

A Risk Based Cleaning and Disinfection Program



- ❖ **Regulatory Requirements**
- ❖ **Cleanroom Bioburden Control**
- ❖ **Cleaning and Disinfecting Technologies**
- ❖ **Cleaning and Disinfection Techniques**
- ❖ **Rotation and Residues**

Regulations and Guidance Documents

“C) On 06/08/2020, I observed visible black and brown stains on the ISO 5 Cleanroom ceiling tile stationed directly adjacent to the right of Table 2, direct compounding area (DCA), within Cleanroom”

6/15/2020

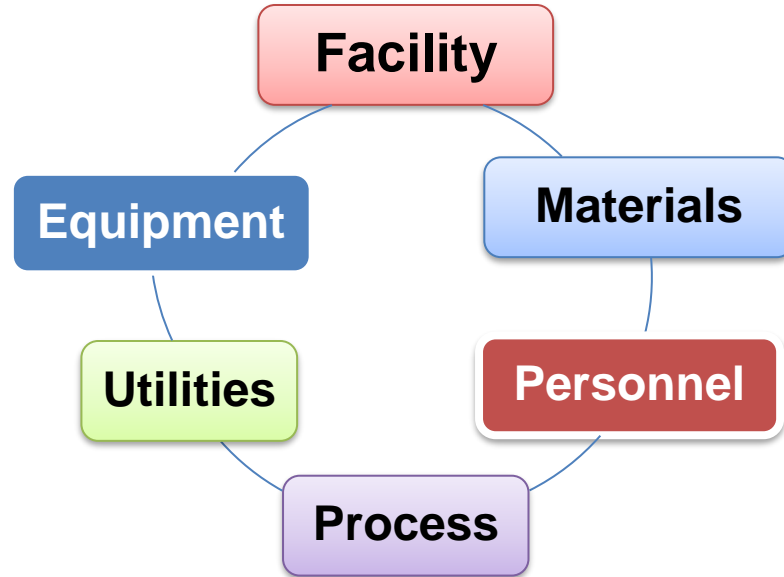
<https://www.fda.gov/media/140568/download>

“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>

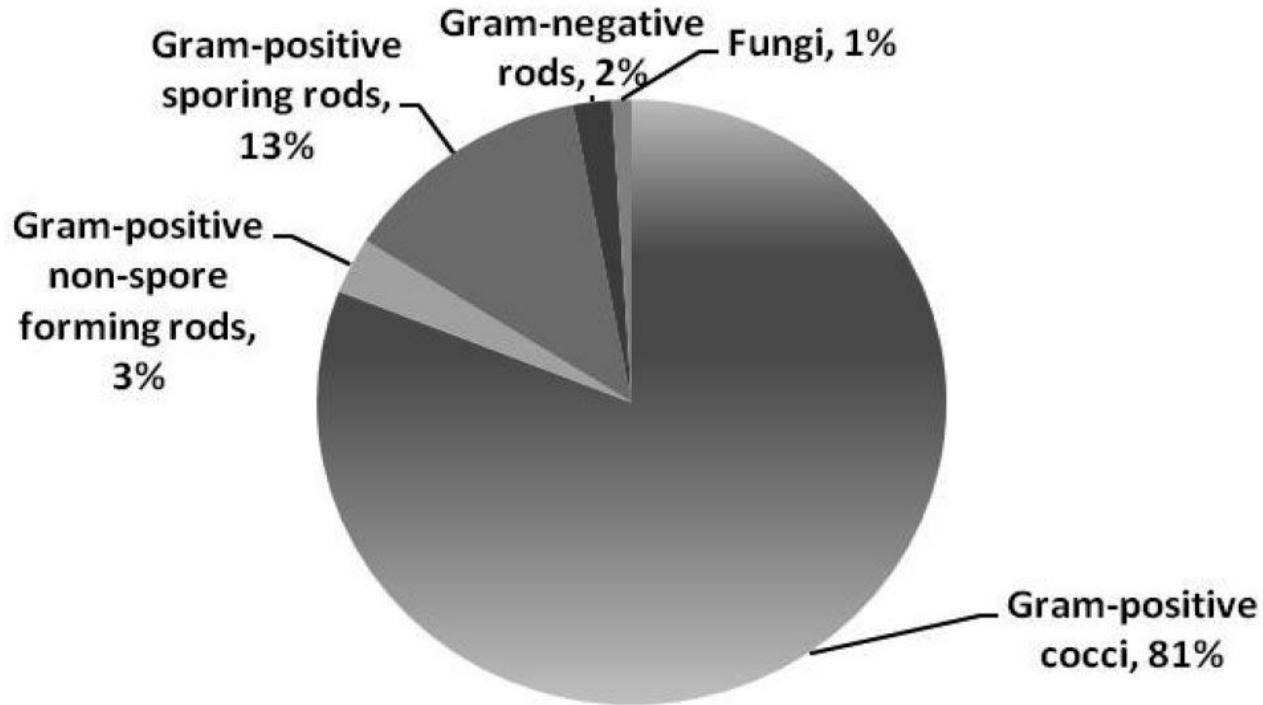
Cleanroom Bioburden Control



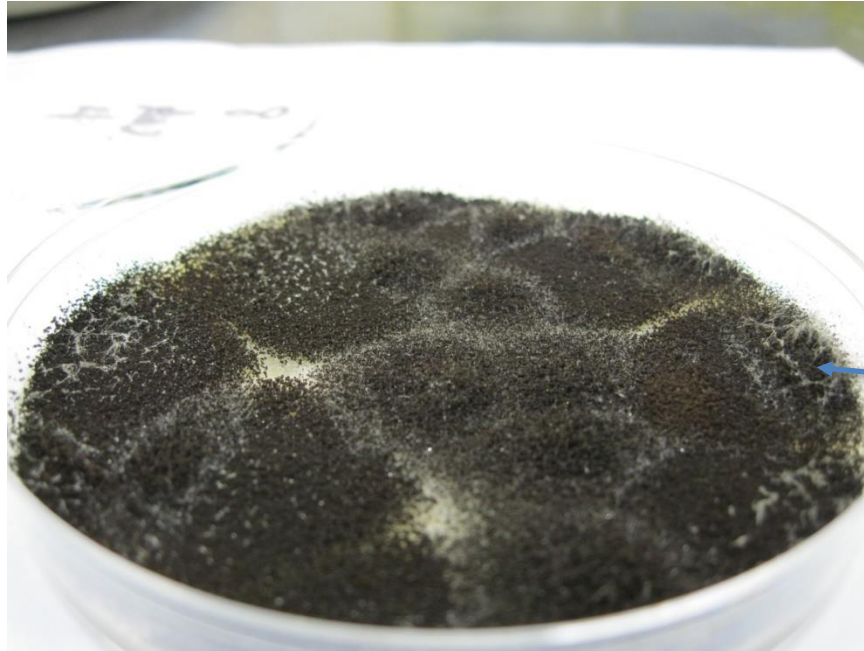
- Tim Sandle
- PDA J Pharm Sci and Tech 2011, 65:392-403
- **A Review of Cleanroom Microflora: Types, Trends, and Patterns**

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

Grade A and Grade B microflora by group, 2001-2009



Aspergillus Spores



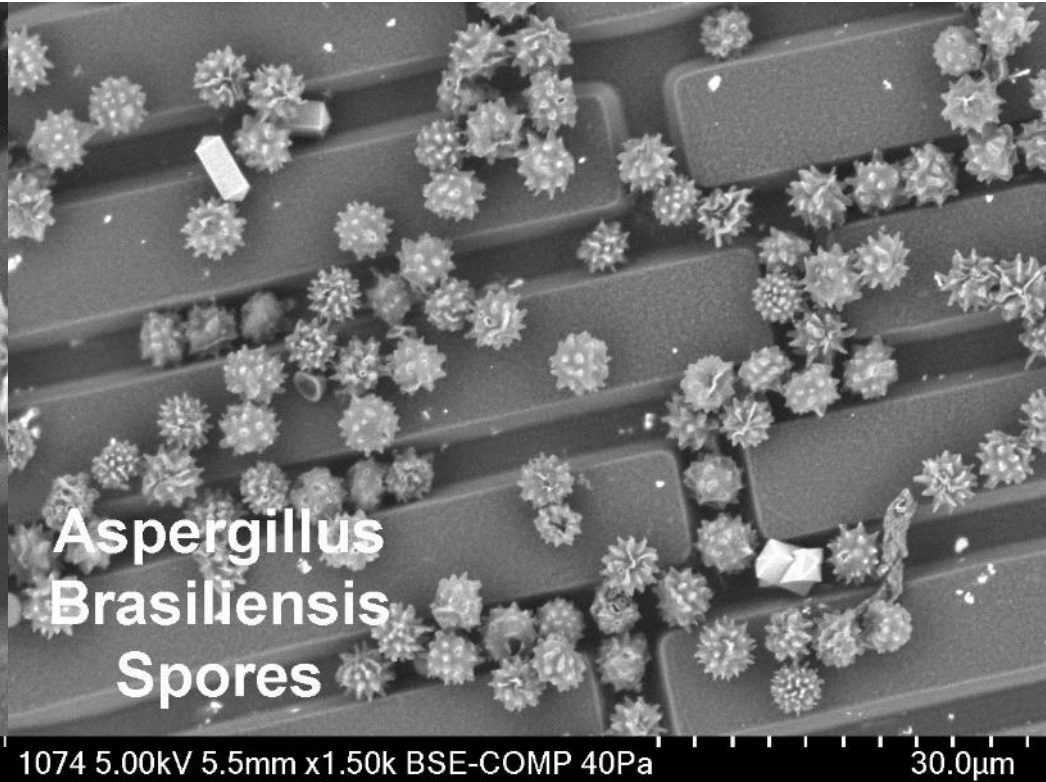
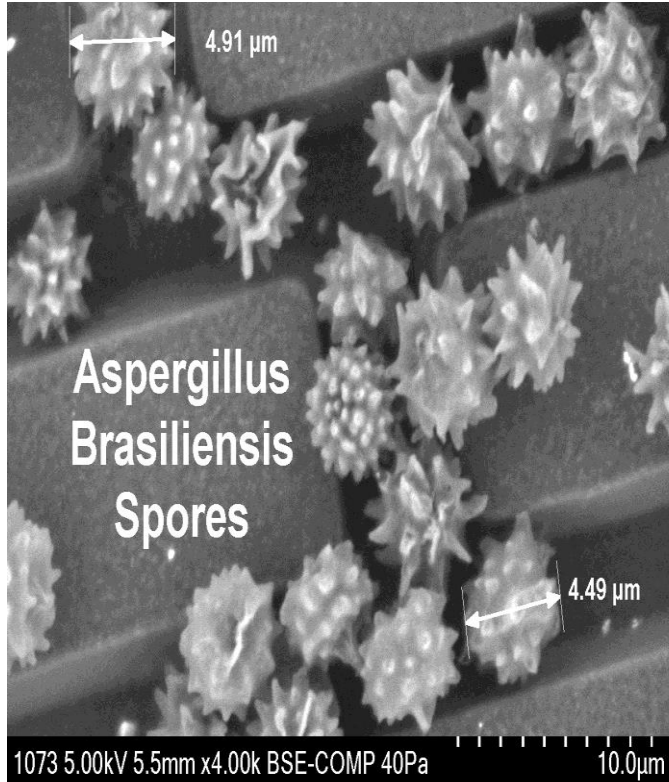
Conidia
spores

Cleanroom Fungi



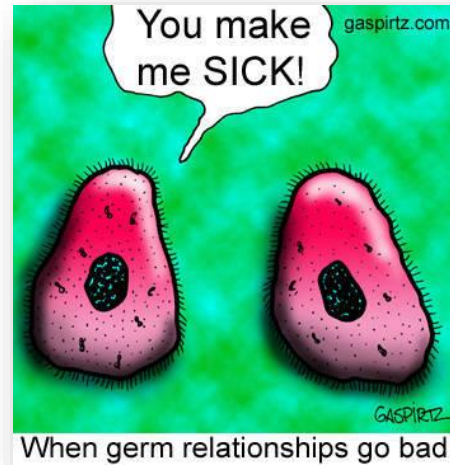
Courtesy Dan Klein

Aspergillus Spores



Technologies

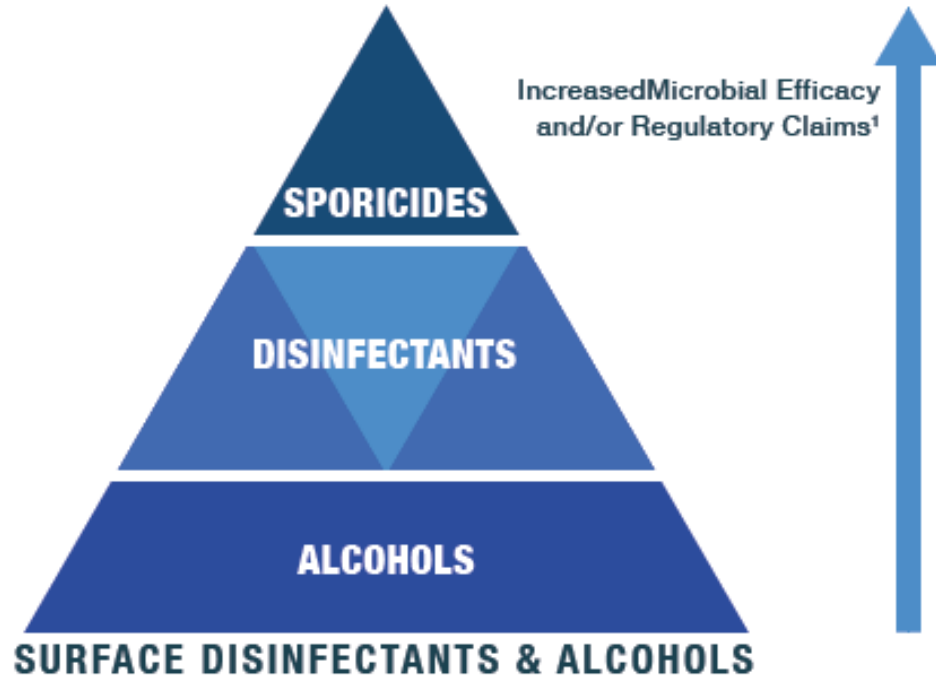
- EPA Classifications
 - Sanitizer
 - Disinfectant
 - Sterilizer (Sporicide)



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

- 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 bacteria
 - 3 Log reduction viruses
 - May or may not require pre-cleaning
 - Serum efficacy - 5% BSA and EN methods differ example: “clean” and “dirty” as a soil load

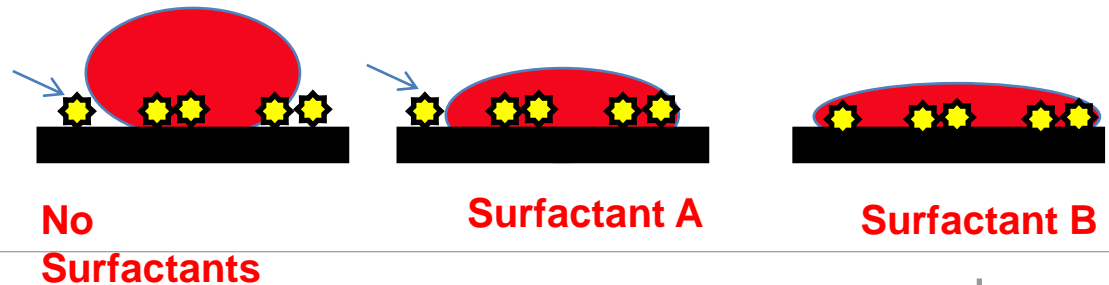
- Sterilant
 - Proper use results in 100% kill of all microorganisms, including bacterial endospores (*B. subtilis*, *C. sporogenes*)
 - 6 Log reduction
 - Always requires pre-cleaning
 - Water quality is important

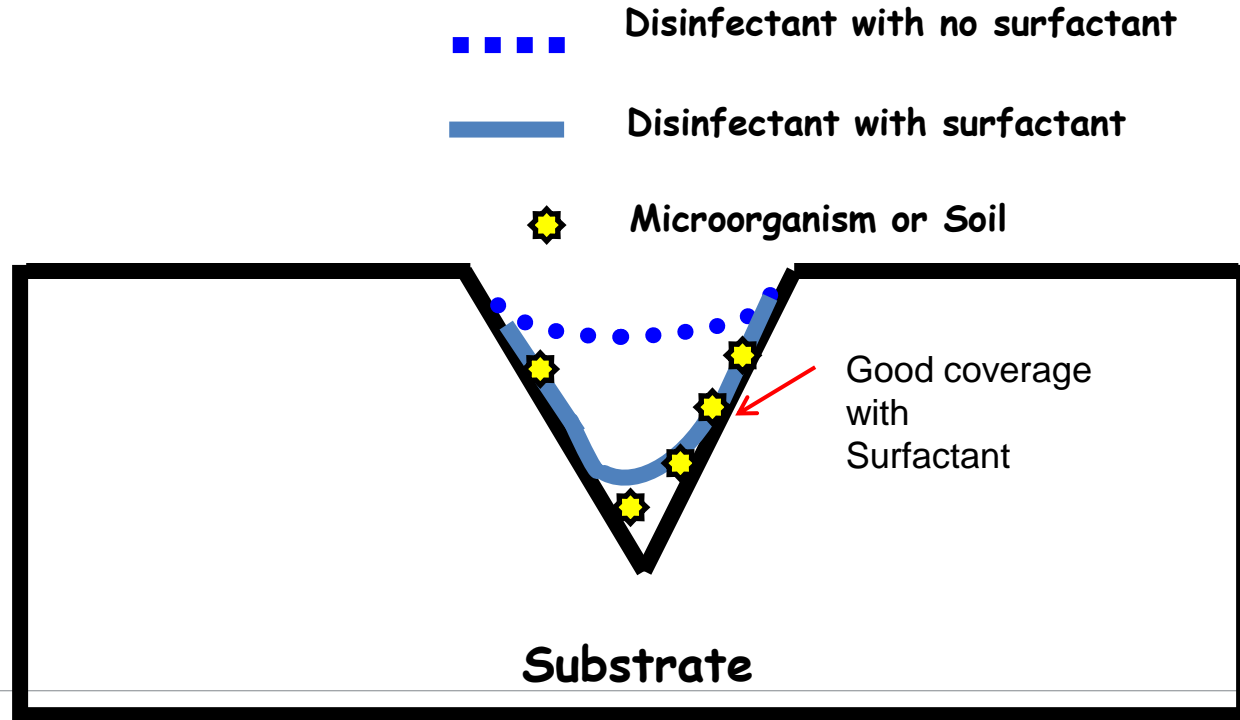


¹Products that fall into the categories at the bottom of the pyramid are most frequently used and are generally not sporicidal. Progression up the pyramid indicates stronger performance overall and a broader spectrum of claims.

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 (H ₃ PO ₄)
Surfactants	Emulsification, Wetting

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

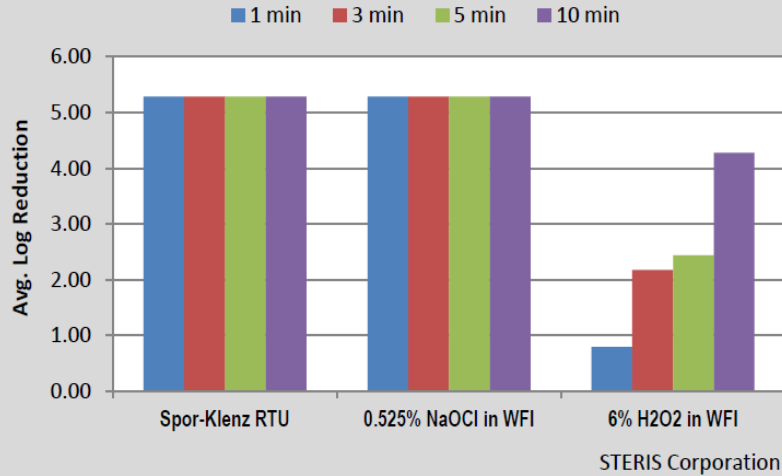




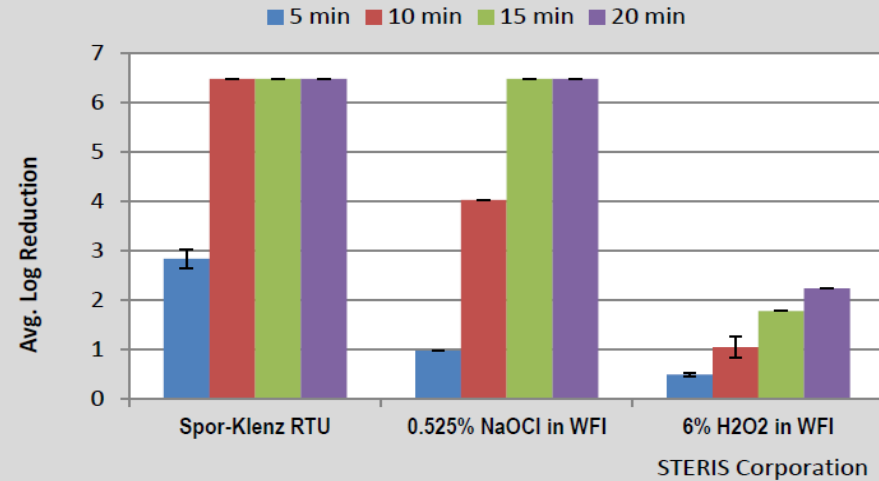
- Disinfectants and sanitizers
 - Phenolics
 - Quats
 - Alcohols
 - Hydrogen Peroxide 3%
- Sterilants and sporicides (potentially)
 - Sodium hypochlorite
 - Chlorine dioxide
 - Hydrogen peroxide 6%
 - Peracetic acid
 - Peracetic acid/hydrogen peroxide blends
 - Glutaraldehyde/formaldehyde
 - Ozone
 - Nitrogen Dioxide
 - Vaporized Peracetic Acid and VHP®



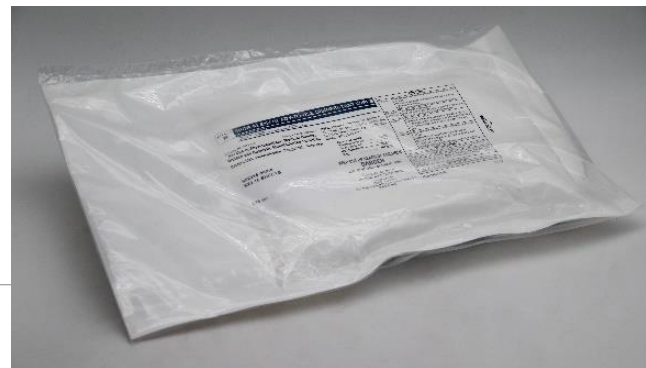
Efficacy of Aseptic Products in a Time Kill Study
A. brasiliensis ATCC 16404 Baseline 5.28 log₁₀



Efficacy of Aseptic Products in a Time Kill Study
B. subtilis ATCC 19659 Baseline = 6.48 log₁₀



- Challenges
 - Efficacy
 - Wet Contact Time
 - Full Contiguous Coverage
 - Delegated Task
 - Complex Surfaces
 - Technique Dependent
 - Sporocidal Wipes



Technology Selection

Disinfectants are a Balance





Grade D (ISO 8 at rest)

Surface	Method	Cleaning Agent	Frequency	Rinse
Floors <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• General	Wipe or Mop	Disinfectant with surfactant	Monthly	Not necessary after each application†
<ul style="list-style-type: none">• Doors, Handles, High-Traffic Areas	Wipe or Mop	Disinfectant with surfactant	Daily	
Equipment <ul style="list-style-type: none">• Adjacent to Access Port	Spray or Wipe	Disinfectant with surfactant	Daily during processing	As needed to remove residue buildup
<ul style="list-style-type: none">• Surface Upstream Airflow Path to Process Opening			Weekly	
Other Surfaces <ul style="list-style-type: none">• 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)

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)³⁰

Surface	Method	Cleaning Agent	Frequency	Rinse
External Hoods <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 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	

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 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.


Cleaning and Disinfection Application Methods

- 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-CC018.5
- 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**.

Figure 1. Proper Surface Cleaning

Illustration of Pull-lift Technique



1st Stroke

2nd Stroke

3rd Stroke

1st Stroke: Lift the sponge mop and place it on the surface at a manageable distance. Pull it toward you.

2nd Stroke: Lift the mop again, place it down at the start of the first stroke, overlapping the first stroke by around 10% to 20%. Pull it toward you.

3rd Stroke: Repeat.

Photo: Courtesy of Molecular Cleanrooms

- 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.



- 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.*

- 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

Disinfectant Rotation & Rinsing Programs

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



“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”

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.

520 4.36 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected 521
thoroughly in accordance with a written programme. **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 programs should effectively remove disinfectant**
528 **residues.**

KEY ISSUES

Prior Cleaning

Is it necessary?

NO

Rotation

Is Sporicide a
Disinfecting Agent?

YES

Residue

Is it only from
disinfectants?

NO

- 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.**”

“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>

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



People



Transport of Materials and Supplies



Treatments On Walls & Floors



Drug Components



Processing Equipment

7.1.1 Types of Clean Room Disinfecting Agents

“Disinfectants...characteristically leave **residues... [that] should be removed via IPA wipe-down.**”

9.2 Application Methods “The use of a mopping system for either walls or floors removes residues...**Wiping, as with mopping, cleans the surface of residues...**”

9.0 Cleaning and Disinfection “Cleaning is a critical step... because of the buildup of antimicrobial **chemical agent residues, product residues, particulates, and other contaminants** can inhibit an antimicrobial chemical agent’s efficacy.”

KEY ISSUES

Visually Clean

Is periodic rinsing necessary?

YES

Physical Removal

Do mopping and wiping prevent residue buildup?

YES

Residue

Is it only from disinfectants?

NO

48

Process changes, if required, should be risk based and data driven based on current best practices

- Pre-cleaning – None, unless there is excessive soil
- Disinfectant – Should be able to handle some soil and have broad spectrum efficacy
- Sporicide – Based on Environmental Monitoring data
 - Different chemistry which provides your basis for rotation
- Rinsing – Goal is Visually Clean
 - WFI or Alcohol on a routine basis, based on experience or risk assessment
 - Cleaners can be used for buildup or after shutdowns

- **USP 43 <1072> Disinfectants and Antiseptics**
- **Draft Annex 1 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**
- **Japanese and Chinese Pharmacopoeias**
- **PHSS Technical Monograph #20 “Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas**
- **IEST-RP-CC018.5 Cleanroom Housekeeping: Operating & Monitoring Procedures (2020)**

- ✓ Regulatory Requirements
- ✓ Cleanroom Bioburden Control
- ✓ Cleaning and Disinfecting Technologies
- ✓ Cleaning and Disinfection Techniques
- ✓ Rotation and Residues

Jim Polarine

- Senior Technical Service Manager
- STERIS Corporation | Life Sciences
- Mobile: 314-616-9931
- E-Mail: Jim_Polarine@steris.com
- Web: www.sterislifesciences.com

STERIS Technical Services