

Establishing a Cleaning and Disinfection Program

Dan Klein

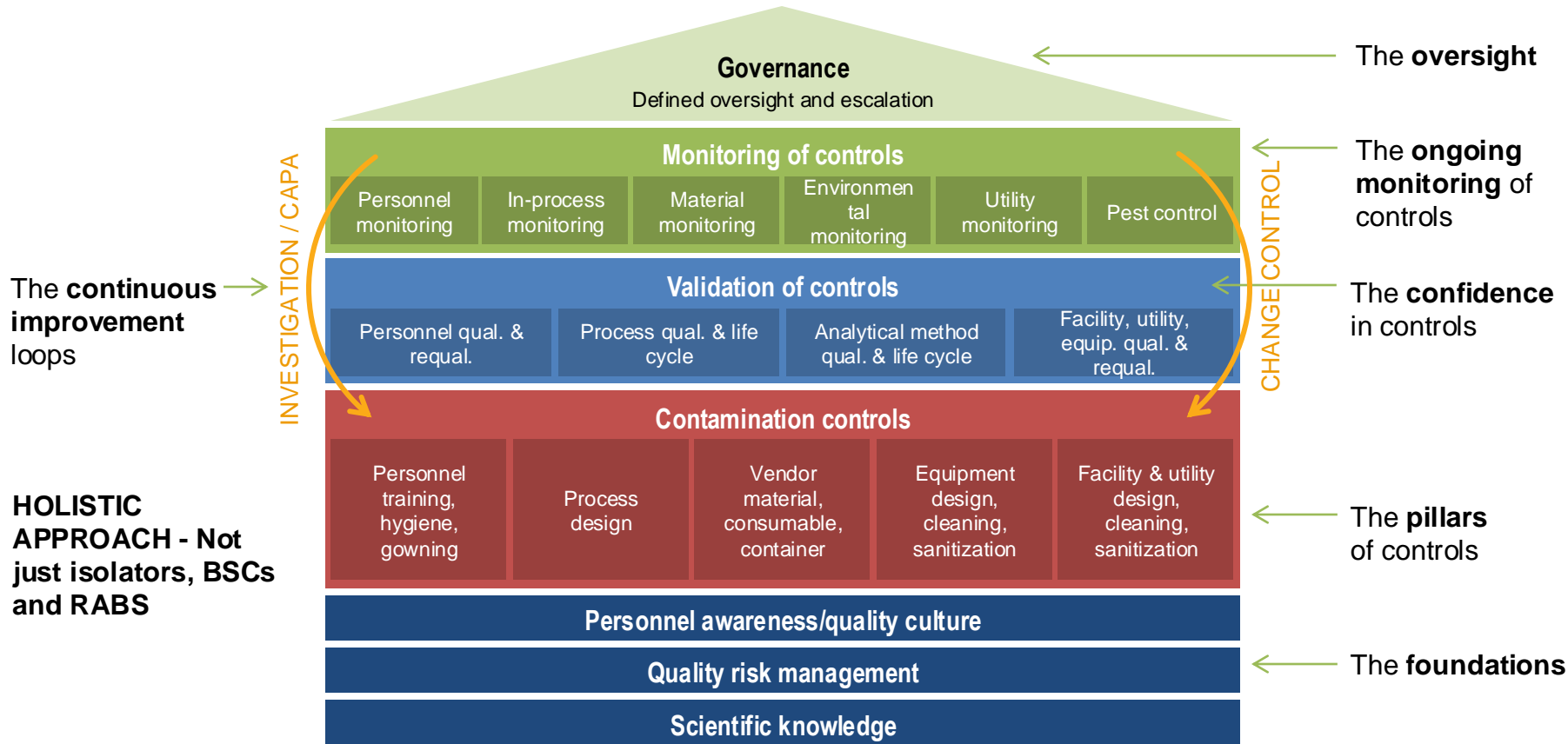
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Adapted from PDA TR 90

Establishing a Cleaning and Disinfection Program

The “Basics”

- Disinfectant selection
- Rotation strategy
- Disinfectant Frequency
- Pass-through
- RABs and Isolators

The “Details”

- Technique, technique, technique!
- Residue and Rinsing

Disinfectant Selection



Rotation Strategy

Can be confusing...

- 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.

- Rotation of Antimicrobial Strategies
 - 2 disinfectants in sequence, regular rotation, with sporicidal agent as needed
 - One disinfectant daily, with sporicidal (typically weekly or monthly)
 - **Microorganisms will not acquire disinfectant resistance**
- “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.” USP 43 <1072> Disinfectants and Antiseptics
- Current industry guidelines (PDA TR No. 70):
 - “pharmaceutical & biotechnology industries have moved away from the rotation of 2 disinfecting agents. This formerly common practice led to high residue levels and subordinate efficacy performance... **The rotation of a disinfectant with a sporicide is superior to the use of rotations of multiple disinfectants.**”
- Best Practice: One disinfectant and one sporicide used in rotation

- **The topic of disinfectant resistance has been around for decades (30+ years)**



The screenshot shows the header of an article on the American Journal of Infection Control (AJIC) website. The header includes the AJIC logo, navigation links (Submit, Log in, Register, Subscribe, Claim), and a search icon. Below the header, the article title is "Could antibiotic-resistant pathogens be cross-resistant to hard-surface disinfectants?". The authors listed are Kimberly A. Haines, BS, Daniel A. Klein, BS, Gerald McDonnell, PhD, and Denise Pretzer, PhD. The date of publication is circled in red as "OCTOBER 01, 1997". The DOI is [https://doi.org/10.1016/S0196-6553\(97\)90096-1](https://doi.org/10.1016/S0196-6553(97)90096-1). There are also icons for Purchase, Subscribe, Save, Share, Reprints, and Request, and a PlumX Metrics logo.

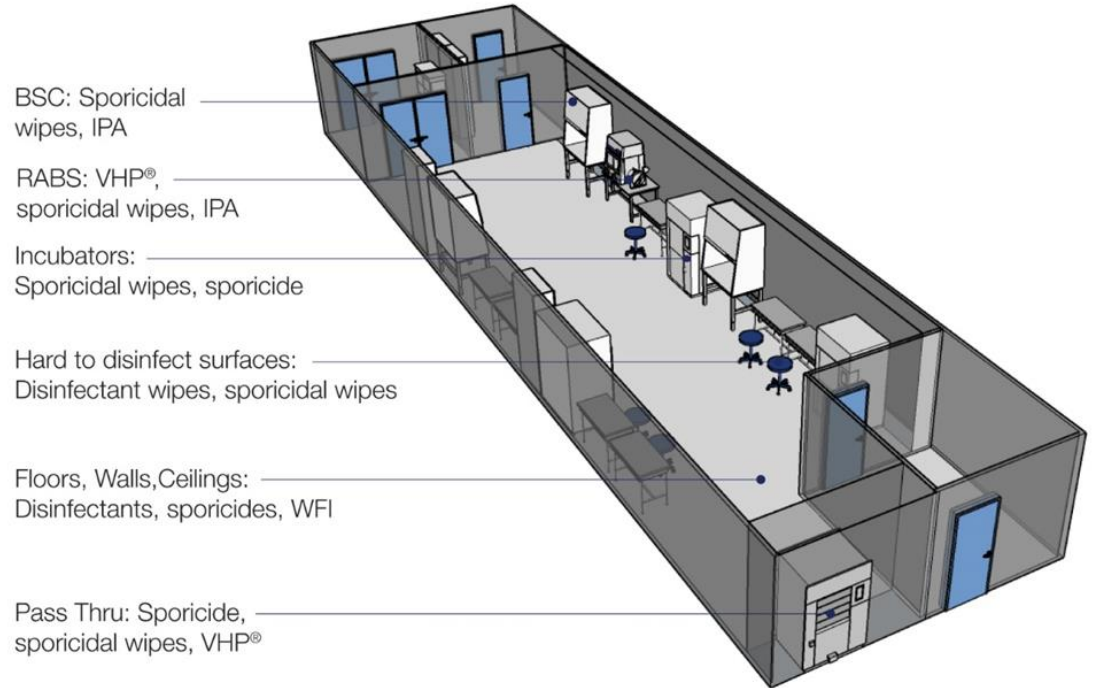
- **Newer (and much better) articles also exist**

Disinfectant Frequency

- Proposed frequency of disinfectant and sporicide use

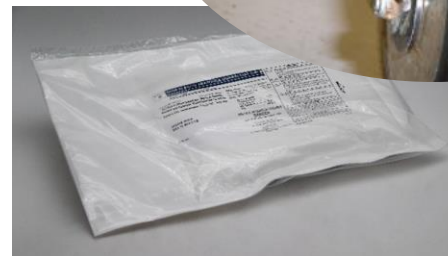
	Daily	Weekly	Monthly	Yearly
Controlled Area				
Floors	X	X		
Ceilings				X
Walls			X	
Fixtures/Equipment			X	
Class 100,000 (ISO 8)				
Floors	X			
Ceilings				X
Walls			X	
Fixtures/Equipment		X	X	
Class 10,000 (ISO 7)				
Floors	X			
Ceilings			X	X
Walls		X		
Fixtures/Equipment	X			
Class 100 (ISO 5)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

Disinfectants, Sporicides
and Sanitizers used in
various dosage forms to
maintain a state of microbial
control



Pass-through

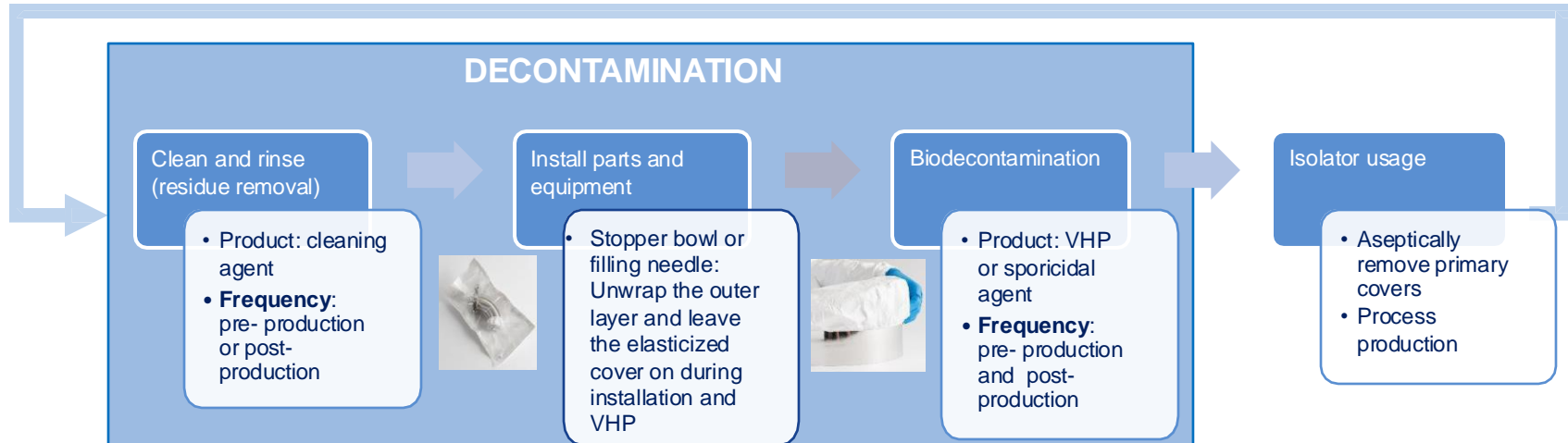
- Pass through items are a source of hard to kill bacterial spores and fungi
- Essential to have a good decontamination process with thorough application
 - Vaporized Hydrogen Peroxide can be an option - VHP®
- Use of an effective sporicide
 - Wipe applications are useful
 - Cart wheels are notoriously hard to disinfect
 - Contact areas where spores reside
 - Decontaminate thoroughly
 - Underneath surfaces
 - Recessed areas on handle
 - Ensure full contact time



Isolator cleaning and biodecontamination

4.22The biodecontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g., gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent.

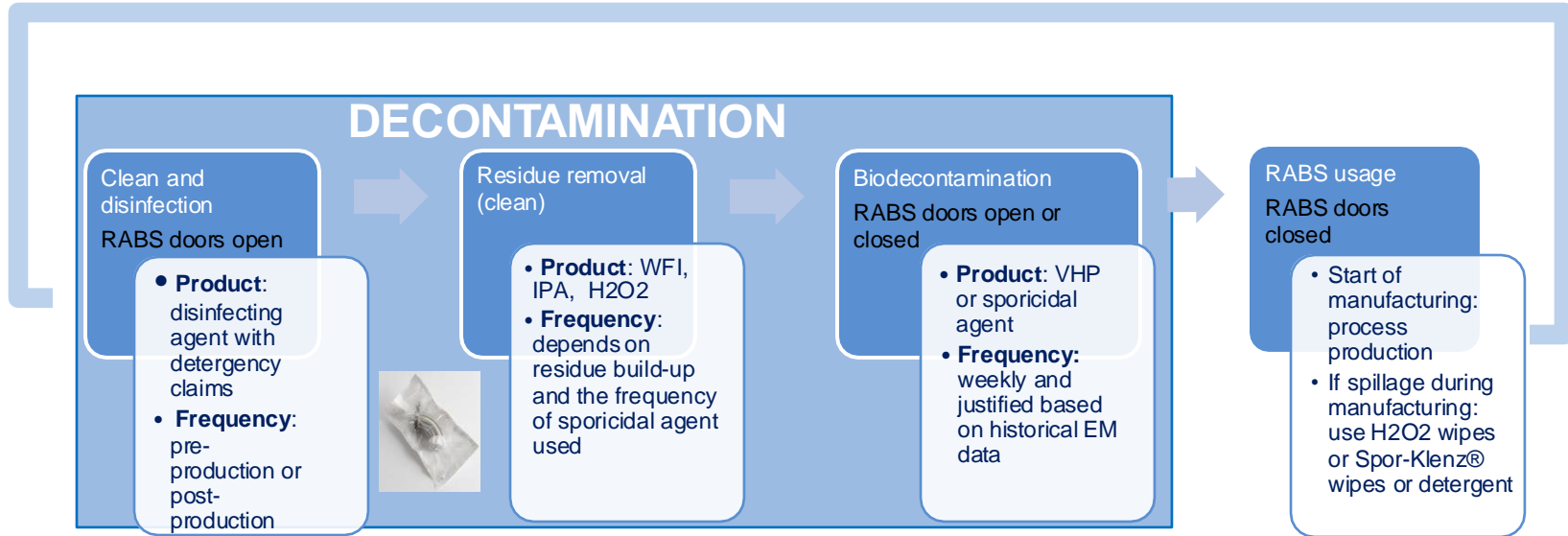
Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.



RABS cleaning and disinfection or biodecontamination

Option 1:
Use of a daily sporicidal agent

Option 2:
Daily use of disinfectant; weekly use of sporicide



VHP Applications

- Material transfer of components
- Manufacturing suite biodecontamination
- Biosafety cabinet (BSC) biodecontamination
- RABS/isolator biodecontamination



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The “Details”

- Technique, technique, technique!
- Residue and Rinsing

Technique

- Most critical areas to least critical areas
- 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 (2022)
- 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**.

Two bucket (disinfectant in both buckets)

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 (disinfectant in two buckets)

- Mop in bucket #2 (rinse bucket)

- Next Bucket #3 (ring out bucket)

- Next Bucket #1 (clean bucket)

- Next Bucket #3 (ring out bucket)

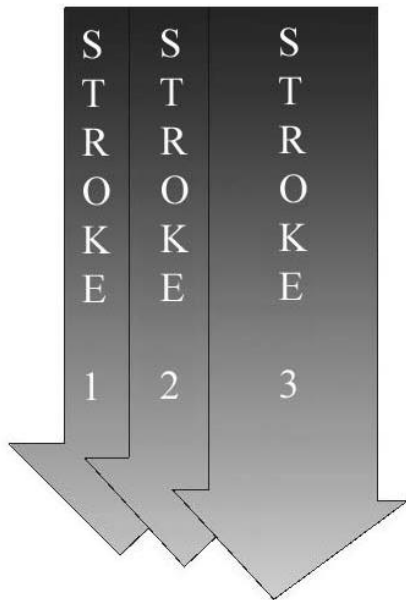
- Mop the floor

- (Mop rides in Bucket #2)

8-16 feet covered in mopping passes #1 and #2

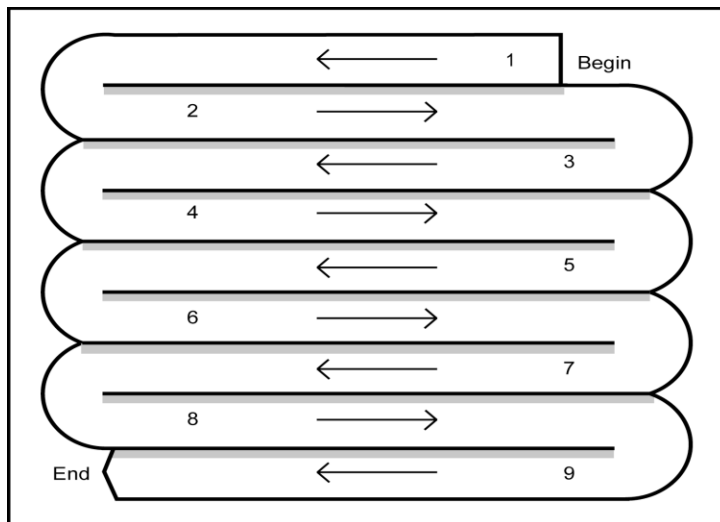


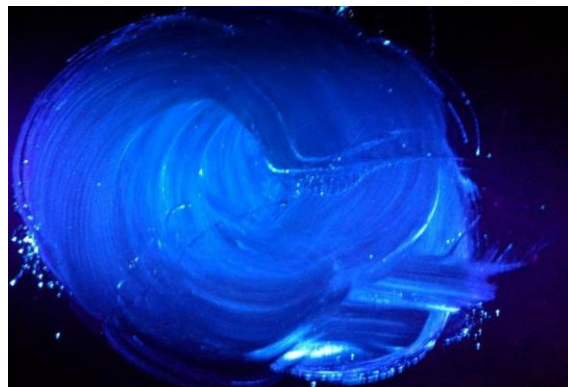
Figure 1 – “Pull and Lift”



From ceiling toward floor for walls.
From wall toward aisle for floors.

Figure 2 - Modified Figure “8”



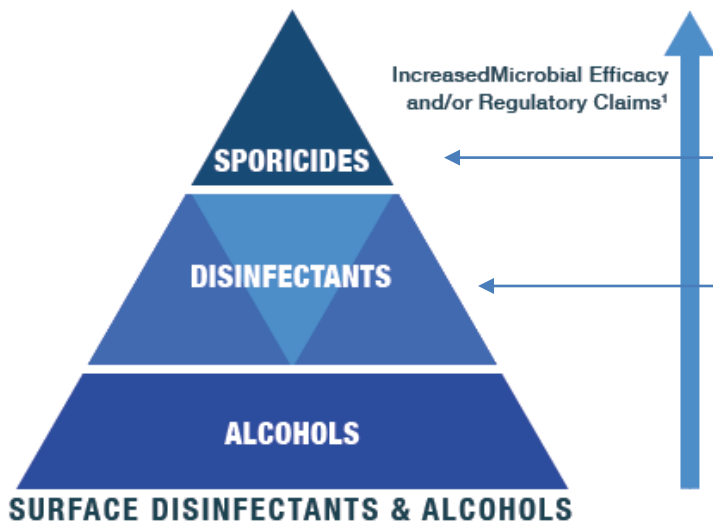


Circular wipe pattern



Unidirectional
Overlapping Strokes

Residue and Rinsing



Sporicides can leave trace amounts of stabilizer as a residue. Usually only visible on stainless steel and glass surfaces.

ALL 1-step cleaner/disinfectants WILL leave some residue from the surfactants and active molecules.

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.

- Dried residue is not inherently problematic, but a rinsing program should be in place to avoid:
 - Slippery or tacky floors
 - Aesthetics

- Do not walk on wet floor, with or without residue
 - In January 2023, a European Customer completed a DMAIC process to Define, Measure, Analyze, Improve, and Control complaints about slipperiness
 - “SlipAlert” slip test was performed by a consultant in 11 locations with the findings that there was “Limited Difference between Vesta-Syde and WFI Application”. Any minor differences in the results were not significant
 - Dry floors for both WFI and VSSQ applications showed “low risk”, and the closing conclusion was that any wet floor presented a higher risk and should be avoided

- “As Necessary”. Not needed after every application. Visually clean as the standard
 - Rinse with WFI
 - Alcohol for reflective surfaces
- Residues are mentioned in EU GMP Annex 1
 - “Cleaning programs should be effective in the removal of disinfectant residues”
- Should fit within rotational program
 - Example Program
 - Daily Disinfectant Decontamination
 - Monthly Sporicide Rotation
 - Monthly WFI water rinse

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.

- Similar care should be taken with the water rinse as the disinfectant application
- Unidirectional, overlapping strokes
- Two or three bucket system
- Quat residues are very water soluble, but can just be redeposited
 - Quats are surfactants
- Phenolic residues are soluble for a shorter period of time, but will solubilize for removal

A. Rinsing step using water for a three-bucket system:

The first bucket contains Water (PW or WFI) (Water Rinsing solution). The second bucket contains water (PW or WFI) (Water Cleaning Solution). The third bucket is empty (Waste).

- i. Immerse the mop into the bucket “Water Rinsing Solution” and wring-out the mop slightly with the wringer. The mop should be wetted to wet the surface and remove detergent residue from the surface.
- ii. The rinsing with the wet mop must be performed in overlapping strips in the form of a stroke from the back to the front (toward the door). Refer to figure 1.
 - a. Press on the mop to remove the residue on a defined area. The area is defined based on the capacity of the mop to wet the surface while removing detergent residue (e.g., 10-meter square).
 - b. Note: If the surface is highly wet (pooling or did not dry within 1-2 minutes), do not allow the surface to dry, use a dry mop to remove the excess solution from the surface.
- iii. For further use of the mop, immerse it into the bucket “Water Cleaning Solution” and wring-out the mop slightly with the wringer in the third bucket and continue as described above starting from step ii.
- iv. Visually evaluate the floor to determine if a second water rinse is necessary.
- v. When the rinsing is completed, dispose bucket’s solution, and clean the buckets and mops (if not single use).

- Does residue hide microorganisms and promotes microbial growth?
 - **Dried disinfectant residue demonstrates antimicrobial activity**
- Does residue inhibit sporicides?
 - **STERIS disinfectant residues do not negatively affect Spor-Klenz RTU efficacy**
- Does residue build up with each application of disinfectants?
 - **The mechanical action of wiping and mopping effectively limits the amount of residue left on a surface**

Does residue hide microorganisms?



Prepared residue coupons with 1 or 10 applications of Phenolic Disinfectant (1:128) or alcohol and allowed to dry



A wet inoculum of *P. aeruginosa* (ATCC15442) was pipetted onto residue coupons

Sterile coupons were used as a control
Two inoculum volumes with a similar number of CFU used



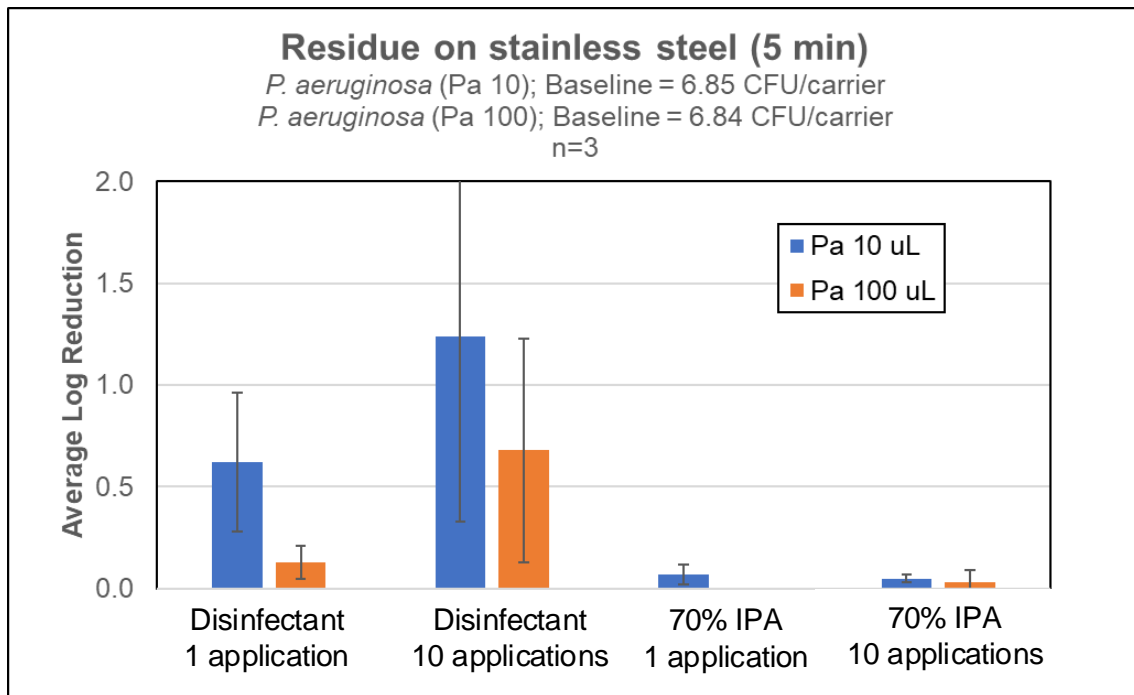
After a contact time of 5 minutes, neutralizer was added

Inoculated residue coupons were put in a Nalgene cup and vortex mixed
A neutralization confirmation procedure was performed



The contents were serially diluted and plated

Does residue hide microorganisms?



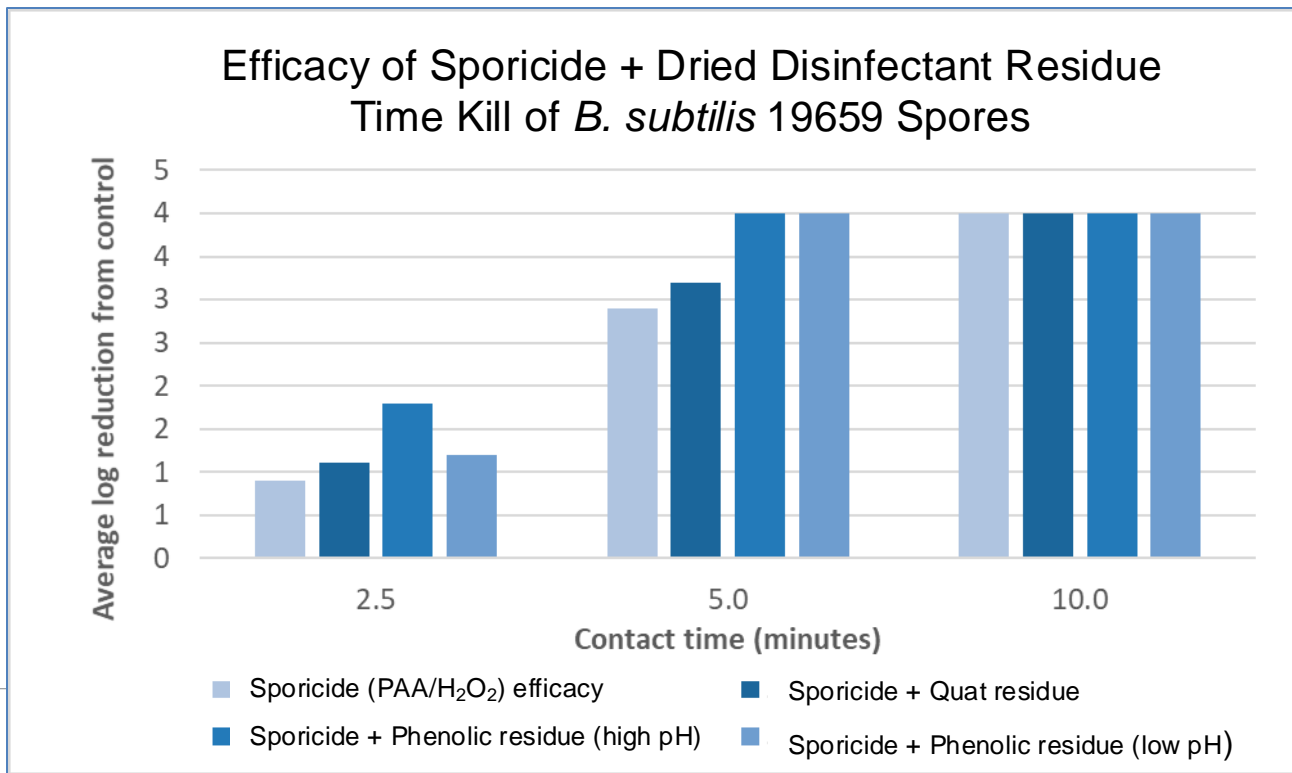
- Alcohol solution shows no activity
- Disinfectant shows some (although variable) activity
 - Activity increases w/ more applications

Does residue inhibits sporicides?

Does dry disinfectant residue affect sporicidal efficacy?

- Disinfectant diluted in water (1:20 v/v) to yield a 4.9% solution
- 2.36 g of the solution was placed in a weigh dish and dried in a hood to represent worst-case scenario of buildup
- 5 g of PAA/H₂O₂ sporicide was added for a 10-minute contact time
- Mixed for 30 seconds to solubilize disinfectant residue, transferred to sterile container, then inoculated with spore suspension of *Bacillus subtilis* at 3×10^8 CFU/mL
- At post-inoculum timepoints, samples were neutralized, plated, and incubated for 48-50 hours at $37 \pm 2^\circ\text{C}$.

Does residue inhibit sporicides?



Does residue build up?

Disinfectant applied to 316L stainless steel coupons with swab

Four coupons with 15 successive applications

Disinfectant completely dried after 10 -15 minutes

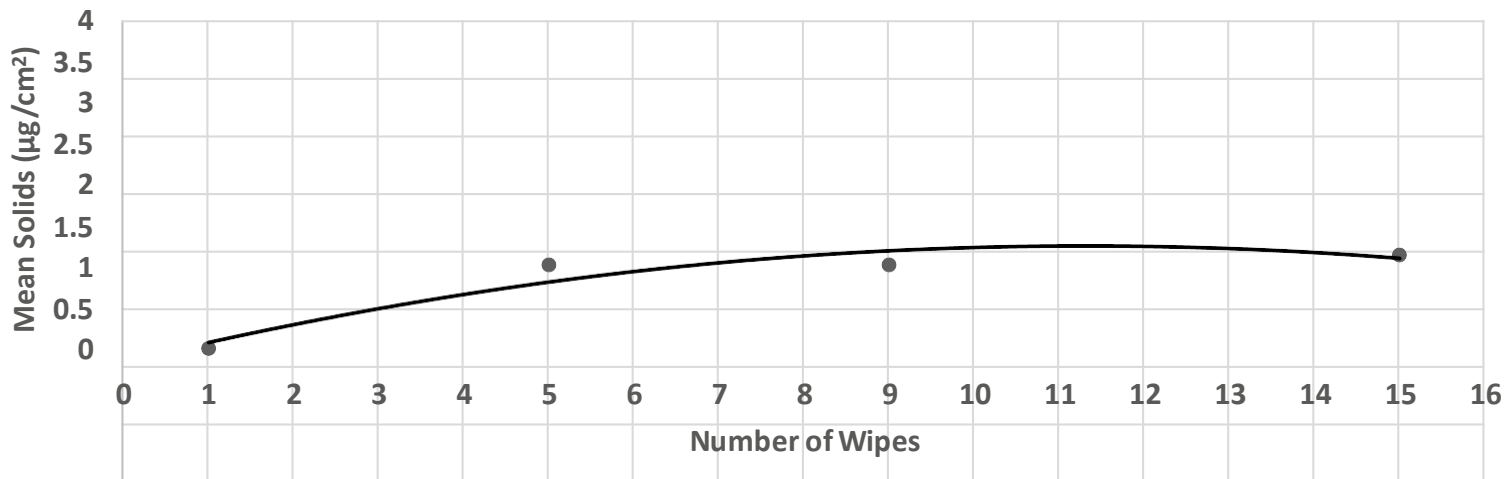
Analysis at 1, 5, 9, and 15 minutes. The amount of the disinfectant equivalent to 1 application was spiked onto coupons with a pipet and dried for use in the recovery calculation

Both wiped and spiked coupons along with three blanks were recovered using swabs

Swab extract solutions analyzed for total organic carbon (TOC)

Does residue build up?

Quaternary Ammonium Disinfectant (1:128 v/v), Wiping Data



Staining and Incompatibility

- Important to note
 - Avoid incompatible chemistries
 - Quats (cationic) and phenolics (anionic) will interact
- Staining is different from routine residue build up
 - Requires additional investigation
 - Can be interaction of chemistries
 - Oxidizers, disinfectants, etc. all mixed at a dump sink
 - Can be incompatibility with materials
 - Mop heads or mop handles, Stain or rust transferred
- Surface incompatibility also different
 - Inappropriate Surfaces, damaged surfaces, improper materials

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Thank You!

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