Developing a Successful CCS: Updates on Cleaning & Disinfection and Materials Transfer

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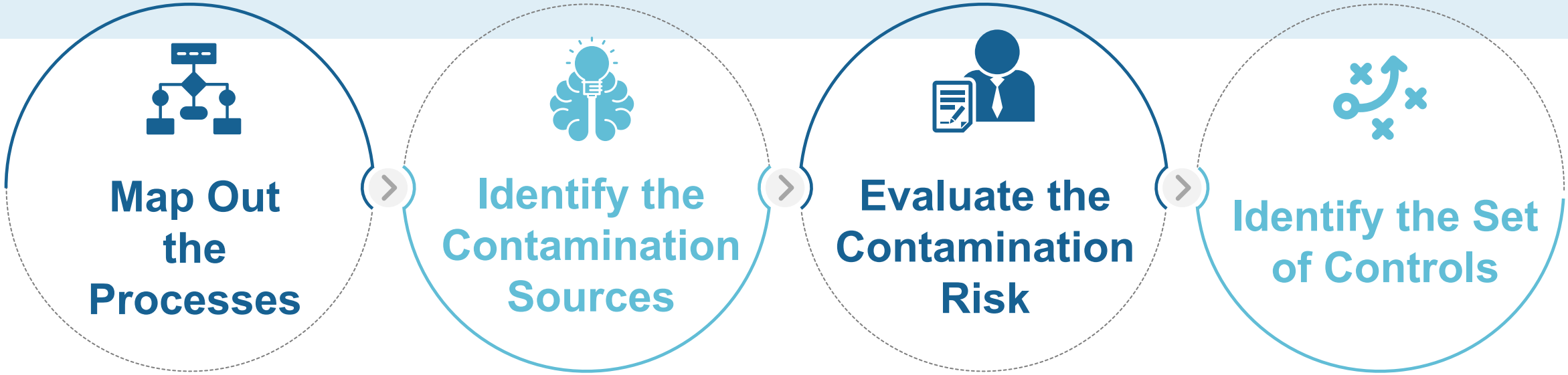
Connecting People, Science, and Regulation

AGENDA

1. Updates on Cleaning and Disinfection
2. Points to Consider for Material Transfer

Contamination Control Strategy



- "2.4 Contamination control and steps taken to *minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources* includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together."

USP <1072> Proposed Updates

- Disinfectant Rotation Discussion Expanded
- Added Log Reduction for Fungal Spores 2 Log
- Additional Feedback on Coupon Testing Methods
- Validation Section Expanded: Microorganisms, Surfaces, Neutralization Methods, Recovery Methods
- In-Use Testing Studies Expanded
- Discussion on Value Added Testing from Suppliers vs End Users
- Discussion on Risk Assessments for Coupon Selection
- PDA reviewers had 85 Pages of Comments and Feedback

Revised PDA Technical Report #70 Cleaning and Disinfection

- 130 Pages Several New Sections and Very Robust
- 20 Task Force Members from the Industry (Merck, Takeda, Emergent, JNJ, Lilly, and several others)
- Utilizing Risk Assessments
- Validation section includes in depth discussions on risk assessments, log reductions, rounding, neutralization, recovery methods, microbial selection, and validation frequencies.
- Cleaning and Disinfection Methods and Cleaning Frequencies
- Rinsing Methods and Rinsing Frequencies
- Conducting Excursion Investigations
- Cleaning and Disinfection BSCs, RABS, and Isolators
- Glossary of Terms and Several Appendixes
- Currently editing
- August 2026 Publication Goal

Recent FDA Warning Letter on Cleaning and Disinfection Program

- A CAPA plan, based on the retrospective assessment of your cleaning and disinfection program, that includes appropriate remediations to your cleaning and disinfection processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning and disinfection. Describe improvements to your cleaning and disinfection program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning and disinfection execution for all products and equipment; and all other needed remediations.
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/global-pharma-healthcare-private-limited-657325-10202023

Cleaning and Disinfection: Rotation

- Alternation of antimicrobial actives
  - 2 disinfectants in sequence, regular rotation, with sporicidal agent as needed
  - One disinfectant daily, with sporicidal weekly or monthly
    - Resistance does not occur in cleanrooms!

OUTDATED!

- 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."

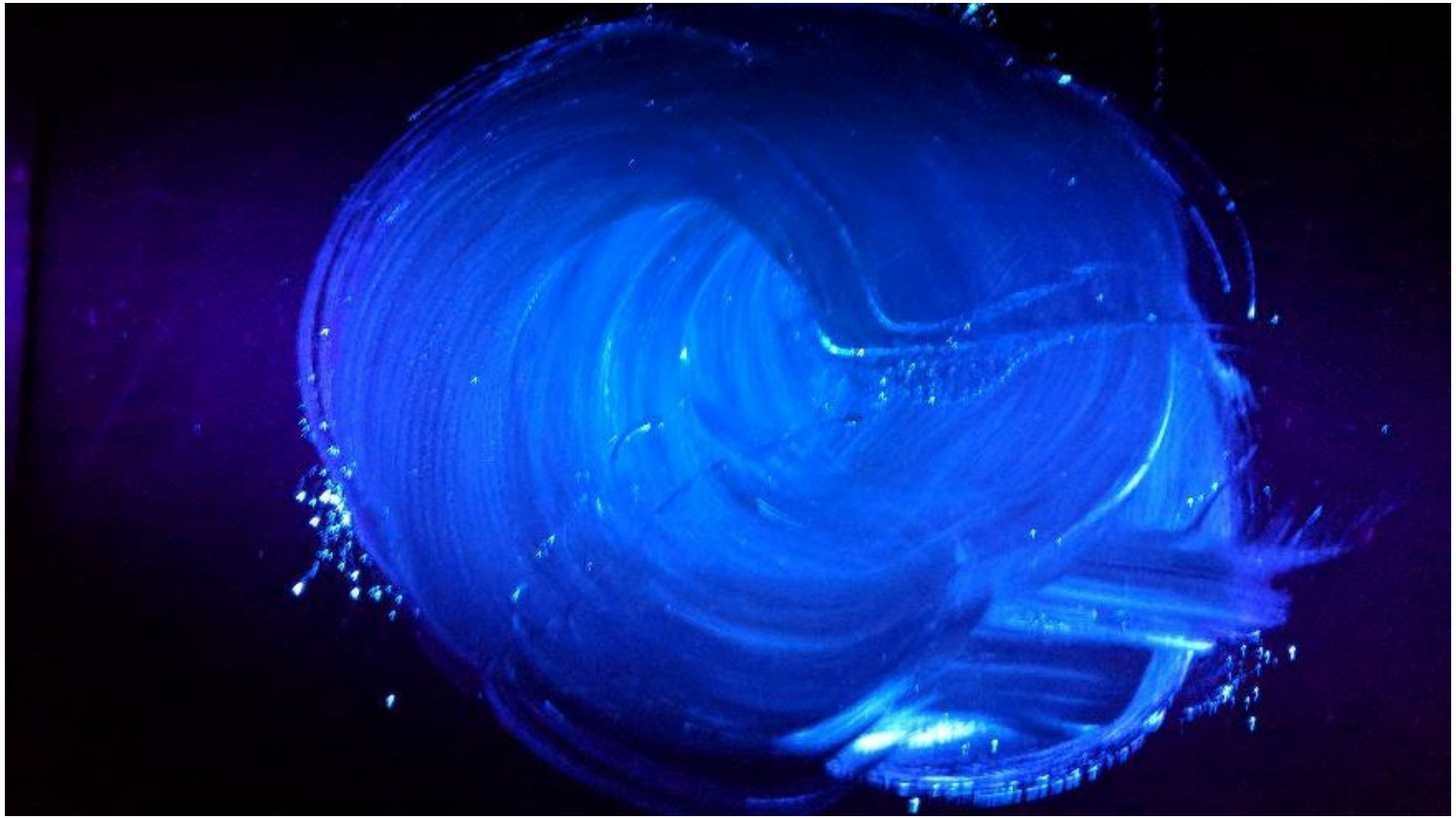
Cleaning SOP Development

	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

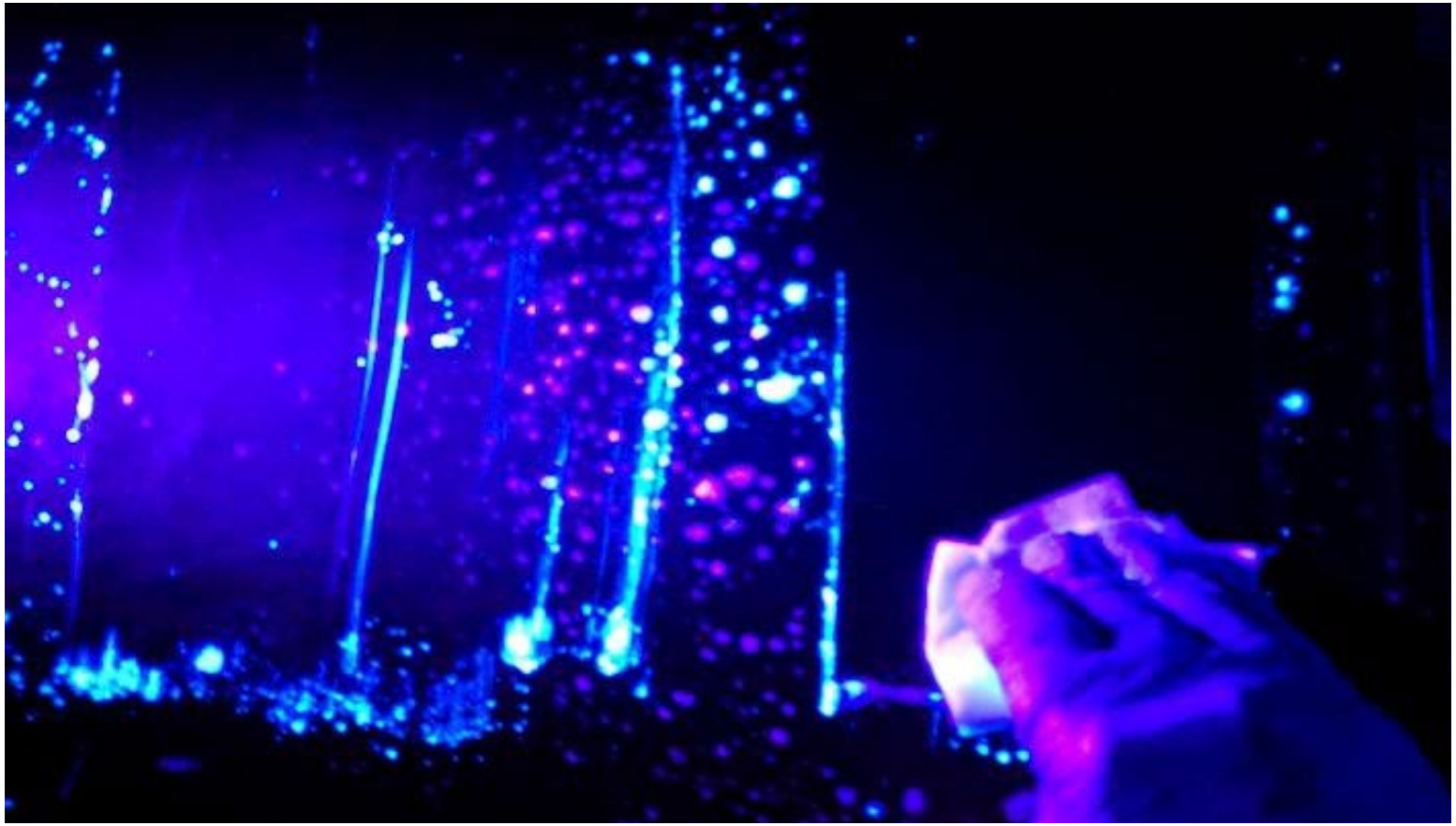
*70% IPA is routinely used on glass, stainless steel, mirrors, racks and sinks.
** Clean Corridor is an ISO 8 to ISO 7 transition area due to gowning area into Fill Room 1.

Cleaning Methods

Cleaning Methods: Wax on Wax Off



Cleaning Methods: Removal of Residues, Particles and Microbes



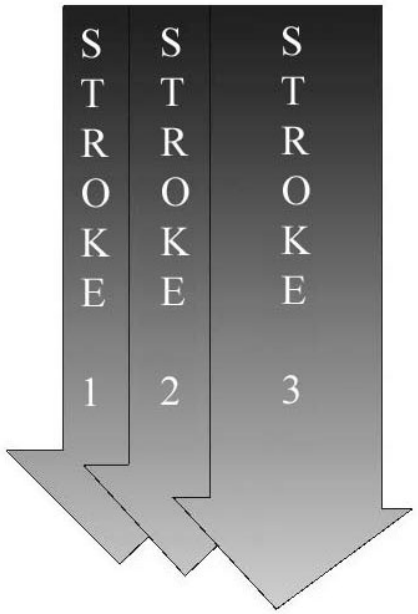
Mopping

- 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-CC018.7 (2026)
- Pull and lift
- Cutting out fire alarms, switches, and sprinklers
- Overlapping strokes (by 20% or 5 cm)
- Modified Figure 8 (String Mop) or Unidirectional overlapping mopping strokes
  - Cove is part of the floor
- 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.**

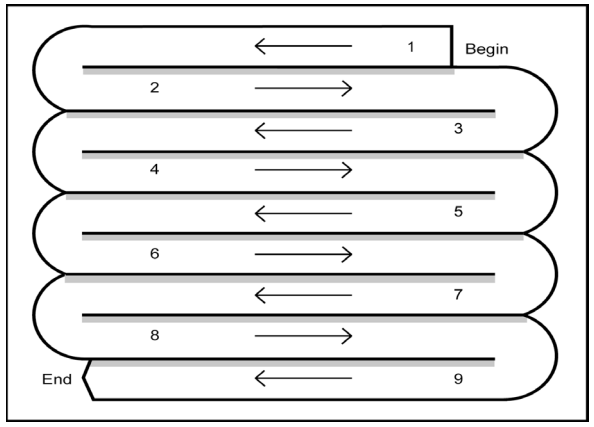
Disinfectant / Sporicide Application - Mopping

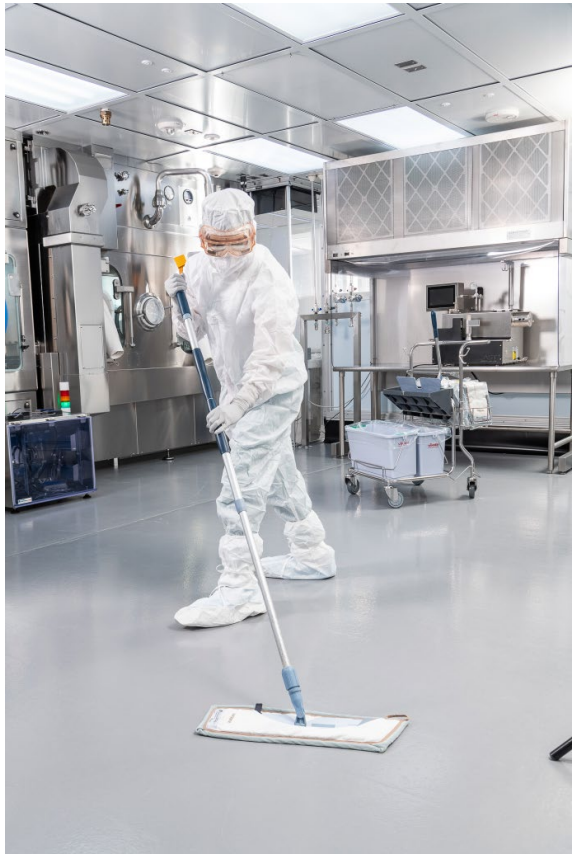
Figure 1 – “Pull and Lift”



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

Figure 2 - Modified Figure “8”





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

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

Drain Cleaning

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)

Rinsing and Residue Removal & Disinfectant Validation

Sources of Residue

People

Transport of Materials and Supplies

Treatments On Walls & Floors

Drug Components

Processing Equipment

Draft PDA Technical Report #70

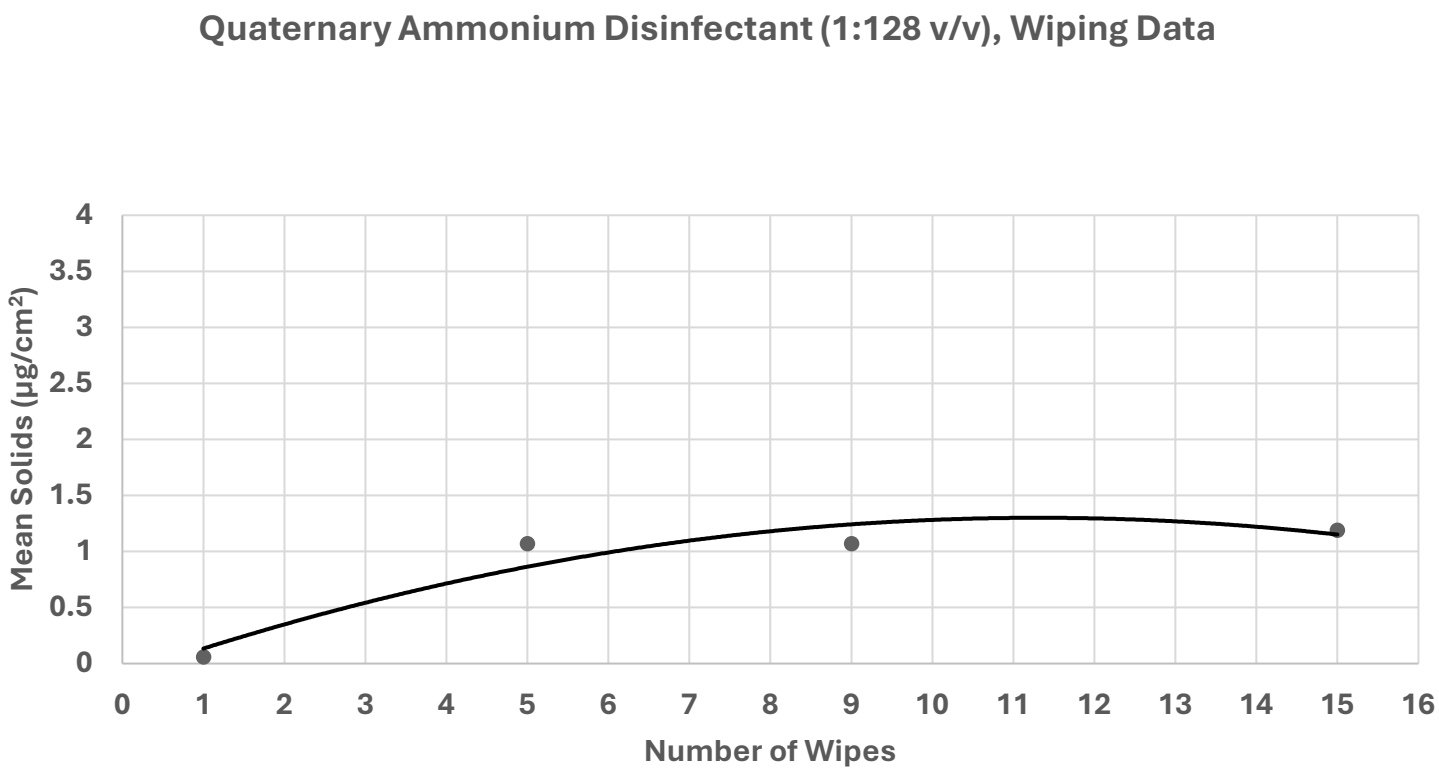
"The residue management program needs to be assessed and tailored to the nature of the residues to be removed. **As a rule of thumb, historically, companies have been using Water for Injection (WFI), 70/30 IPA or detergent for the removal of residues.** This practice could be appropriate if the chemical profile of the residue matrix is compatible and reacts appropriately with the previously mentioned solutions. However, each company could assess different approaches based on their residual scenario (i.e IPA at lower alcohol%, in combination with the type of wipe/mop substrate). If the residue matrix is soluble in the rising solution, then it is solubilized and wipe dry/mopped down. If the residue matrix is not soluble, then, it can be resuspended in the appropriate rising solution. The rising solution recollected/absorbed from the area."

"**The frequency for residue removal needs to be aligned with the applicable regulatory body.** If not dictated, it can be assessed based on process, Risk Assessment, residue matrix characterization as function of material compatibility, removal methodology characterization, environmental monitoring data, among others."

Cleaning and Disinfection: Rinsing

- 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: Cleaning programs should be effective in the removal of disinfectant residues.**

Residue Removal



Annex I: Disinfectant Validation

- “The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and should support the in-use expiry periods of prepared solutions.”

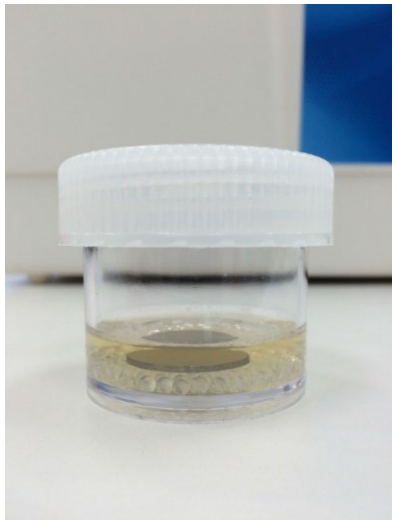
Disinfectant Qualification Test Methods

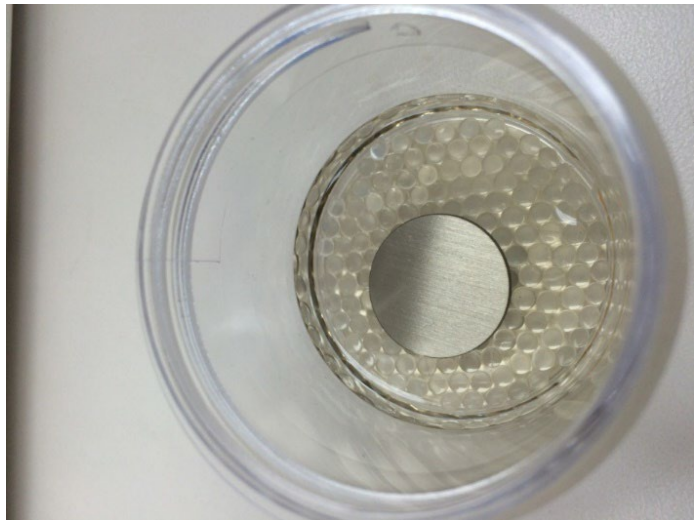
ASTM E-2197-17

EN 13697 (2023)

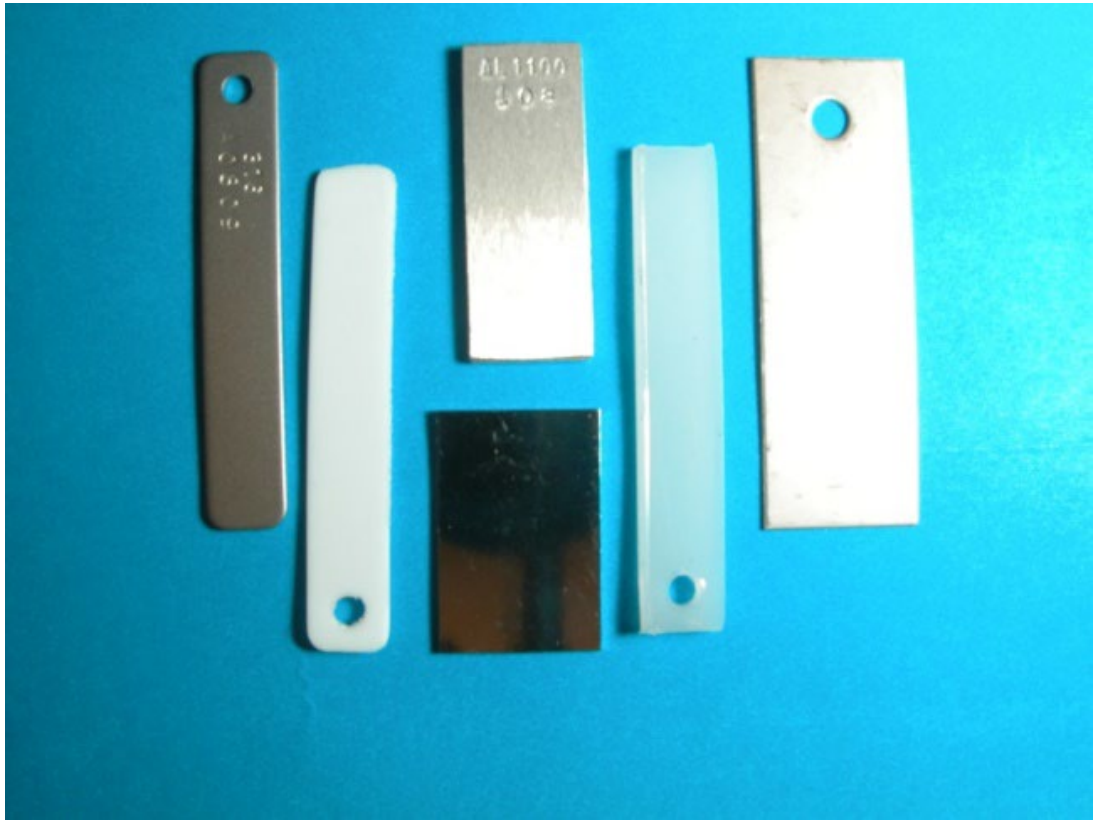
EN 13697

Standard coupon testing method





Substrates for Coupon Testing



- Cleanroom disinfectant qualifications – representative materials
  - Stainless steel (316, 304)
  - Glass
  - Polycarbonate
  - Various plastics and elastomers
  - Lexan curtains
  - Trespa panels and Kingspan panels
  - Kydex and uPVC
  - Bodycote aluminum wall
  - Epoxy-coated flooring
  - Polymeric flooring
  - MMA Flooring
  - Vinyl Flooring
  - Terrazo Flooring
  - Acyrlic and Grout
  - Saniflex
  - Paints (Epoxy and Water Based) & Sealants
  - Gaskets (EPDM, Teflon)
  - Rubber or Nitrile gloves

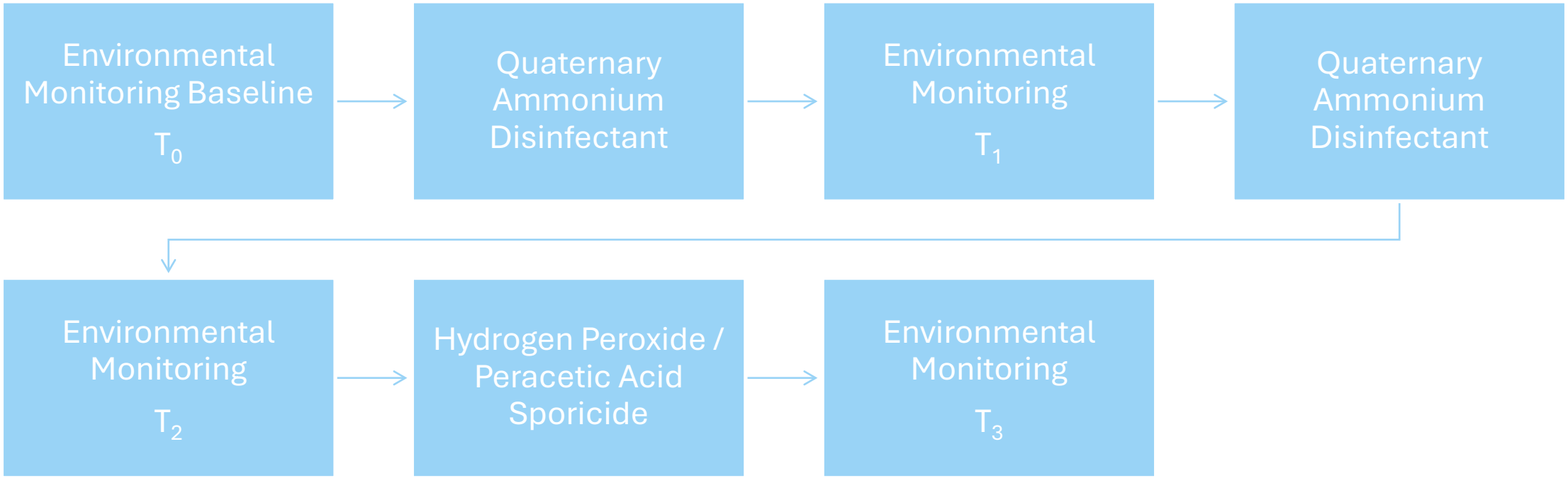
Table 1: Risk parameters and classification of substrates

Risk Parameter	Risk Classification		
	Low (1)	Medium (3)	High (5)
Relative surface roughness	Low surface roughness	Intermediate surface roughness	High surface roughness
Touch point	No contact	Occasional operator contact	High frequency of operator contact
Percentage surface area of substrate in item / cleanroom	Small percentage (<25%)	Intermediate percentage (<25% to 75%)	Large percentage (>75%)
Proximity to critical process	Not in close-proximity	NA	In close-proximity

Table 2: Risk assessment

Description			Risk Assessment				
Category	**Area**	**Substrate**	**Surface Rough-ness**	**Touch-point**	**% surface area**	**Proximity to critical area**	**Total**
Cleanroom	Floor	Terrazzo tiles	3	5	3	1	45
	Wall	Powder coated galvanized steel sheet	3	3	5	1	45
	Ceiling	Powder coated galvanized steel sheet	3	1	3	1	9
	Windows	Glass	3	3	3	1	27
	Sealant	Silicone	3	1	1	1	3
Furniture	Tables, chairs, trolleys, shelves	Stainless steel 304L	3	5	5	1	75
	Caster wheels of trolleys	Polyurethane	5	5	1	1	25

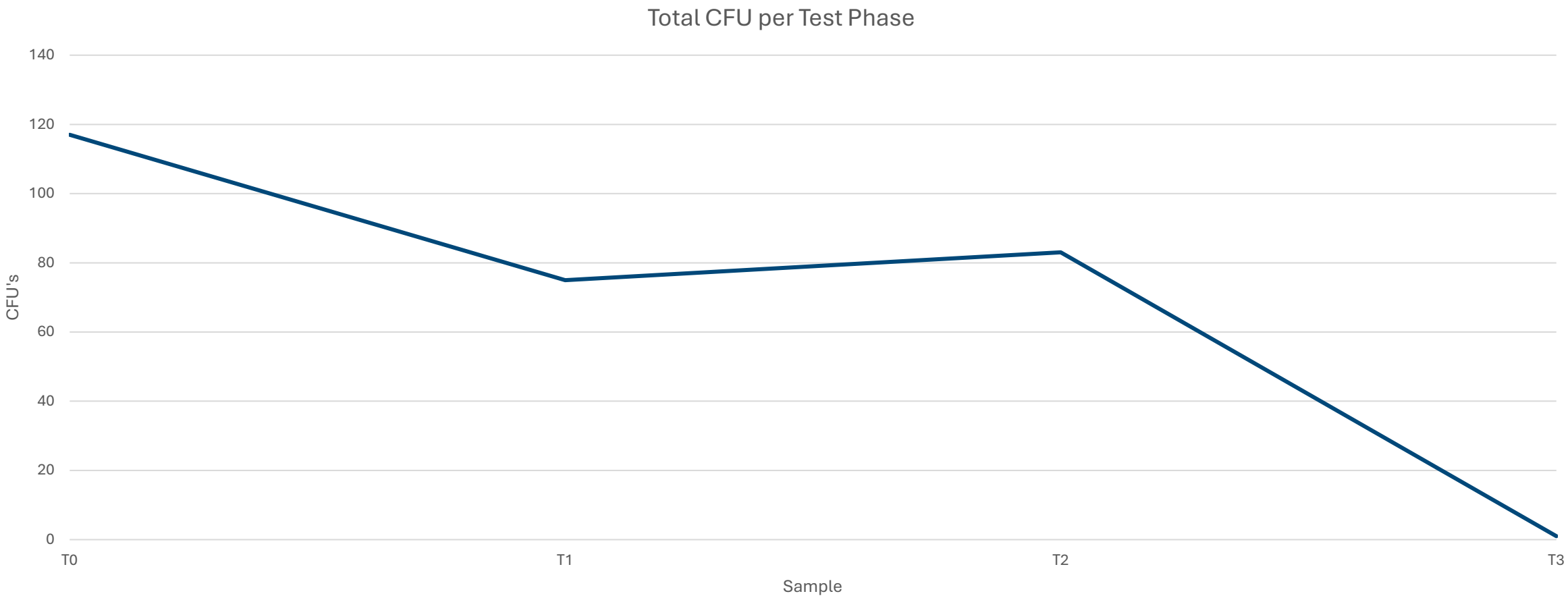
Second Quaternary Ammonium Case Study



Sampling Data

Summary: Sample Collection and Test Results													
Room	ISO Class	Samples				CFU count				CFU/Plate			
		T_0	T_1	T_2	T_3	T_0	T_1	T_2	T_3	T_0	T_1	T_2	T_3
B107 Clean Corridor	8	16	16	16	16	10	8	10	0	0.63	0.50	0.63	0.00
B120 Prep Room	8	12	12	12	12	9	5	6	0	0.75	0.42	0.50	0.00
B123 Material Entrance	7	5	5	5	5	0	0	0	0	0.00	0.00	0.00	0.00
B125 Aseptic Gowning	7	6	6	6	6	4	3	0	0	0.67	0.50	0.00	0.00
B124 Compounding Room	7	16	16	16	16	15	7	5	0	0.94	0.44	0.31	0.00
B118 Pass Through	7	6	6	6	6	4	2	3	0	0.67	0.33	0.50	0.00
B116 Filling Suite	7	19	19	19	19	24	30	21	1	1.26	1.58	1.11	0.05
B116 Laminar Flow Hood	5	3	3	3	3	2	0	0	0	0.67	0.00	0.00	0.00
B116 Behind Curtain	5	10	10	10	10	10	2	0	0	1.00	0.20	0.00	0.00
B116 Fill Machine	5	14	14	14	14	29	3	0	0	2.07	0.21	0.00	0.00
B116 Isolator Finger Tips	5	13	13	13	13	4	0	0	0	0.31	0.00	0.00	0.00
B114 Material Exit	7	6	6	6	6	0	0	0	0	0.00	0.00	0.00	0.00
B113 Personnel Exit	7	6	6	6	6	6	15	37	0	1.00	2.50	6.17	0.00
Overall	**NA**	**132**	**132**	**132**	**132**	**117**	**75**	**83**	**1**	**0.89**	**0.57**	**0.62**	**0.01**

Reduction in Cleanroom Bioburden



Material Transfer

FDA Warning Letters

Adulterated Drug Products

1. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

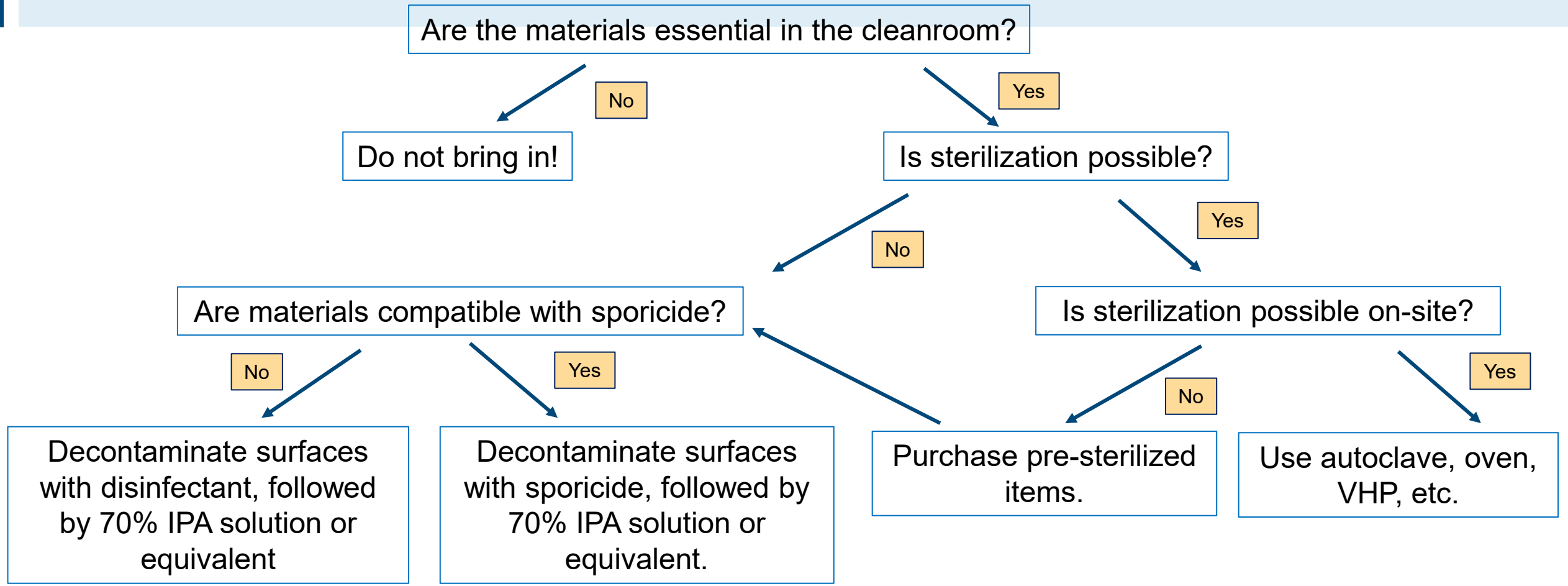
2. Operators dragged the underside of their gowning sleeves on the work surface of the ISO 5 hood during aseptic production. This practice may introduce contamination into the ISO 5 work area.

3. Your firm did not *adequately disinfect materials during transfer from the ISO 7 cleanroom into the ISO 5 hood*.

4. You failed to *adequately disinfect containers of sterile drug components immediately prior to puncturing critical sites* for use in operations.

MARCS-CMS 687936 (Jul 2024)

Material Transfer Decision Tree



Material Transfer – Efficacy of Sporicide & IPA

Organism	Surface	Treatment (Contact Time)	Baseline Inoculum	Log Reduction	Percent Kill
A. brasiliensis	Self-seal pouch	70% IPA (1 min)	5.58	0.11 ± 0.08	22.72%
		Sporicide (5 min)	5.58	> 4.58	> 99.99%
		Sporicide (5 min) + 70% IPA (1 min)	5.58	> 4.58	> 99.99%
B. subtilis	Self-seal pouch	70% IPA (1 min)	5.24	0.01 ± 0.01	2.48%
		Sporicide (5 min)	5.24	1.47 ± 0.07	96.61%
		Sporicide (5 min) + 70% IPA (1 min)	5.24	1.98 ± 0.03	98.96%

Points to Consider for Material Transfer

Equipment surface compatible with sanitizers / disinfectants / sporicidal agents?

Packaging materials compatible with sanitizers / disinfectants / sporicidal agents?

Sufficient layers?

Disinfectant validated? Risk of residues?

Maintaining wet contact time

Sanitization procedure in place

Material & Equipment Transfer

Material Transfer Airlocks & Pass Through Hatches

Pass through hatches to protect the higher-grade cleanroom

Passive pass through /Active filtered-air supply pass through

Cleaning & disinfection

Interlocking system

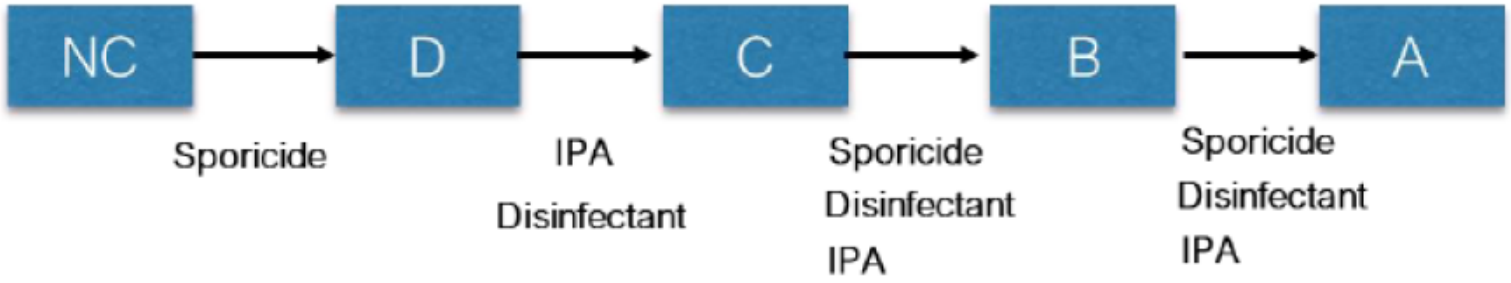
Material Transfer

"4.12 (ii) The movement of material or equipment from lower grade or unclassified area to higher-grade clean areas should be subject to *cleaning and disinfection* commensurate with the risk and in line with the CCS."

"8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying *disinfection of the exterior of the sealed packaging*..."

"8.49 For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilised , an *effective and validated disinfection* and transfer process should be in place..."

Example:



Manual Disinfection

Advantages	Disadvantages / Challenges
• Other sterilization methods can be used that could have better material compatibility for parts • Movement of items that cannot be sterilized / electronics • Less expensive • Shorter processing time	• High operator interaction • Reduced repeatability • Consistency in process • Time consuming • Porous material to wipe • Disinfectant efficacy

Points to Consider

- Detailed SOP and training
- Efficacy of disinfectants
- Consistency in wiping method
- Testing for bioburden reduction

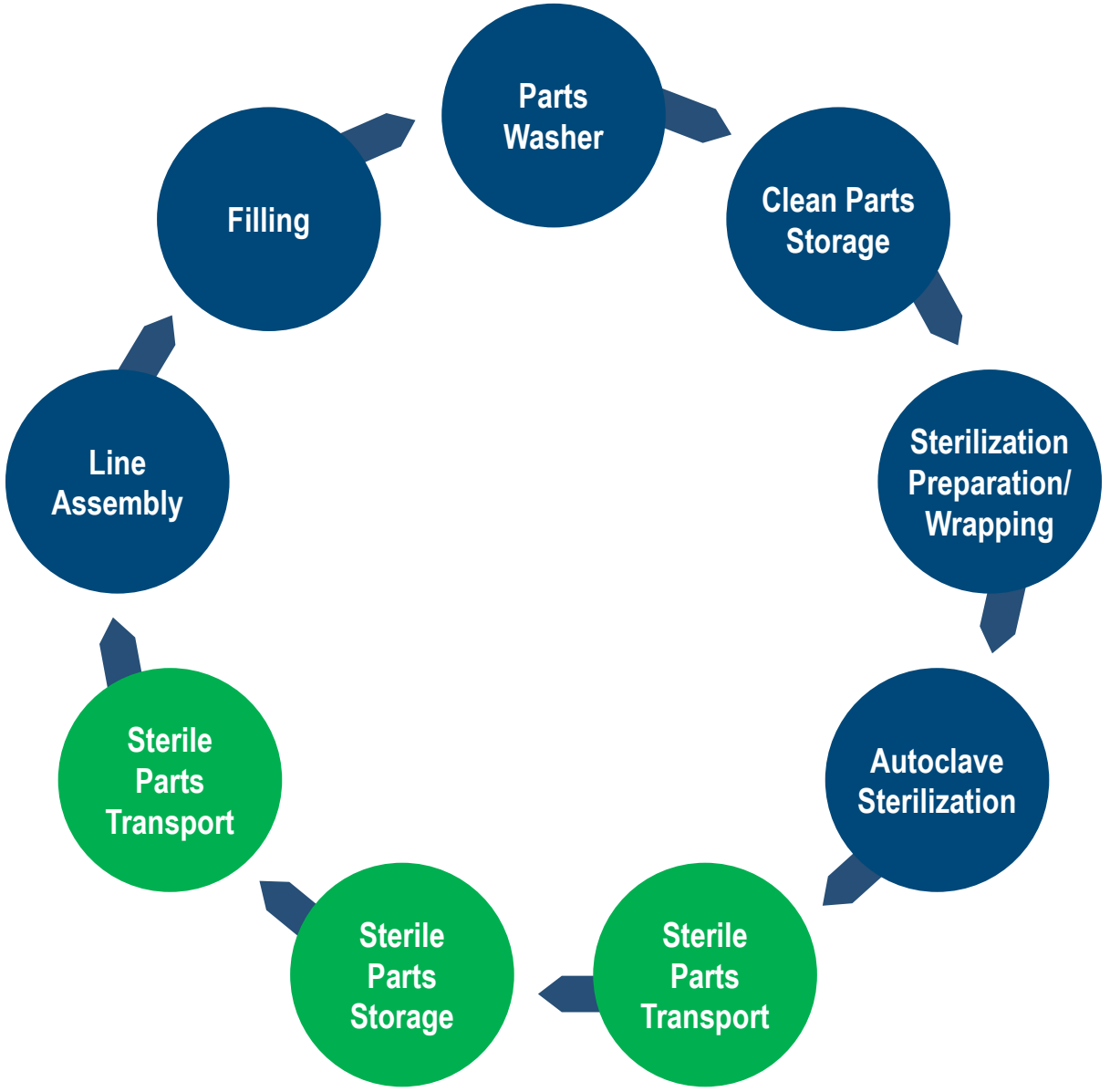
Transportation and Assembly of Sterilized Equipment

Transportation and Assembly of Sterilized Equipment

Annex 1

"4.10 **The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination**. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented…."

"4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible**, items should be sterilized and passed into these areas through double-ended sterilizers (e.g., through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilization upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g., using an effective transfer disinfection process**, rapid transfer systems for isolators or for gaseous or liquid materials, a bacteria-retentive filter). …"



Evaluate Contamination Risk

Process Step	Microbial	Endotoxin/Pyrogen	Particle
Parts Washing	1	3	2
Clean Parts Storage	3	3	3
Sterilization Preparation/Wrapping	4	2	4
Autoclave Sterilization	3	1	1
Sterile Parts Transport	4	1	3
Sterile Parts Storage	2	1	3
Line Assembly	5	2	5
Filling Process	3	2	3

Risk Score
1 = minimal or no risk
5 = maximum risk

Identify and Implement Controls

Process Step	Control	Impact
Parts Washing	Validated Cycle Detergents	Process Consistency, Effectiveness Efficiency
Clean Parts Storage	Room Classification Equipment Covers	Minimize Risk of Contamination
Sterilization Preparation/Wrapping	Wrapping Materials Work Instructions	Efficiency, Reproducibility
Autoclave Sterilization	Validated Cycle Wrapping Materials Process Monitoring (Alarms, BIs, CIs)	Process Consistency, Effectiveness Efficiency Sterilization Confirmation
Sterile Parts Transport	Wrapping Materials (Multiple Layers) Sterility Maintenance Bags Surface Disinfection	Microbial Barrier Disinfectant Compatibility
Sterile Parts Storage	Room Classification Sterility Maintenance Bags HEPA/LAF Cabinet Equipment Covers	Minimize Risk of Contamination
Line Assembly	Wrapping Materials Work Instruction Sequence of Activities RABS/Isolator Decontamination (VHP™)	Minimize Risk of Contamination Process Consistency, Effectiveness Efficiency Decontamination Compatibility
Filling Process	Aseptic Process Simulation Interventions Pre-Sterilized Tools	Aseptic Confirmation

Questions & Discussion?

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