A Risk Based Cleaning and Disinfection Program

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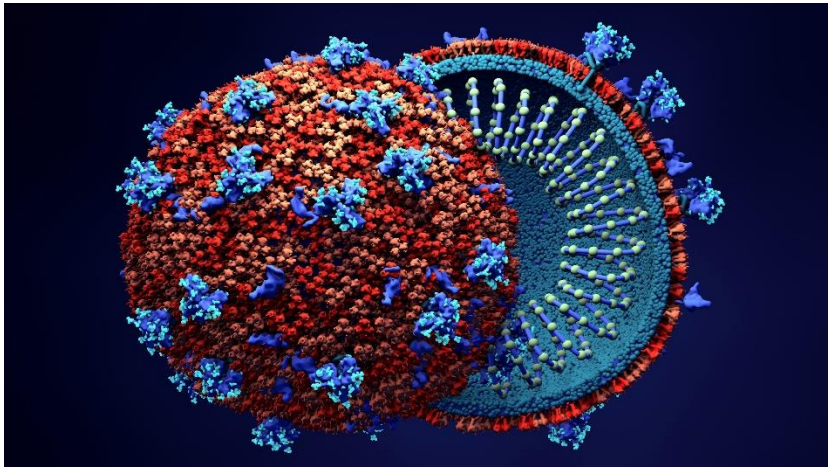
PDA
May 26, 2020
Jim Polarine Jr., MA.
Senior Technical Service Manager

SARS-CoV-2 Virus



Companies are doing the following based on recent surveys:

- Social Distancing
- Temperature Checks & Testing
- GM 7 Ford-Watches to assist in social distancing
- Increased handwashing and wearing masks

Biography

Mr. Polarine is a senior technical service manager at STERIS Corporation. He has been with STERIS Corporation for twenty years. His current technical focus is microbial control in cleanrooms and other critical environments. Mr. Polarine is a 2019 PDA Michael S. Korczynski Award recipient. He has lectured in North America, Europe, Middle East, Asia, and Latin America on issues related to cleaning and disinfection, microbial control in cleanrooms and validation of disinfectants. Mr. Polarine is a frequent industry speaker and published several PDA book chapters and articles related to cleaning and disinfection and contamination control. He is active on the PDA's COVID-19 Task Force and the PDA's Microbial Diviations Task Force. He was a co-author on PDA's Technical Report #70 on Cleaning and Disinfection. Mr. Polarine teaches industry regulators as well as the pharmaceutical, biotech, and medical device industries at the PDA and the University of Tennessee. Mr. Polarine currently teaches the cleaning and disinfection course as part of the PDA Aseptic Processing Course and at the University of Tennessee Parenteral Medications Course. Mr. Polarine is current President for the PDA Missouri Valley Chapter and Technical Coordinator for the IEST.

Jim Polarine has a Master's of Arts in Biology from the University of Illinois in Champaign, IL..

Topics Covered

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

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Regulations and Guidance Documents

USP 43 <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"

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 Annex I (2020)

4.36 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action and their combined usage is effective against all bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use). Cleaning programs should effectively remove disinfectant residues.

Recent FDA 483

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"Your firm failed to conduct adequate cleaning and disinfection in the APA. No additional cleaning and disinfection or environmental sampling was conducted following the shutdown of the ISO-5 hoods."

FDA 483 2/20/2020

https://www.fda.gov/media/135875/download

Recent FDA 483

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"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

Recent FDA 483

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"Specifically, according to your Pharmacy Technician, your firm is using non-sterile[(b) (4) I Disinfectant and non-sterile[(b) (4) I to clean and disinfect the Cleanroom and ISO s[(b) (4) 'Flow Hood. In addition, the sterile wipes utilized during cleaning can potentially shed particulates."

February 28, 2020.

https://www.fda.gov/media/135889/download

Recent FDA 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

Recent WL on Cleaning and Disinfection

"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

"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

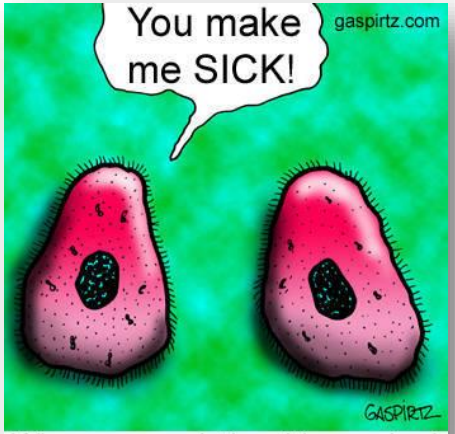
Recent WL

"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)



Cleaning and Disinfection: Product Selection

- 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: “clean” and “dirty” as a soil load

Cleaning and Disinfection: Product Selection

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

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Cleanroom Bioburden Control

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

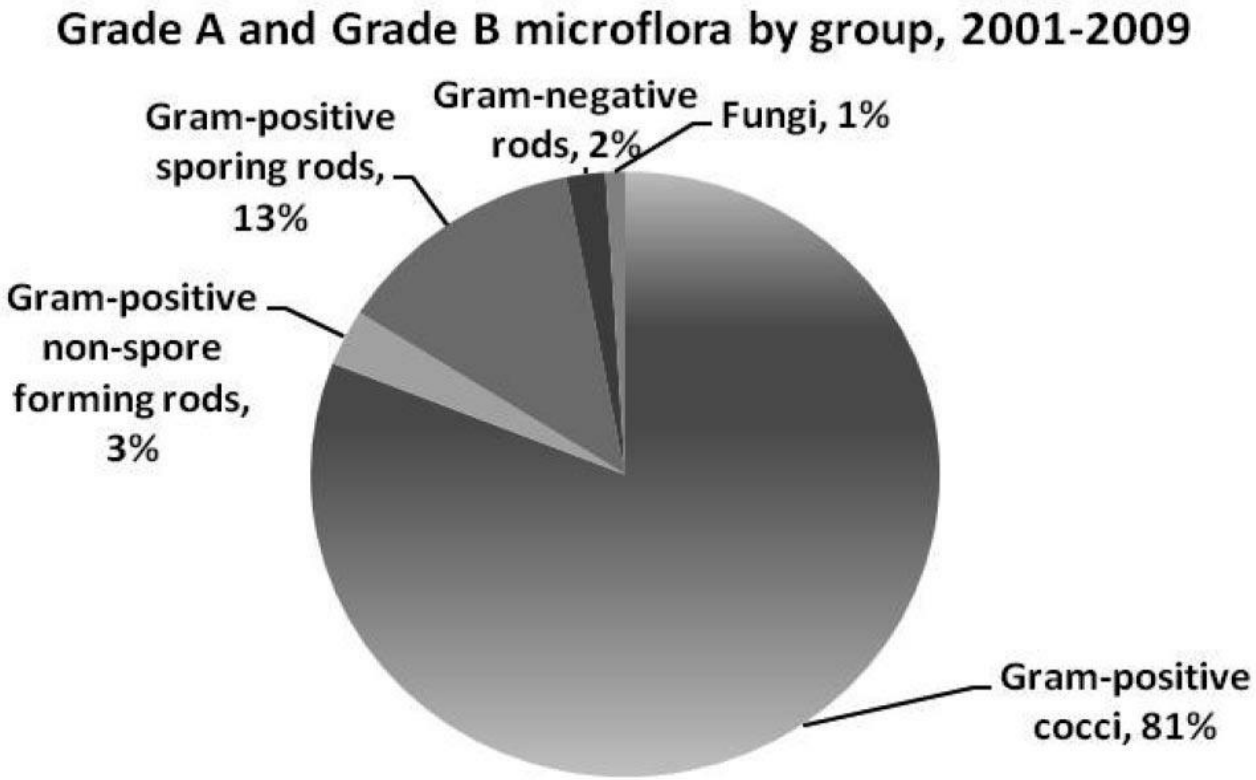
From McDonnell, "Antisepsis, Disinfection, and Sterilization: Types, Action, and Resistance" 2007, ASM Press

Review - Microflora in Cleanrooms (U.K.)

- 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.)



Review - Microflora in Cleanrooms (U.K.)

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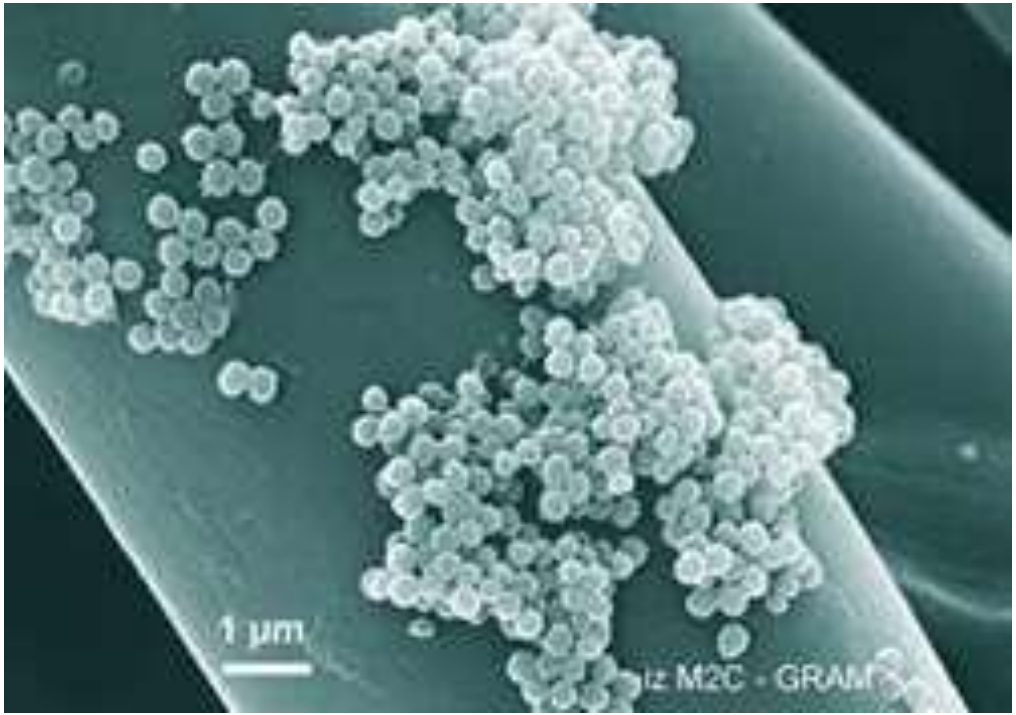
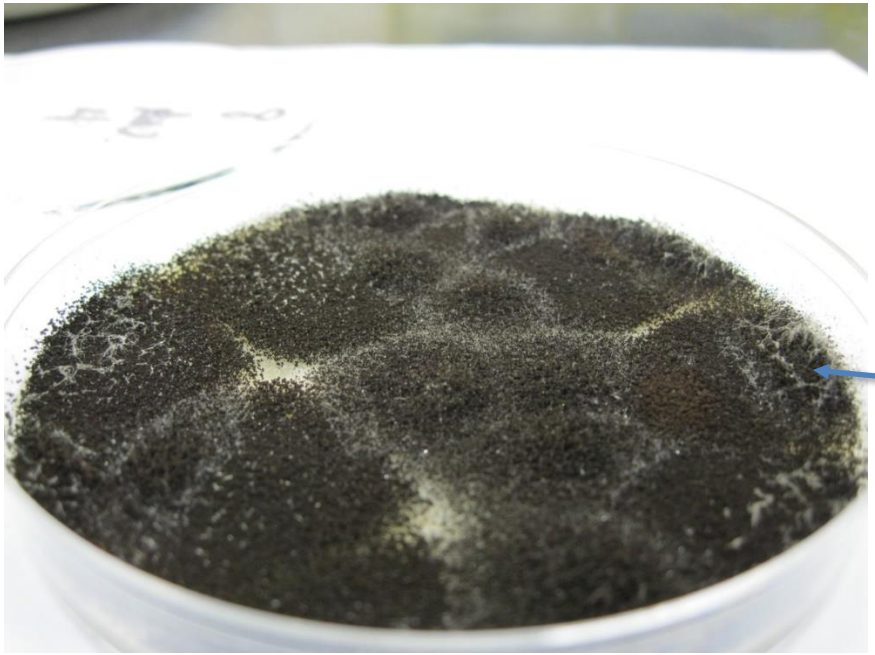
Genus	A/B (6729)	C/D (2500)
Micrococci (and related)	38%	40%
Staphylococci	21%	11%
Bacillus (and related)	13%	10%
Pseudomonas (and related)	<1%	8%
Corynebacterium (and related)	3%	5%
Rhodococci	<1%	N/A
Fungi	N/A	3%

Staphylococcus haemolyticus



Courtesy Grace Thornhill

Aspergillus Spores



Cleanroom Fungi

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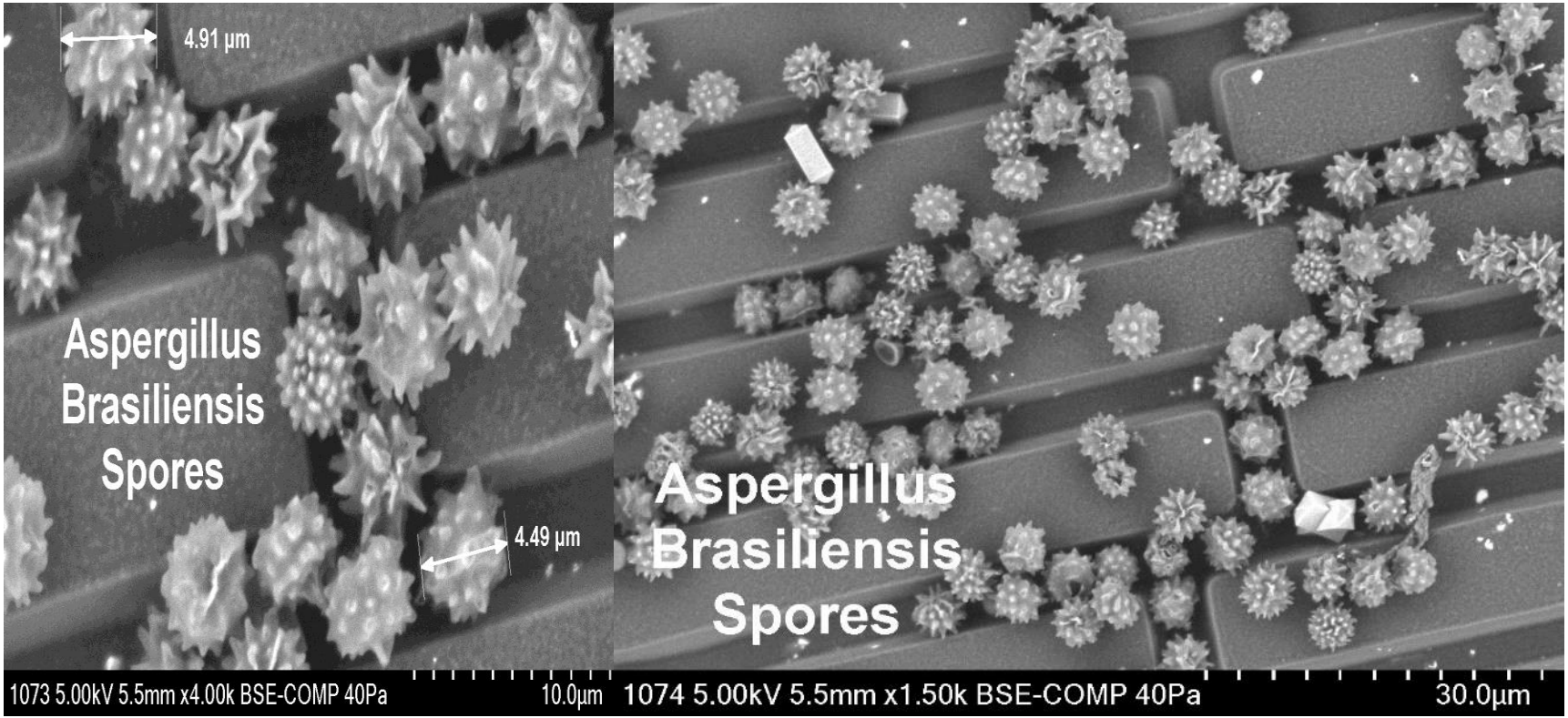
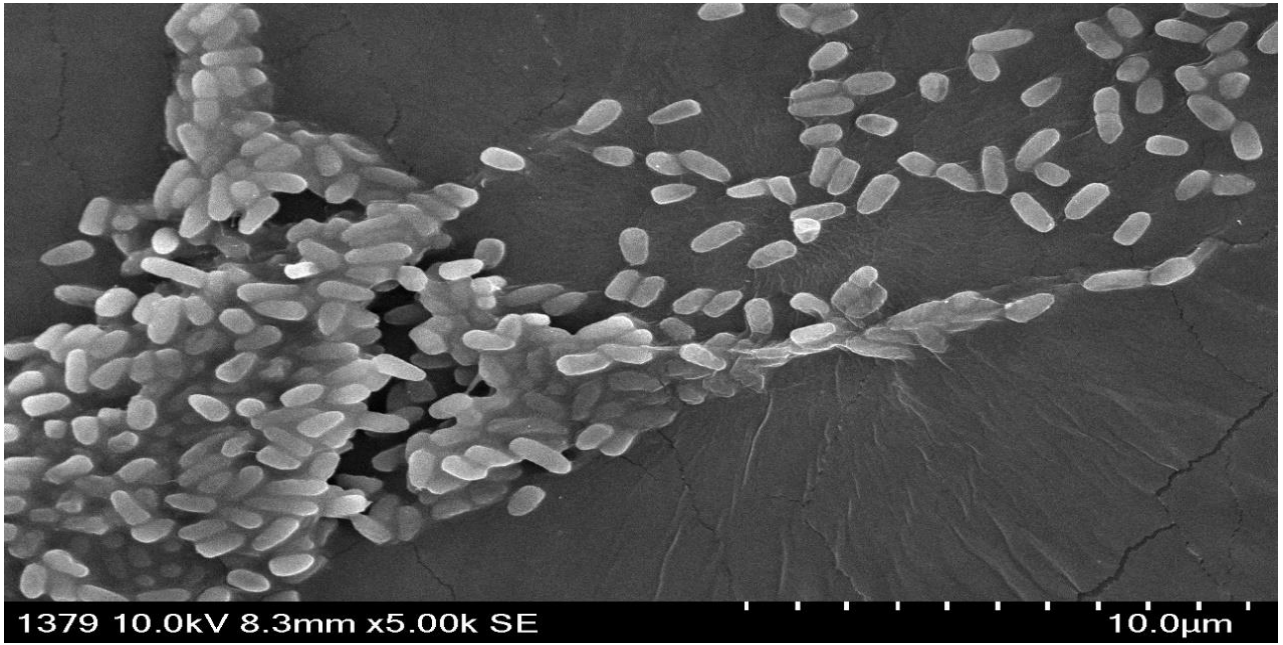
Courtesy Dan Klein

Aspergillus Spores



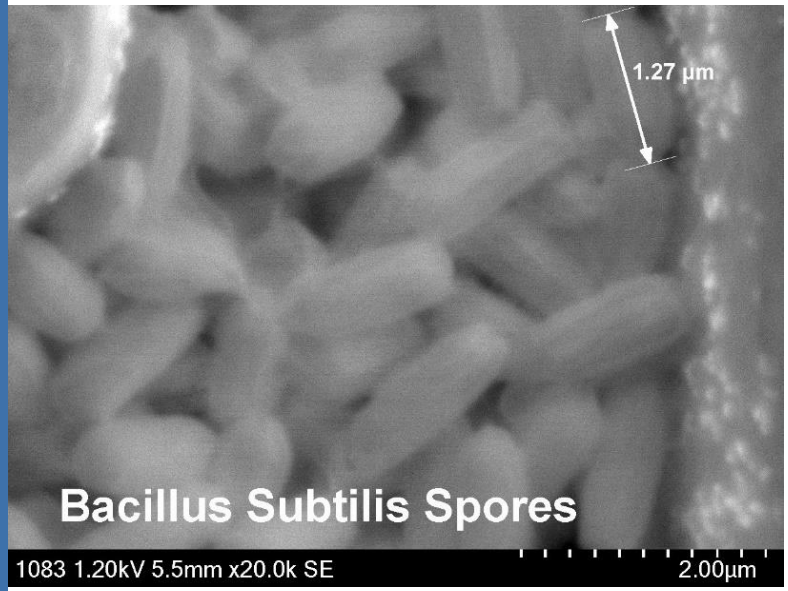
Courtesy Bruce Ritts

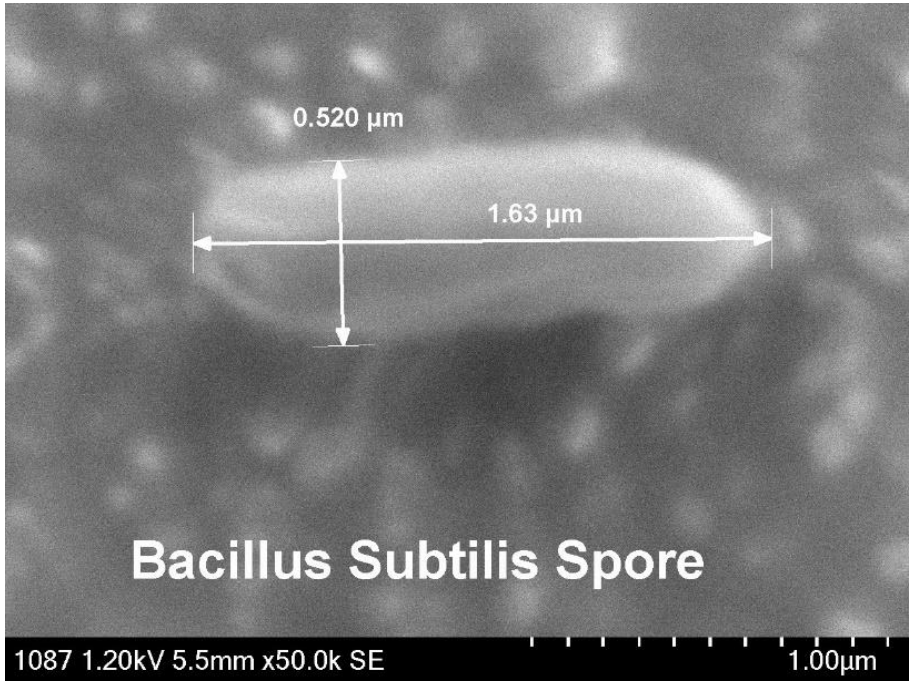
SEM: Pseudomonas 5,000X magnification



Courtesy Dan Klein

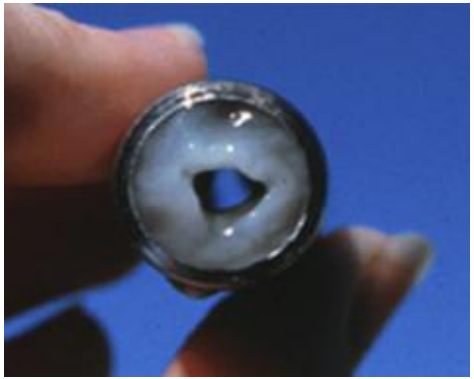
Bacillus Subtilis





Courtesy Bruce Ritts

Biofilms



Courtesy Dan Klein

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Technologies

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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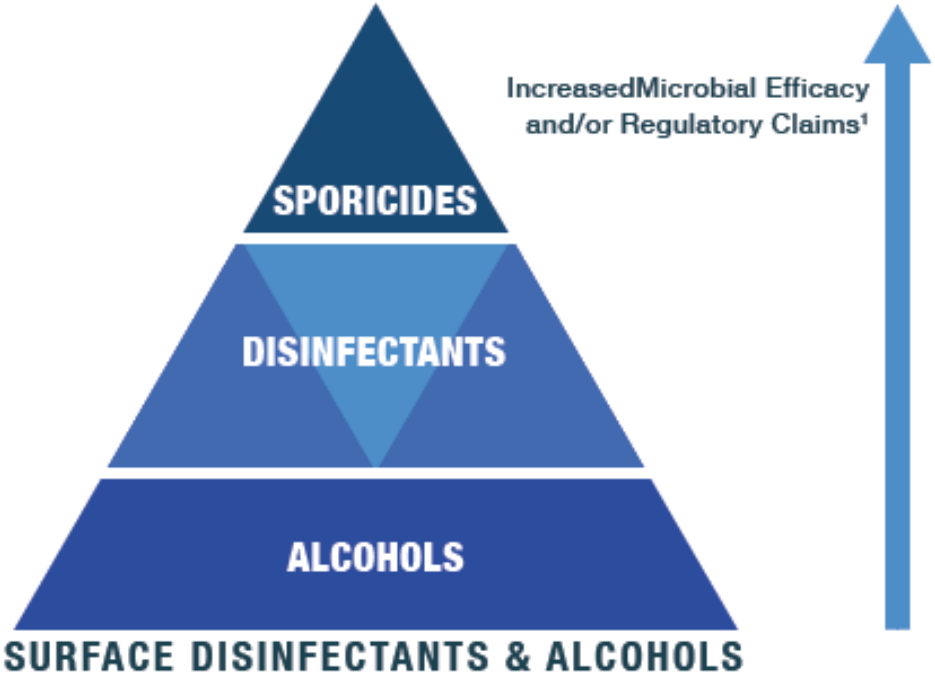

SURFACE DISINFECTANTS & ALCOHOLS

¹Products 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.

Disinfectant Components

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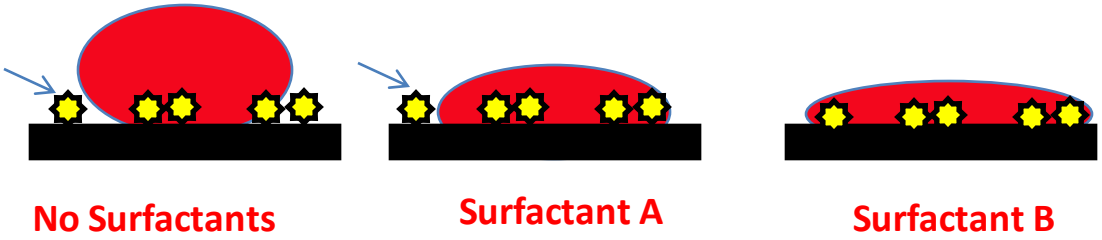
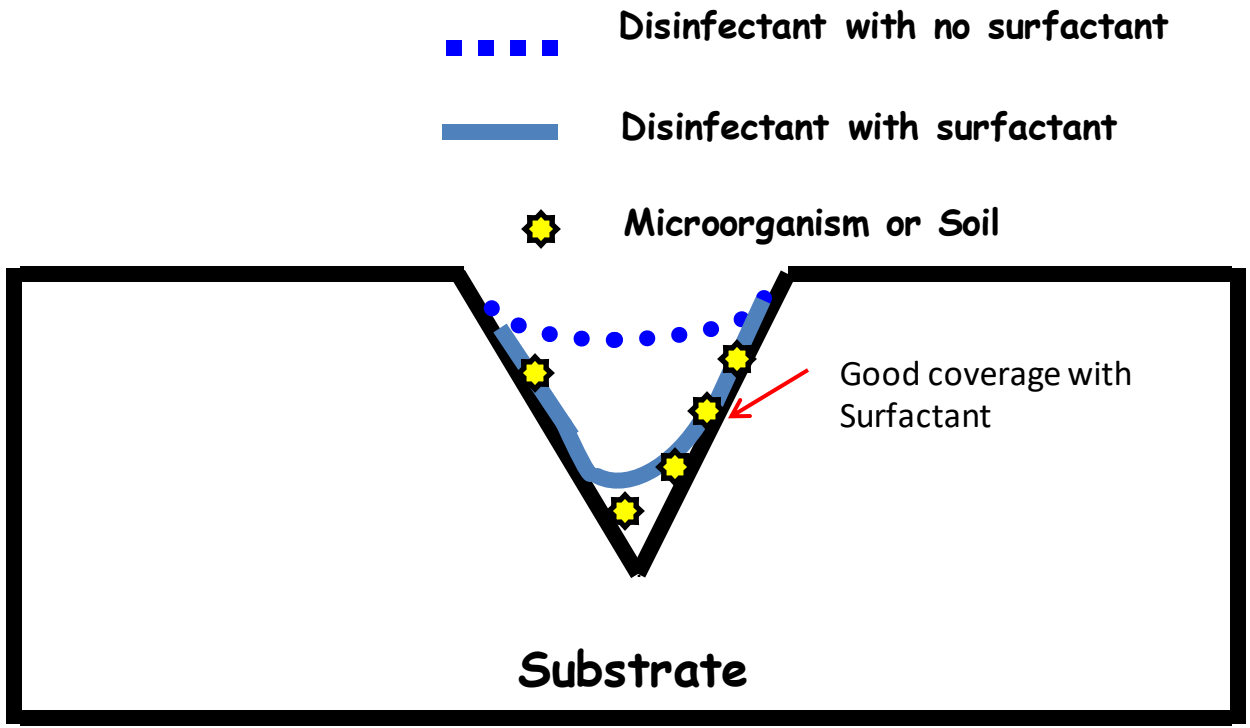
Component	Function in Disinfectant
Water	Solvent
Antimicrobial	Kill, reduce microbes
Oxidants	Oxidize, kill microbes
Chelants	Tie up calcium, iron, stabilize oxidants, potentiates antimicrobial action (ex. EDTA, Citric Acid)
Solvents	Solubilization and stabilization of formula
Bases	Alkalinity source, 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



Microbial Technologies

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Phenolic Advantages

- Tuberculocidal
- Broad spectrum activity
- Good cleaning ability
- Well suited for high risk areas
- Don’t use on the same surfaces as Quats due to surfactant compatibility issues

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Phenolic Disadvantages

- Some areas have disposal restrictions against phenolics
- Not sporicidal

Microbial Technologies

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Quat Advantages

- Broad spectrum activity
- Good deodorizer
- Excellent cleaner

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Quat Disadvantages

- Not generally tuberculocidal
- Not sporicidal
- Effectiveness reduced by presence of soaps or the anionic compounds

Microbial Technologies

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Chlorine Advantages

- Relatively quick microbial killer
- Generally not affected by hard water
- Economical to use
- Available in granular and liquid forms
- Effectiveness in pH dependent

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

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

Holweida (1928)

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Chlorine Disadvantages

- Inactivated by heavy organic material, exposure to ultra-violet light or heat
- Objectionable odor
- No sporicidal claim (not registered with EPA as a sanitizer or disinfectant)
- Deteriorates during storage
- Irritates skin
- Poor cleaner
- Corrosive to metals if misused
- May cause whitening or bleaching (floors)

Microbial Technologies

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Alcohol Advantages

- Good broad-spectrum activity
- Tuberculocidal (TB)
- Leaves no residue
- Excellent at removing residues
- Effective at low temperature
- Evaporates readily

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Alcohol Disadvantages

- No detergency
- Flammable, volatile
- VOC's (California)
- Not sporicidal
- Sets off Particle Monitors
- TLV=200ppm

Microbial Technologies

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Hydrogen Peroxide/Peroxyacetic Acid Advantages

- Relatively quick microbial kill
- Sporicidal
- At sterilization dilution levels – less corrosive than chlorine dioxide and acidified Bleach
- Easier to prepare for use than chlorine dioxide
- Low skin sensitivity
- Low or negligible inhalation toxicity

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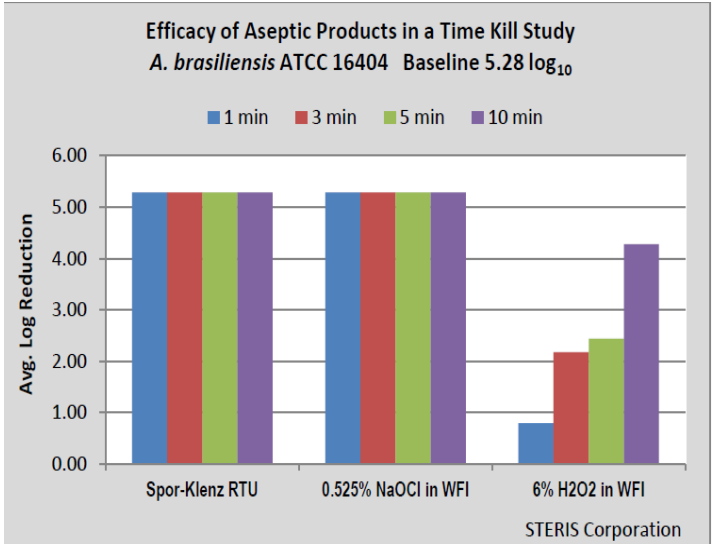
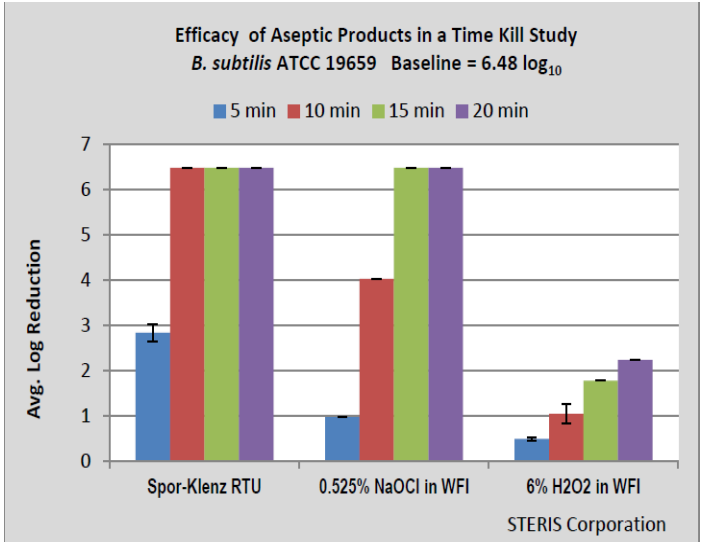
Hydrogen Peroxide/Peroxyacetic Acid Disadvantages

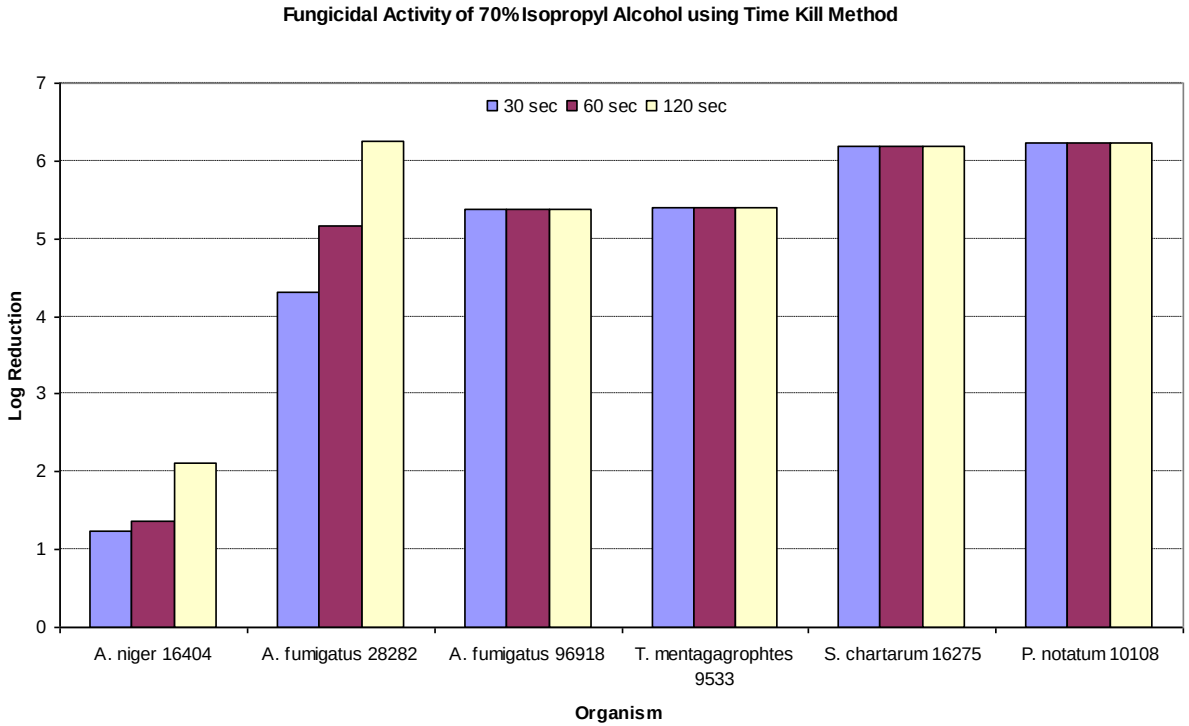
- Corrosive to soft metals
- Odor
- Some product formulas require dilutions made with good quality water (Ex. WFI)
- Can not be mixed with bleach or other oxidizing agents
- Apply to precleaned surface only

Efficacy of Sporicides





70% IPA Efficacy against Molds



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Technology Selection

Selecting Decontamination Chemistries

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Sanitizers, Disinfectants, Sporicides are selected based on:

- ✓ Microbial efficacy
- ✓ Toxicity (Disposal)
- ✓ Material substrate compatibility

Disinfectants are a balance

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Properties of Disinfectant

- Performance – may need multiple products
  - Routine disinfectant for most microorganisms
  - Sporicide for hard to kill organisms like *Bacillus* spores
  - Decontaminating rinse agent such as 70% IPA or WFI
- Contact time requirements
- Substrate compatibility
- Cleaning ability
- Ease of application
- Ease of validation

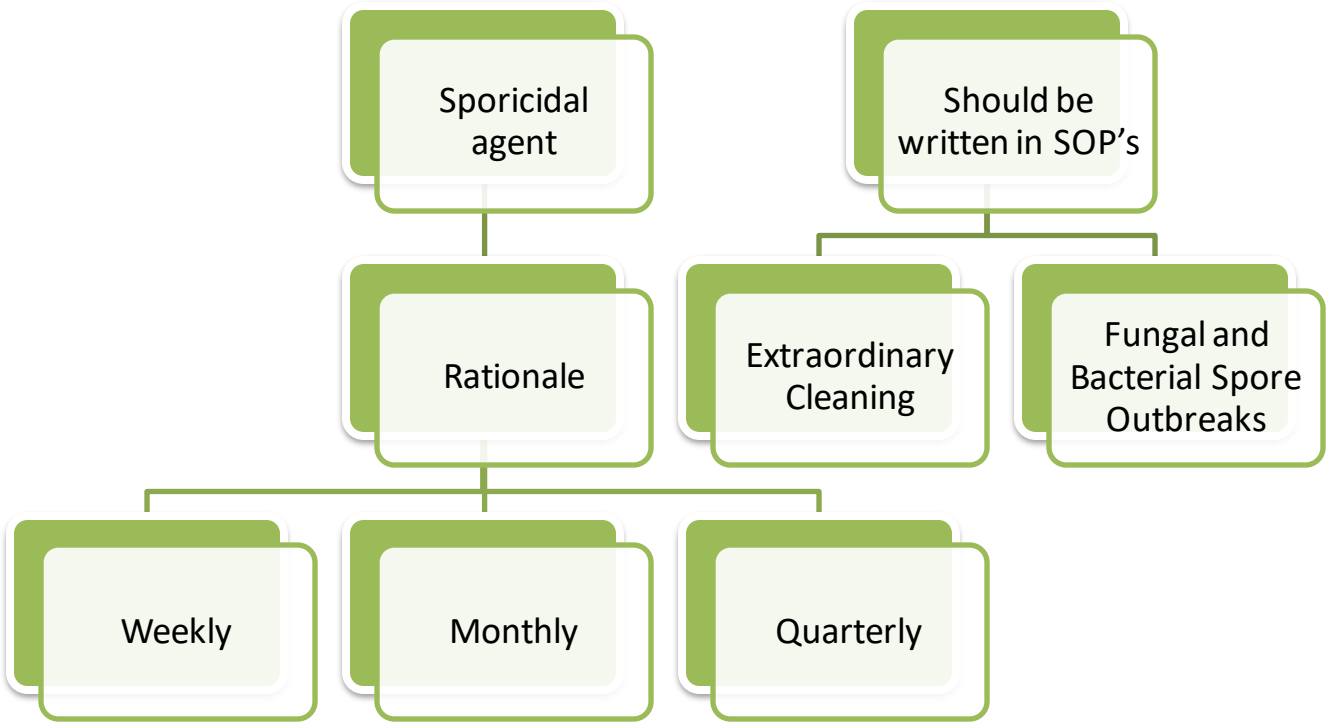
Properties of Disinfectant Manufacturer

- Provide reliable formulations
  - Maintain same formulation whenever possible
  - Minimal formulation changes
  - Change control SOP to notify Customers as needed
  - Avoid discontinuing products without ample notification
  - No product recalls for contamination
- Products are globally available with necessary registrations
  - Easy for global Customers to qualify same disinfectant for all sites
- Management of Supply Chain Security
  - Minimal raw material supplier changes
  - Alternate sourcing of raw materials to ensure supply

Supporting Documentation & Testing of Disinfectant

- SDS available in multiple languages
- COA provided with every lot for traceability and quality control
- Stability Studies
  - Opened Container
  - Closed Container
  - Use Dilution
- Analytical Methods
  - Rinsability
  - Compatibility
  - Toxicity Studies
- Industry Technical Expertise

Sporicidal Application Frequency



CNC Area Cleaning Frequency

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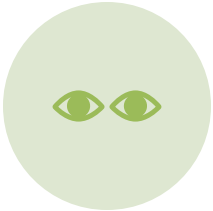
Hallways and Floors ---Mop daily ---Rinse as needed

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

	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.

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Cleaning and Disinfection Application Methods

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% or 2 inches)
- Figure 8 (String Mop) or Unidirectional overlapping mopping strokes
- Modified Figure 8 with Flat Head Mops for Walls

* 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.**

Application Techniques

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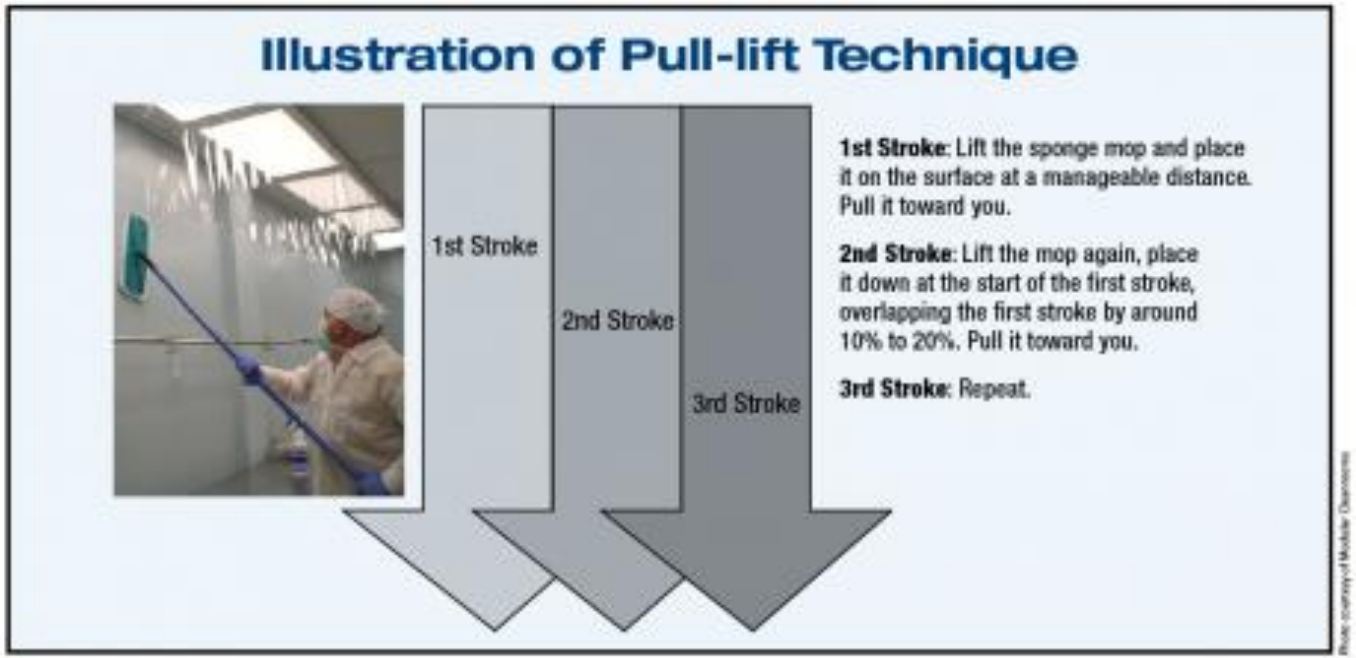
Figure 1. Proper Surface Cleaning



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

Two Bucket System & Three Bucket System

- Two Bucket
  - Mop is placed in Bucket 2 (Rinse Bucket)
  - Wring it Out
  - Mop is placed in Bucket 1 (Clean or Primary Bucket)
  - Wring it Out
  - Apply to the floor
- Triple Bucket
  - Mop in Bucket 2 (Rinse Bucket)
  - Next Bucket 3 Ring Out Bucket
  - Next Bucket 1 (Clean Bucket)
  - Next Bucket 3 Ring Out Bucket
  - Mop the Floor
  - (Mop Rides in Bucket 2)
  - 8-16 feet covered in mopping passes 1 and 2

Mopping Technologies

- 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.

Cleaning and Disinfection: Techniques

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- Pharma Pump up sprayer
  - Compatible with H2O2/PAA, Phenolics, Quats
  - 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

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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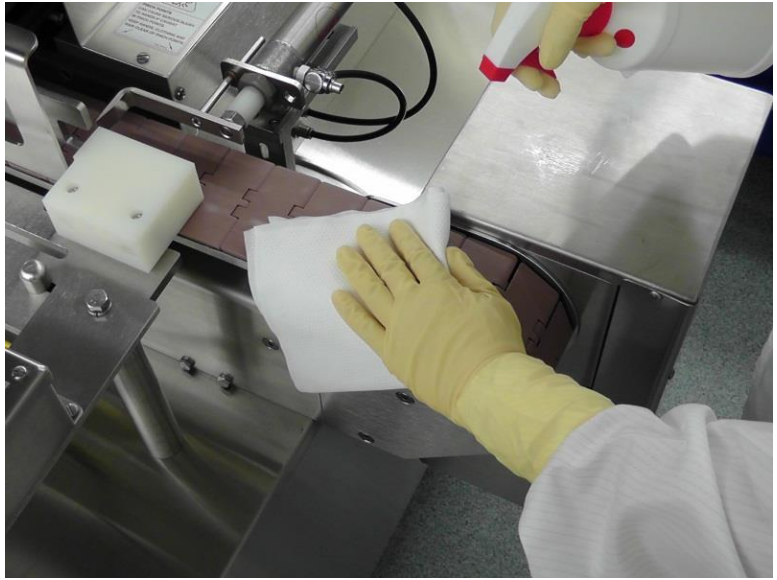
Routine:

- 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)

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

Disinfectant Rotation & Rinsing Programs

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


The Rotation of Disinfectants Principle: True or False?

A

Cleaning and Disinfection: Rotation

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USP 43 <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”.

Japanese Pharmacopoeia

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"A disinfectant program for when a microorganisms that are resistant to a using disinfectant are discovered. In which a disinfectant with different efficacy is used until those microorganisms are no longer detected or disinfectants with different mechanisms of action are alternately used for certain periods of time in turn. The effectiveness of this method should be evaluated before its implemented"

Disinfectant Rotation: Chinese Pharmacopeia Chapter 9305

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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.

Annex I Draft 2020

- 521 For disinfection to be effective, prior cleaning to
- 522 remove surface contamination should be performed. More than one type of disinfecting agent should
- 523 be employed to ensure that where they have different modes of action and their combined usage is
- 524 effective against all bacteria and fungi. Disinfection should include the periodic use of a sporicidal
- 525 agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the
- 526 disinfection program and to detect changes in types of microbial flora (e.g. organisms resistant to the
- 527 disinfection regime currently in use).

Cleaning and Disinfection: Resistance & Rotation

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- PDA TR No. 70
- "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

PDA Expert Panel October, 2019

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- Conclusions
  - Resistance does not occur in cleanrooms
  - A sporicide must be part of the rotation
  - One or two disinfectants are acceptable

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 2017 WL reference: https://www.fda.gov/iceci/enforcementactions/warningletters/2017/ucm558496.htm
- Dr. Sharon Thoma FDA (Residue build up may hide other issues.)

Cleaning and Disinfection:

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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
  - Sterile Cleaners: Acidic, Basic or Neutral (low concentrations)
- **Annex I Draft: Cleaning programs should be effective in the removal of disinfectant residues.**

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

Residues

- Myths:
  - Residues promote microbial growth.
  - Residues inhibit sporicides.
  - Residues hide microorganisms.
  - All residues come from disinfectants.

Mean Log Reduction of *B. subtilis* using phenolic residues and sporicidal agent solution

Minutes, Post Inoculation	2.5	5	7.5	10	20
Mean Log Reduction: Sporicidal agent + Water	0.7	3.85	4.16	4.16	4.23
Mean Log Reduction: Sporicidal agent + low pH phenolic disinfectant	3.82	4.15	4.16	4.16	4.23
Mean Log Reduction: Sporicidal agent + high pH phenolic disinfectant	3.32	4.15	4.16	4.16	4.23

Mean Log Reduction of *B. subtilis* using *dried* phenolic residues and sporicidal agent solution

Minutes, Post Inoculation	2.5	5	7.5	10	20
Mean Log Reduction: Sporicidal agent + Water	0.7	3.85	4.16	4.16	4.23
Mean Log Reduction: Sporicidal agent + low pH phenolic disinfectant	3.82	4.15	4.16	4.16	4.23
Mean Log Reduction: Sporicidal agent + high pH phenolic disinfectant	3.32	4.15	4.16	4.16	4.23

PDA TR #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

Industry References

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- USP 43 <1072> Disinfectants and Antiseptics
- Draft Annex 1 (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
- PHSS Technical Monograph #20 "Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas
- IEST-RP-CC018.4 Cleanroom Housekeeping: Operating & Monitoring Procedures (2020)

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