the use dilutions* (2-3 Bucket routines)
  - 600 sq. ft (56 sq. meters) in ISO-5,6 (A & B)
  - 1,000 sq. ft (93 sq. meters) in ISO- 7,8 (C & D)
  - IEST-RP-CC018.4
- Grid (Blueprint of the Room)
- Pull and lift
- Overlapping strokes (by 20%)
- Figure 8 (also called figure S) or Unidirectional overlapping mopping strokes

* Anne Marie Dixon, Ch. 11, Cleaning of Non-Product Contact Surfaces, p 226, *in* Cleaning and Cleaning Validation for the Pharmaceutical and Medical Device Industries, Vol. 1 Basics, Expectations, and Principles. Paul L. Pluta, Ed., PDA, Bethesda, MD, and DHI Publishing, LLC, River Grove, IL. **2009.**

Two Bucket System

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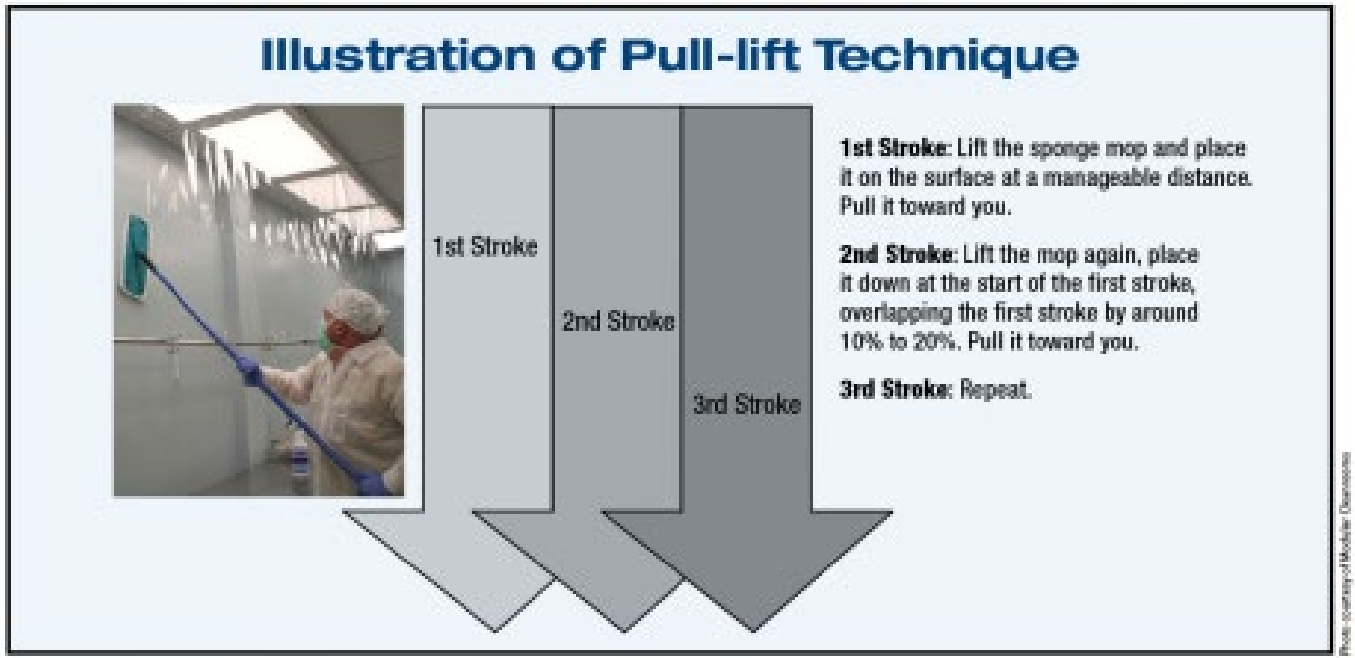
- Sterilant (Disinfectant) in front bucket, optional to put some sterilant (Disinfectant) in waste bucket (bucket beneath the ringer)
- Dip mop head into front bucket, let excess liquid drain off, apply to the surface.
- When mop head appears to be dragging on the surface, dip into waste bucket, then wring out. Go back to front bucket and dip mop head, let excess liquid drain off and apply to the surface.
- Repeat above steps

- Other Mopping Systems: Single Bucket, Triple Bucket, MicronSwep System by Vileda and the Mop King System.

Application Techniques

Figure 1. Proper Surface Cleaning



http://www.pppmag.com/article/714/June_2010/Cleaning_Practices_for_Cleanroom_Contamination_Control/

Bucket Systems

- Mop King Jr.
- http://www.am-king.com/mopkingjr.htm

- Stainless steel
- Battery operated and electronically monitored
- Holds 15 Rayon or Microfiber flat mops
- Holds 1.5 gal solution
- Dispensed with the precise amount of solution
- Fits on housekeeping cart
- Flat mops guided along rail to a wetting tray
- Pump activates, dispenses solution to mop head

AmKing Technologies, Bedford, NH

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MicronSwep system by Vileda Professional and Micronclean (www.micronswep.com)

CE Duo
Features and Benefits

- Combines microfiber and foam technologies
  - You get disinfection and removal in the same tool. 99.99% reduction in surface bacteria without disinfectant.
- Two sided cleaning tool
  - Doubles the floor space cleaned with each bucket dip.
- Only mop system that will clean floors, walls and ceilings
  - Eliminates the cost and inefficiency of maintaining multiple systems.
- Lightest and most ergonomic tool on the market
  - Reduces fatigue and potential for muscle strains.

Courtesy of Vileda Professional

Two & Three Bucket Systems

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Courtesy of Micronova Mfg.

Commonly Used Equipment

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Courtesy Micronova Mfg.

Latest Equipment

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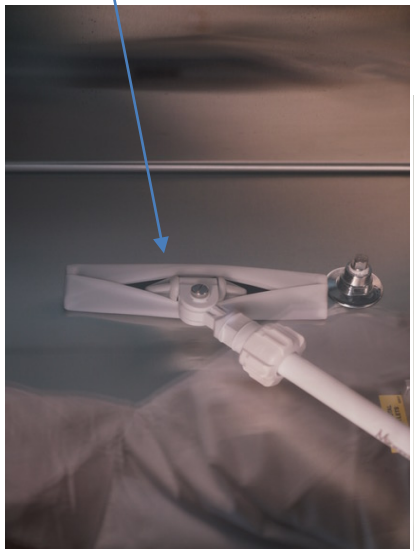
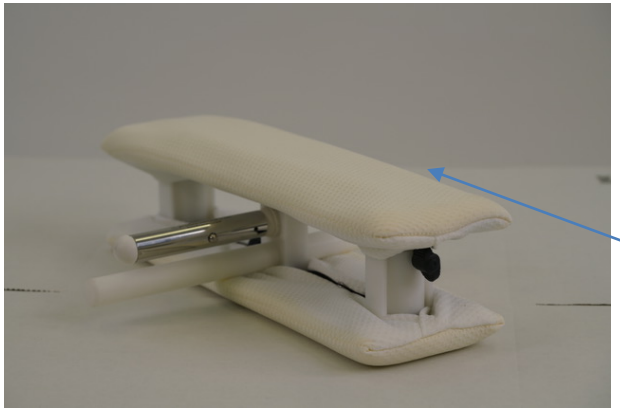
Isolator Tool

Courtesy of Micronova Mfg.





Lyo Tool

Cleaning and Disinfection: Techniques

- Pharma Pump up sprayer
  - Compatible with Sporicides and Disinfectants
  - Specifically designed to be compatible
  - 1.5 Gallon
  - Up to 120°F and 45 psi
  - cGMP ready:
    - Materials of Construction
    - Certificate of Conformity (Serial Number)
    - Assembled using SOP
    - Quality Control performance checks

Product Selection Criteria

- How to choose???
  - Performance – may need multiple products
  - Substrate compatibility
  - Cleaning ability
  - Change Control
  - Globally Available
  - Supply Chain
  - Disaster Response Plan
  - Ease of application
  - Validatability
    - SDS, COA available
    - Stability Studies (Closed Container, Opened Container, Use Dilution)
    - Toxicity Studies, Analytical Methods, Rinsability Studies
  - Application and contact time requirements

Disinfectants are a balance

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Cleaning and Disinfection Best Practices

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How often to clean???

- Environmental cleaning frequency determined by:
  - ISO Classification of area
  - Evaluate the level of risk
  - Activity level in area or use
  - Environmental monitoring feedback
  - Type of process being performed & equipment used

Sporicide: Application

- Sporicidal agent
  - Rationale
    - Weekly
    - Monthly
    - Quarterly
- Should be written in SOP's
  - Extraordinary Cleaning
  - Used Based on Risk
  - Fungal and Bacterial Spore Outbreaks

CNC (Controlled Not Classified) Area Cleaning Frequency

- Hallways and Floors ---Mop daily ---Rinse as needed
- Walls and Ceilings---Mop monthly—Rinse as needed
- Equipment (carts, racks, trash receptacles, etc.)---Wipe weekly---Rinse as needed
- Rinsing is based on visual observation and safety

Grade D (ISO 8 at rest)

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Surface	Method	Cleaning Agent	Frequency	Rinse
Floors • Around Drains • Foot Traffic Paths • Spill Areas • Access Ports	Mop	Disinfectant with surfactant	Daily at shutdown, between process changeover	Not necessary after each application†
Walls, Ceilings • General	Wipe or Mop	Disinfectant with surfactant	Monthly	Not necessary after each application†
• Doors, Handles, High-Traffic Areas	Wipe or Mop	Disinfectant with surfactant	Daily	
Equipment • Adjacent to Access Port	Spray or Wipe	Disinfectant with surfactant	Daily during processing	As needed to remove residue buildup
• Surface Upstream Airflow Path to Process Opening			Weekly	
Other Surfaces • Sinks • Benches • Trash Containers	Wipe	Disinfectant with surfactant	Daily	Not necessary after each application†

A sporicidal agent must be used quarterly, semi-annually or as needed in response to microbial monitoring.[5,6]

† Any contamination control program should incorporate a residue removal component. See the Residue Removal Section for details.

Grade C (ISO 7 at rest, ISO 8 in operation)

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Surface	Method	Cleaning Agent	Frequency	Rinse
Floors • Normal Traffic Paths	Mop	Disinfectant with surfactant	Daily after transfers	As needed to remove residue buildup
• Proximity to Open Process or Transfer Areas		Disinfectant with surfactant followed by a sporicide	Weekly or monthly, if necessary	
Walls • General	Wipe or Mop	Disinfectant with surfactant followed by a sporicide, if necessary	Weekly or monthly	
• Door Plate		Disinfectant with surfactant	Daily	
Equipment • Shelving • Portable Tanks • Processing Items	Spray or Wipe	Disinfectant with surfactant	Before and after use	
• Carts (wheels)		Sporicide		
Other Surfaces • Furniture	Spray or Wipe	Disinfectant with surfactant	Daily	
• Chair (wheels)		Sporicide		

Grade A (ISO 4.8) or B (ISO 5 at rest, ISO 7 in operation)

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Surface	Method	Cleaning Agent	Frequency	Rinse
External Hoods • Back, Sides, Top	Wipe	Sterile disinfectant with surfactant	Daily	Sterile WFI or 70% IPA as needed to remove residue buildup
• Door, Sliding Panel	Wipe	Sterile disinfectant with surfactant	Daily	
		Sterile Sporicide	Weekly or in response to microbial monitoring	
Inside Hood or Curtain • Work Surface • Sidewalls • Apparatus/Critical Surfaces	Wipe	Sterile disinfectant with surfactant	Daily, preuse and postuse	
		Sterile Sporicide	Weekly or in response to microbial monitoring	
• Curtains	Wipe or Mop	Sterile disinfectant with surfactant	Daily	
		Sterile Sporicide	Weekly or in response to microbial monitoring	
Adjacent Flooring and Walls	Mop	Sterile disinfectant with surfactant	Daily, between lots and shifts	
		Sterile disinfectant with surfactant followed by a sterile sporicide, as necessary	Weekly or in response to microbial monitoring	

Recommended Frequency

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	Daily	Weekly	Monthly	Yearly
Controlled Area				
Floors	X	X		
Ceilings				X
Walls			X	
Fixtures/Equipment			X	
Class 100,000 (ISO 8)				
Floors	X			
Ceilings				X
Walls			X	
Fixtures/Equipment		X	X	
Class 10,000 (ISO 7)				
Floors	X			
Ceilings			X	X
Walls		X		
Fixtures/Equipment	X			
Class 100 (ISO 5)				
Floors	X			
Ceilings	X			
Walls	X			
Fixtures/Equipment	X			

Cleaning SOP development

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	Daily (Scheduled working days)		Weekly (Every 7 days ±3 days)		Monthly (Every 30 days ± 10 days)			Semi-Annual (Every 189 days ± 30 days)	Annual (Every 365 days ± 30 days)
Cleaning Agents	**LpH Or Vesphene**	**70% IPA**	**LpH Or Vesphene**		**LpH, Vesphene or * 70% IPA**	**LpH Or Vesphene**	**SporKlenz**	**LpH Or Vesphene**	**LpH Or Vesphene**
Surfaces	**Floors**	**High contact areas**	**Floors**	**Walls**	**Fixtures/ Furniture/ Equipment and High contact areas**	**Walls**	**Floors**	**Walls**	**Ceilings**
ISO Class 8 Rooms									
Equipment Prep Room 110	D	D			M	M	M		A
Wipe Down Room Room 112	D	D			M	M	M		A
Clean Corridor Room 114	D	D			M	M	M		A
Fill Room 3/Pre-IR Room 117	D	D			M	M	M		A
Gowning Room Room 122	D	D			M	M	M		A
ISO Class 7 Rooms									
**Clean Corridor Room 109	D	D		W	M		M		A
Fill Room 1 Room 115	D	D		W	M		M		A
ISO Class 5 Laminar Flow Hood									
Laminar Flow Hood Room 115	Clean before and after each use and weekly (7 days ±3 days) if not in use during the week.								
Unclassified Rooms									
Packaging Room			W		M			S	A

*70% IPA is routinely used on glass, stainless steel, mirrors, racks and sinks.
** Clean Corridor is an ISO 8 to ISO 7 transition area due to gowning area into Fill Room 1.

Hoods, Cabinets and Benches

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Clean and Disinfect prior to and after use

Spray with cleaner, then wipe: top to bottom and back to front, include all sides and work surface

Take care not to wet filter media

Following cleaning, disinfect with a sporicidal agent

Spray work surface and sides and keep wet for validated contact time

Following sporicide, wipe down with 70% IPA and dry wipe to remove residues

Note: *Cleaning frequency depends on the process. Normally only disinfection is needed.*

Non-Product Contact Surfaces

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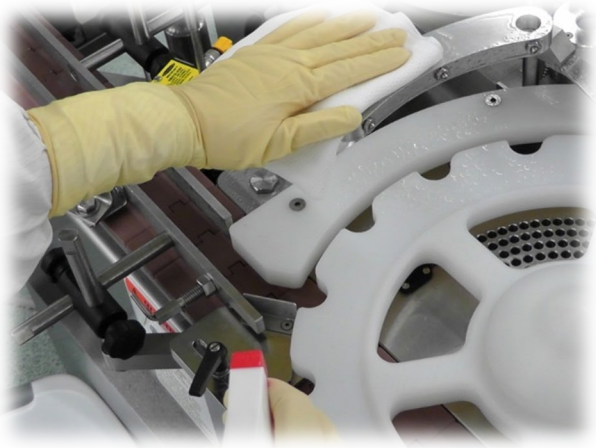
Precautions:

If in close proximity to product contact surfaces



- Eliminate residues carefully
- Inadvertent transfer to product contact surface
- Residues are possible source of contamination

Note: *Disinfectants that leave no residual should be employed OR use a rinse step with IPA/WFI after disinfectant application for critical, near product contact parts.*

Non-Structural Cleanroom Surfaces

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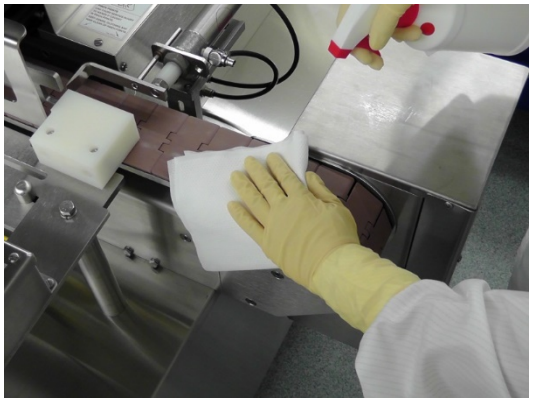
Routine:

- Tanks, Carts, Racks, Bins, Stairs, Tubing/Pipes (Exterior), Monitors, Samplers, Tools

Hard to Clean:

- Tops of doors, Tracks, Conveyors, Phones, Underside of tanks/carts, Wheels

Frequency: Dependent upon classification and process



Tools

Procedure dependent upon where tool is used

- Consider whether materials can withstand disinfection or sterilization
  - Electronics, materials, or gaskets
- Sterilize if you can
- Otherwise, clean, disinfect, wipe with alcohol

Drains

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Do not place drains in Grade A or B areas

- Limit to Grade C and D

Cap drains if possible

Routine interior disinfection difficult

- Cannot assure wetting of all surfaces
- Biofilm prevents penetration, and returns quickly

Disinfect exterior with sporicide (bleach, hydrogen peroxide/peracetic acid)

PDA TR # 70: Drain Cleaning

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"Drains will most probably incorporate a biofilm on the inside of the drain that would prevent penetration of the disinfecting agent through the biofilm and from contacting the drain surface. Disinfecting the exterior of the drain's visible surface with sodium hypochlorite or peracetic acid and hydrogen peroxide may reduce bioburden, but such bioburden is expected to return within a short time period."

- PDA TR #70.

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Disinfectant Rotation & Rinsing

Cleaning and Disinfection: Rotation

- Alternation of antimicrobial actives
  - Two disinfectants in sequence, regular rotation, with sporicidal agent as needed
  - One disinfectant daily, with sporicidal weekly or monthly


CLEANING & STERILIZATION

The Rotation of Disinfectants Principle: True or False?

Cleaning and Disinfection

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- USP 42 <1072> Disinfectants and Antiseptics
  - *"The development of microbial resistance to antibiotics is a well-described phenomenon. The development of **microbial resistance to disinfectants is less likely to occur** at significant levels, as disinfectants are more powerful biocidal agents than antibiotics."*

Disinfectant Rotation: ANVISA

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Article 315

Item1: ”these areas should be cleaned and sanitized frequently in accordance with a specific program approves by Quality Assurance.”

Item 2 says “the areas should be monitored regularly to detect the emergence of resistance microorganisms”.

Cleaning and Disinfection: Disinfectant Rotation

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“Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant and/or spore-forming strains.”

MHRA - Rules and Guidance for Pharmaceutical Manufacturers and Distributors. (2019 Draft Doc.)

Disinfectant Rotation: Japanese Pharmacopeia

- “A disinfectant program for when microorganisms that are resistant to a using disinfectant are discovered. In which a disinfectant with different efficacy is used until those microorganisms of action are alternately used for certain periods of time in turn. The effectiveness of this method should be evaluated before its implementation.”

Disinfectant Rotation: Chinese Pharmacopeia Chapter 9305

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The Third Exposure Draft (2020)

laboratories, and to make monitoring of microbial contamination of disinfectants and detergents. And use shall be made within the specified validity period. Sterile or germ-treated disinfectants and detergents shall be used in level A/B clean areas. The chemical disinfectant used shall be verified or the disinfection effect shall be proved. And the chemical disinfectants shall be more than one type and changed periodically to prevent the production of resistant strains. Ultraviolet disinfection shall not be used to replace chemical disinfection. If necessary, suitable methods such as gas and fumigation can be adopted to reduce the microbial pollution in the sanitary dead angles in the clean area, and the residual level of ~~fumigant~~ disinfectant shall be verified.

Cleaning and Disinfection: Resistance & Rotation

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- PDA TR No. 70 2015

"*The antimicrobial agents typically employed in cleanrooms continue to be effective because they have numerous effects on a number of aspects of cellular physiology. That means multiple mutations would be required in a short period of time (ex. 5 minutes) with exposure to low numbers of cells typically found in a cleanroom to overcome their detrimental effects. As such, resistance of a cell to agents used in a disinfection process would be highly unlikely given the environmental conditions and low cell number.*"

Cleaning and Disinfection: Rotation

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PDA TR No. 70

"Given this knowledge, the pharmaceutical and biotechnology ***industries have moved away from the rotation of two disinfecting agents****. This formerly common practice led to high residue levels and subordinate efficacy performance. Today most firms use a system whereby a* ***disinfectant is rotated with a sporicide to more effectively reduce the bioburden*** *levels. The rotation of a disinfectant with a sporicide is* ***superior to the use of rotations of multiple disinfectants.****"*

Recent Rotation Article

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"Regardless of the terminology, there is a regulatory expectation to establish an adequate system for cleaning and disinfection in order to keep microbial contamination under control. The use of an effective disinfectant with a periodic shock to the environment with a **sporicide** is considered superior and is encouraged over the rotation of multiple disinfectants. In my opinion, until the industry coins a better term than "rotation" for the current standard industry practice, the confusion over disinfectant rotation may continue. So, when regulators ask if you rotate your disinfectants, skip the "yes-or-no" debate. Clearly explain your cleaning and disinfection program, and then demonstrate through data how your program is effective in microbial contamination control."

Pharmaceutical Online, Crystal Booth, 9/14/18.

https://www.pharmaceuticalonline.com/doc/should-you-rotate-disinfectants-industry-experts-weigh-in-0001

Cleaning and Disinfection: Rotation

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- USP 42 <1072> Disinfectants and Antiseptics
- Annex 1 (Draft 2018) and MHRA Orange Guide (2016)
- FDA Aseptic Processing Guide (2004)
- FDA, MHRA, HPRA, CFDA, ANSM, ANVISA, CFDA, FDAHA, Swissmedic, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince, Rebecca Smith, Crystal Booth, Jeanne Moldenhauer)
- PDA Cleaning and Disinfection TR No. 70 (2015)
- PDA TR #69 on Biofilms (2015)
- The CDC Handbook - A Guide to Cleaning & Disinfecting Cleanrooms (Tim Sandle 2018)
- A Guide to Disinfectants and their use in the Pharmaceutical Industry (Pharmig 2019)
- USP 42 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
- PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (2014)
- WHO Annex 6
- PHSS Technical Monograph #20 “Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas

Cleaning and Disinfection: Rinsing

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Do I need to rinse?

483 observations (2013)

- Your firm does not always keep laminar flow hoods visually clean of residue on HEPA filter surfaces and covering grates……I observed **white and yellow residue** on the HEPA filters…..and in areas up to approx. eight inches square on the filter…..
- I observed **white particles** on the floor of the clean room…approximately two to three millimeters square.
- Recent WL reference: https://www.fda.gov/iceci/enforcementactions/warningletters/2017/ucm558496.htm
- Dr. Sharon Thoma's view on residues

Cleaning and Disinfection: Rinsing

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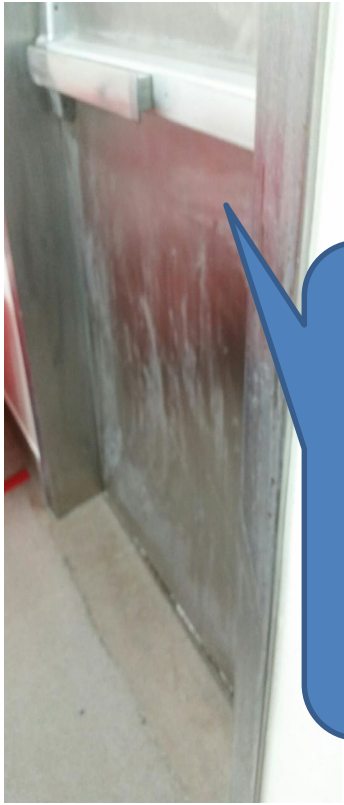
- Rinse as needed to control residue
  - Appearance
  - Functionality – sticky or opaque surfaces
  - Product risk
  - Interaction/interference with other chemical agents being used
  - Safety issue (stickiness, tackiness, slippery)
- Rinse agents
  - Alcohols or Water
  - Cleaners: Acidic, Basic or Neutral (low concentrations)
  - Periodic rinsing based on aesthetics and safety
- **Annex I Draft 2019: Cleaning programs should be effective in the removal of disinfectant residues.**



This is a problem? Why? We clean the door all the time…

Surface Types and Topography

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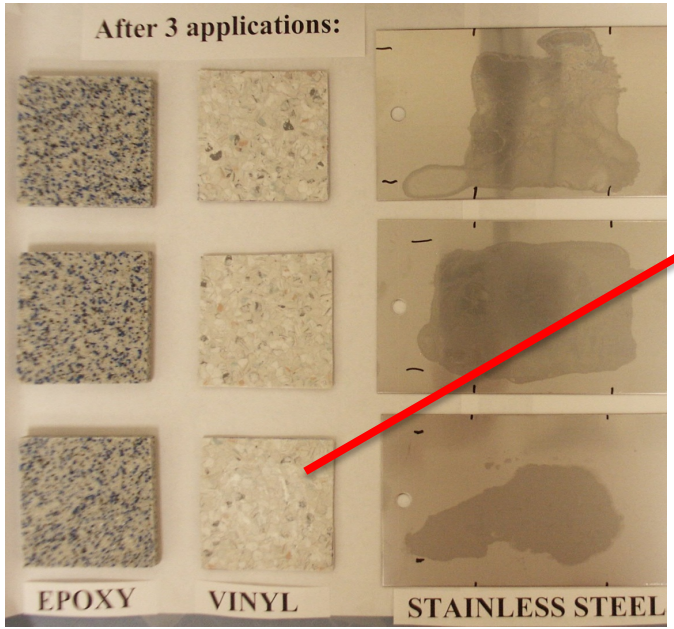

-Sticky mats

-Drains

-Edges and corners

Surface Conditions Effect Performance

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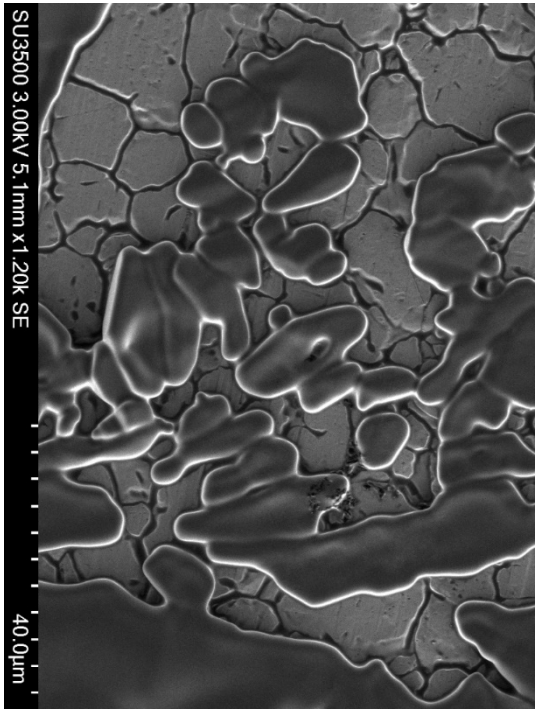

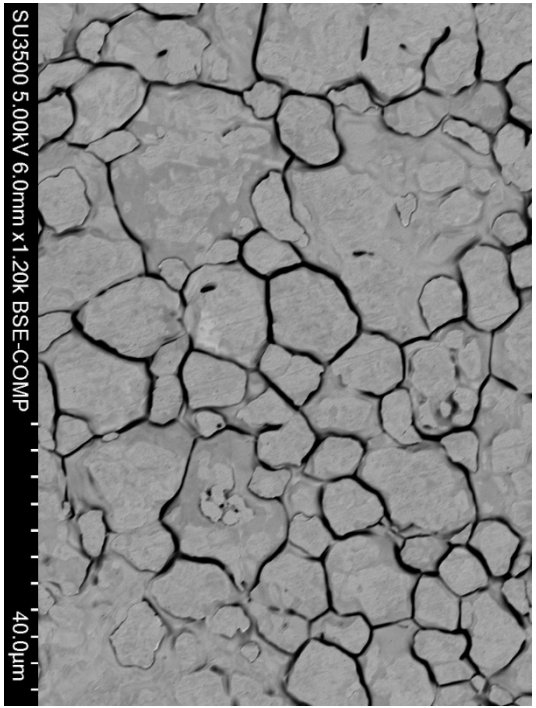

Courtesy Bruce Ritts

PDA TR No. 70: Conducting Investigations related to Cleaning and Disinfection

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Common Causes:

- Application issues
- Dilution issues
- Insufficient contact times
- Expired product
- Incorrect biocide for cleanroom bioburden
- Lack of adherence to protocols
- Equipment issues (rusting and pitting)
- Using inadequate cleanroom tools

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